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Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 7, No. 4, October 2020, 518–526
eISSN 2148-9696

Extracorporeal Shockwave Therapy and Physiotherapy in Patients With Moderate Knee Osteoarthritis

Bina Eftekharsadat[1], Fatemeh Jahanjoo[2], Vahideh Toopchizadeh[1], Fariba Heidari[3], Razieh Ahmadi[1], Arash Babaei-Ghazani[4*]

Abstract

Objectives: Extracorporeal shockwave therapy (ESWT) has recently been evaluated for knee osteoarthritis (KOA) treatment. The present study aimed to investigate the therapeutic effects of ESWT for the treatment of patients with moderate KOA compared with conventional physiotherapy (PT).

Materials and Methods: In this randomized controlled clinical trial, a total of 75 adult patients (70 females and 5 males) with moderate KOA were randomly assigned to ESWT with exercise, PT with exercise, and exercise-only groups. Finally, patients were evaluated using the visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), knee range of motion (ROM), Timed Up and Go (TUG) test, and high sensitivity C-reactive protein.

Results: In either treatment group, VAS, WOMAC, and TUG significantly improved toward 3 weeks and this improvement sustained until the 7-week follow-up session. In addition, patients' knee ROM significantly improved in the ESWT group throughout the course of the study. Based on the results, no significant difference was observed between the ESWT and PT after 3 weeks and both were superior to exercise alone. In the 7-week evaluation, patients in the ESWT group reported lower pain (50.42% improvement in VAS compared to 30.31%; $P<0.001$ and 28.26%; $P=0.008$ in PT and exercise groups, respectively) and better improvement in knee extension ROM ($P=0.004$ and <0.001, respectively).

Conclusions: In general, although PT and ESWT seem to be more effective than exercise alone in the short-term treatment of patients suffering from KOA, medium intensity ESWT is better than PT and exercise in the medium-term rehabilitation of these patients resulting in better pain-relieving and knee ROM improvements.

Keywords: Extracorporeal shock wave therapy, Knee osteoarthritis, Physiotherapy, Exercise

Introduction

The most commonly affected joints in osteoarthritis (OA) are the knees (1). Knee osteoarthritis (KOA) could produce prominent changes in health-related quality of life (2) due to its disabling manner which could affect several daily functions. Currently, several conservative and surgical strategies are used in patients suffering from KOA (3). Conservative treatments are mainly used in the primary phase of the disease, including non-steroidal anti-inflammatory drugs, activity modification, and physical therapy. In addition, surgical procedures such as knee replacement therapy are preserved for the later severe stage of KOA (4).

Patients receiving drug medication often report limited pain relief, and common KOA drugs are often related to serious side effects (5). Therefore, other conservative treatments were evaluated in this respect. The basic physiotherapy (PT) technique for KOA patients is exercise (6). Physical agents such as electro-stimulation, heat and cold modalities, and ultrasound (US) have a limited role in KOA management but could enhance the patient's function when combined with exercise (7).

Extracorporeal shockwave therapy (ESWT) was first introduced for the treatment of kidney stone disease (1). Since then, ESWT indications have been extended, and it is currently used for the treatment of a wide variety of musculoskeletal problems, including plantar fasciitis, epicondylitis, and the calcific tendinopathy of the rotator cuff (1,8). Further, ESWT has recently been introduced in the treatment of KOA with a developing number of successful studies demonstrating its therapeutic effects (9).

Furthermore, several animal studies noted the chondroprotective effects of ESWT on the initiation of KOA changes (10) and the regression of established KOA changes (11). However, few studies have investigated its use in human KOA (1). Accordingly, the present study aimed to evaluate the therapeutic effects of ESWT for the treatment of patients with moderate KOA compared with conventional PT in order to investigate its efficiency

Received 10 January 2019, **Accepted** 20 March 2019, **Available online** 10 May 2019

[1]Physical Medicine and Rehabilitation Research Center, Aging research Institute, Tabriz University of Medical Sciences, Tabriz, Iran. [2]Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. [3]Department of Community Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. [4]Neuromusculoskeletal Research Center, Department of Physical Medicine and Rehabilitation, Iran University of Medical Sciences, Tehran, Iran.

*Corresponding Author: Arash Babaei-Ghazani, Tel: +989120766393, Email: arashbabaie@gmail.com

in alleviating patients' pain and improving their function. Therefore, it could be recommended as an effective and safe alternative method for the conservative treatment of KOA.

Materials and Methods

Study Design and Setting

This randomized clinical trial was conducted at Shohada hospital in 2017-2018. The research was carried out according to the Helsinki Declaration, and informed written consent was obtained from all participants. Additionally, the study was approved by the Ethics Committee of Tabriz University of Medical Sciences in letter No. 19796/D/5 in 2016.6.8 with the registry number of IR.TBZMED.REC.1395.288. The study was also registered in the Iranian Registry of Clinical Trials under number IRCT201608044641N12.

Participants

The inclusion criteria were the presence of KOA based on the American College of Rheumatology criteria (12) including the grades II and III (moderate) of KOA based on the Kallgren-Lawrence radiologic criteria using knee X-ray (13) and the age range of 50-70 years.

On the other hand, the exclusion criteria were grade I (mild) or IV (severe) of OA (13), history of other rheumatological diseases such as rheumatoid arthritis, history of knee surgery and lower limb fracture involving knee articular surface, and electrical implants such as a pacemaker. Additionally, other criteria included a history of heart conduction block, epilepsy, pregnancy, deep vein thrombosis of lower limbs, intra-articular knee injection history over the last six months and taking steroid medications during the last month, as well as balance disorder, neuropathic or impaired sensation disorders, and local infection.

Randomization, Patient's Enrolment and Blinding

In this study, 75 participants were enrolled in the study and randomized into 3 groups using sealed envelopes (A, B, and C) which were produced by a statistician who did not participate in the enrollment. Then, the participants were classified into 3 groups according to the intervention. Group A, B, and C (each containing 25 participants) received ESWT with exercise, PT with exercise, and exercise programs only, respectively. The physician who evaluated clinical outcome measures and the person responsible for data assessment were blinded to the groups.

Intervention

Patients in the ESWT group received 5 sessions of shock wave therapy through 3 weeks via a Zimmer enPulsPro Medizin System GmbH, Germany. Patients were placed in a sitting position, and the affected knee was exposed. Further, the knee was slightly flexed, the hip abducted and externally rotated, and the applicator was directed in the most tender point over the affected knee joint (14). Then, radial ESWT was used with shockwaves of 2000 pulses/session with an energy flux density (EFD) of 0.18 mJ/mm^2, the energy level of 2-4, a frequency of 10-16 Hz, and pulse rate of 160/minute were generally applied each session.

Furthermore, patients in the PT group received 10 sessions (3 sessions, weekly) of physical therapy including hot pack (HP), transcutaneous electrical nerve stimulation (TENS) and ultrasound (US, HP: 74.5°C, 20 minutes on the affected knee, TENS: Pulse duration 20-100 microseconds, 50% duty cycle, current amplitude, maximum tolerated tingling, frequency <200 pps, US: frequency of 1 MHz, the intensity of 2.5 W/cm^2, and duty cycle of 25%, and the probe of US was applied for 10 minutes).

The exercise program was applied to all 3 groups. It consisted of the isometric strengthening of the quadriceps muscle in the form of 3 submaximal isometric contractions with gradually increasing intensity combined with weight-bearing water- and land-based exercises.

Additionally, patients were advised to only use acetaminophen for pain relief in the event of severe pain and activities of daily living modifications (e.g., weight loss and the avoidance of heavy lifting, long-distance walking, and high-impact exercises) were taught as well.

Outcome Measures

Patients' symptoms and functional status were evaluated using the visual analogue scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Timed Up and Go (TUG) test, knee flexion and extension range of motion (ROM), and high sensitivity C-reactive protein value (positive if ≥5 mg/L, negative if <5 mg/L). All outcome measures were evaluated at baseline, and after 3 and 7 weeks of the initial intervention.

Pain intensity was measured using a 10 cm VAS (0 = no pain at all and 10 = the worst pain possible). In addition, patients were asked to sign the place on the VAS that corresponded to their pain level at the rest over the last two days. Bijur et al showed that VAS is a reliable tool for assessing pain (15).

The WOMAC index is one of the most widely used measurements for evaluating OA patients. It is composed of 33 items that are grouped into four dimensions including symptoms (5 items), pain (9 items), stiffness (2 items), and physical function (17 items). Answers to each of the 33 questions are scored on a 5-point Likert-type scale (none = 0, slight = 1, moderate = 2, severe = 3, extreme = 4), with total scores ranging from 0 to 132 and higher scores indicate greater disease severity. The Persian version of WOMAC is a valid and reliable instrument for assessing the OA severity of the knee/hip in Iranian patients (16).

Further, the TUG test is a reliable screening tool for evaluating patients' mobility and falling risk. To perform the TUG test, the patient was timed while rising from a

standard armchair, walking at a normal pace to a line on the floor three meters away, turning and walking back to the chair, and sitting down again. The test was repeated 3 times for each patient and the mean value was recorded accordingly (17).

Flexion and extension ROM were evaluated using a manual goniometer. The goniometer axis was placed on the lateral knee joint with patients in the prone and hip in a neutral position.

Statistical Analysis

All statistical analyses were performed by SPSS software, version 25 (IBM Corporation, USA). The Kolmogorov-Smirnov test was used to check data distribution and normality. Furthermore, the one-way analysis of variance (ANOVA) for parametric data and Crosstabs and Chi-square tests for non-parametric data were used to compare the distribution frequency in each group. Moreover, repeated measure ANOVA and one-way ANOVA were applied to evaluate and compare intra-group differences as well as to compare the results between the two groups, respectively. Finally, the Kruskal-Wallis test was used in the case of a non-normal distribution, and the significance threshold was considered to be less than 0.05.

Results

Seventy-five patients were assessed for eligibility all of whom were enrolled in the study and divided into three 25-member groups. In the follow-up sessions, 2 patients in the ESWT group and 3 in each of the PT and exercise groups were lost due to the inability of attendance. Thus, 23 patients in the ESWT group and 22 patients in PT and exercise groups were analyzed in this study (Figure 1).

Patient Demographics and Baseline Measures

Patients' demographic and baseline characteristics are presented in Table 1. Based on the results, no significant differences were found in the patients' demographic and baseline characteristics among the three treatment groups (Table 1). The patients' mean age was 58.00 (±5.97), 55.76 (±6.06), and 58.16 (±7.20) years in ESWT, PT, and exercise groups, respectively. In addition, 25 (100%), 23 (92%), and 22 (88%) patients in ESWT, PT, and exercise groups were females. Further, the mean VAS scores in ESWT, PT, and exercise-only groups were 7.00 (±1.63), 7.16 (±1.37), and 6.32 (±1.44), respectively.

Furthermore, the reported mean WOMAC score in patients receiving ESWT was 71.68 ± 17.70 including 10.44 (±3.01), 4.12 (±1.94), 18.68 (±3.90), and 38.44 (±11.46) for WOMAC scores of symptoms, knee stiffness, pain, and physical function, respectively. In the PT group, the patients' WOMAC mean score of symptoms, knee stiffness, pain, and physical function was 10.32 (±4.09), 4.72 (±1.21), 19.48 (±4.34), and 34.68 (±10.41), respectively, with an overall score of 69.20 (±14.81). Moreover, the overall WOMAC score was 61.68 (±12.19) in the exercise group. Additionally, patients' symptom severity, knee stiffness, pain, and physical function impairment, which were evaluated with WOMAC, were 9.52 (±3.27), 4.64 (±1.25), 16.84 (±3.69), and 31.20 (±9.40), respectively.

The reported time regarding the TUG test was 13.09

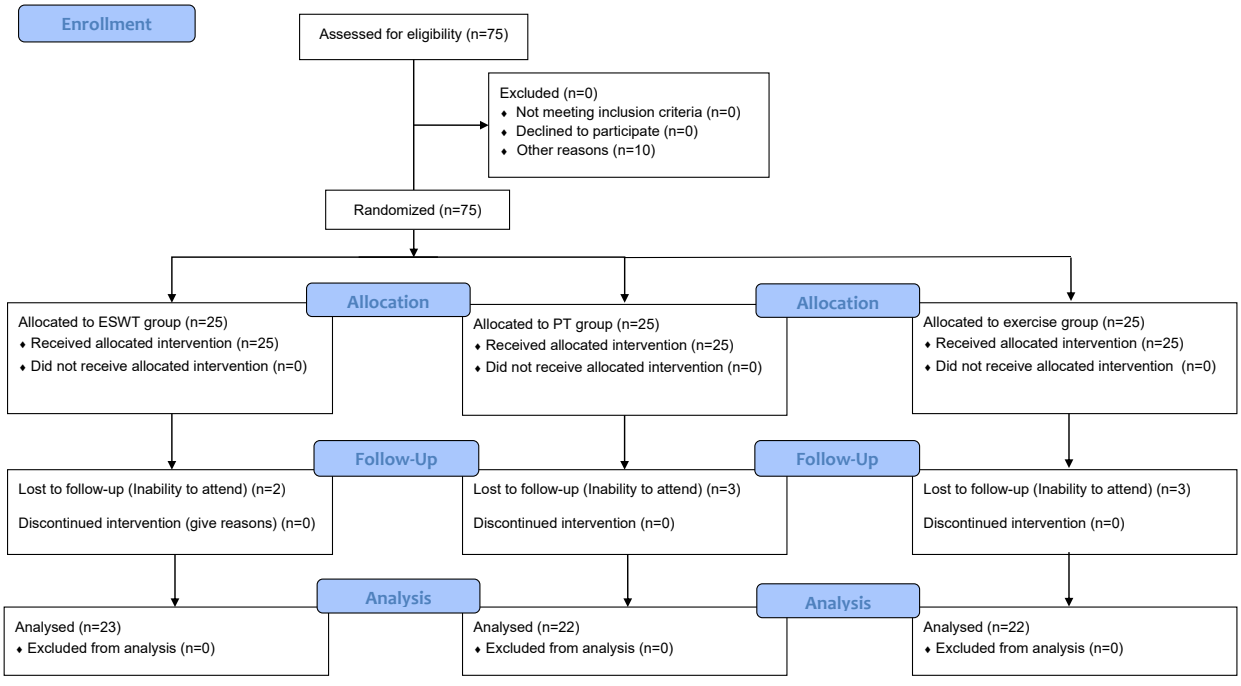

Figure 1. Flow Diagram of the Study Protocol.

(±2.25), 12.63 (±2.31), and 12.68 (±2.66) seconds in ESWT, PT, and exercise groups, respectively. Similarly, baseline knee flexion and extension ROM were 113.88 (±10.86°) and 6.20 (±4.15°), in patients receiving ESWT treatment, respectively. The above-mentioned ROMs were 118.00 (±15.00°) and 3.80 (±6.34°), as well as 118.40 (±15.19°) and 3.80 (±4.85°) in PT and exercise groups, respectively. Of 75 patients enrolled in the study, 2, 4, and 3 cases in ESWT, PT, and exercise groups were positive regarding high sensitivity C-reactive protein value (HSCRP) before the intervention, respectively.

Outcome Measures

The changes during the follow-up evaluation (weeks 3 and 7) of the outcomes are demonstrated in Table 2. As shown, all outcomes improved throughout the course of study in all treatment groups.

In the ESWT group, all outcomes improved toward 3 weeks after the beginning of treatment intervention, and this improvement sustained until the last follow-up session. In addition, this improvement was significant in all measures (P<0.05 for all parameters). In the PT group, all outcomes improved significantly toward 3 weeks of the intervention except for knee extension ROM (P=0.992). These improvements were persevered up to a 7-week follow-up in VAS, overall WOMAC score, and its pain and physical function section, the TUG test, and knee flexion ROM (all with P<0.05). In the exercise group, significant improvement was observed in the VAS, WOMAC overall score, physical function sub-score of WOMAC, and TUG test time 3 weeks after the intervention, which significantly sustained 7 weeks after treatment (P<0.05 for all parameters). Although the changes in symptom, knee stiffness, and pain scores (all evaluated with WOMAC) were not significant in the week 3 follow-up, there was a significant improvement seven weeks after treatment compared to the baseline in the above-mentioned measures (P<0.05 for all parameters).

As demonstrated in Table 3, significant improvement was found regarding all outcome measures in ESWT and PT groups compared to the exercise group 3 weeks after the beginning of intervention session except for the knee stiffness sub-score of WOMAC in the ESWT group (P=0.411) and knee extension ROM in the PT group (P>0.999). The comparison of patients receiving PT and ESWT, no significant differences were observed between the two treatment interventions in this time period except for knee extension ROM which was in favor of ESWT treatment (P<0.001).

The data in Table 4 present the comparison of treatment groups regarding the improvement of each outcome measure after 7 weeks. Patients in the ESWT group reported lower pain based on VAS (50.42% improvement from the baseline toward 7 weeks of follow-up compared to 30.31% and 28.26% in PT and exercise groups) and better improvement in knee extension ROM 7 weeks after treatment compared to PT and exercise groups (P<0.05 for all parameters). The observed improvement regarding knee flexion ROM was in favor of the ESWT group compared to the exercise group (P = 0.004). The results also indicated that the knee stiffness subs-score of WOMAC was significant in the exercise group during this time period compared to the ESWT group (P=0.004). However, there was no difference between PT and exercise groups in terms of 7-week follow-up measures.

As regards inflammatory measures, the number of people with positive HSCRP decreased in all treatment groups, but this decline was only significant in the PT group (P = 0.046), the details of which are provided in Table 5.

Table 1. Baseline Participant Characteristics by Treatment Group

Variable	Group			*P* Value
	ESWT (n = 25)	PT (n = 25)	Exercise (n = 25)	
Age (y), mean ± SD	58.00 ± 5.97	55.76 ± 6.06	58.16 ± 7.20	0.367[a]
Female, n (%)	25 (100.0)	23 (92.0)	22 (88.0)	0.359[b]
VAS, mean ± SD	7.00 ± 1.63	7.16 ± 1.37	6.32 ± 1.44	0.065[a]
WOMAC, mean ± SD				
Symptoms	10.44 ± 3.01	10.32 ± 4.09	9.52 ± 3.27	0.525[a]
Knee stiffness	4.12 ± 1.94	4.72 ± 1.21	4.64 ± 1.25	0.286[a]
Pain	18.68 ± 3.90	19.48 ± 4.34	16.84 ± 3.69	0.065[c]
Physical function	38.44 ± 11.46	34.68 ± 10.41	31.20 ± 9.40	0.056[c]
Overall score	71.68 ± 17.70	69.20 ± 14.81	61.68 ± 12.19	0.057[c]
TUG (s), mean ± SD	13.09 ± 2.25	12.63 ± 2.31	12.68 ± 2.66	0.753[c]
Knee flexion ROM (°), mean ± SD	113.88 ± 10.86	118.00 ± 15.00	118.40 ± 15.19	0.228[a]
Knee flexion ROM (°), mean ± SD	6.20 ± 4.15	3.80 ± 6.34	3.80 ± 4.85	0.052[a]
HSCRP positive, n (%)	2 (8.0)	4 (16.0)	3 (12.0)	0.904[b]

Note. ESWT: Extracorporeal shockwave therapy; PT: Physiotherapy; WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index; TUG: Timed up and go test; ROM: Range of motion; HSCRP: High sensitivity C-reactive protein; SD: Standard deviation; VAS: Visual analogue scale.
[a] Kruskal-Wallis test; [b] Fisher's exact test; [c] One-way analysis of variance.

Table 2. Analysis of Outcome Measures Throughout the Study Period by the Treatment Group

Variable		Group					
		ESWT (n = 23)		PT (n = 22)		Exercise (n = 22)	
		Mean ± SD	MD (95% CI) P-value	Mean ± SD	MD (95% CI) *P*-value	Mean ± SD	MD (95% CI) *P*-value
VAS	Before intervention	7.00 ± 1.63	Reference	7.16 ± 1.37	Reference	6.32 ± 1.44	Reference
	After 3 weeks	4.76 ± 1.64	2.30 (1.73-2.88) < 0.001	4.76 ± 1.30	2.36 (1.73-2.99) < 0.001	5.61 ± 1.34	0.65 (0.17-1.04) 0.001
	After 7 weeks	3.61 ± 1.72	3.35 (1.73-2.88) < 0.001	4.95 ± 1.25	2.18 (1.57-2.79) < 0.001	4.57 ± 1.53	1.70 (1.36-2.04) < 0.001
WOMAC							
Symptoms	Before intervention	10.44 ± 3.01	Reference	12.63 ± 2.31	Reference	9.52 ± 3.27	Reference
	After 3 weeks	9.16 ± 2.61	1.30 (0.62-1.98) 0.001	11.28 ± 2.35	2.54 (1.17-3.92) 0.001	9.52 ± 3.36	0.01 (- 0.28-0.29) > 0.999
	After 7 weeks	8.26 ± 2.53	2.26 (1.23-3.29) < 0.001	10.57 ± 2.74	1.55 (- 0.01-3.10) 0.052	7.39 ± 3.10	2.13 (1.47-2.79) < 0.001
Knee stiffness	Before intervention	4.12 ± 1.94	Reference	4.72 ± 1.21	Reference	4.64 ± 1.25	Reference
	After 3 weeks	3.44 ± 1.47	0.61 (0.07-1.14) 0.022	3.68 ± 1.25	1.00 (0.22-1.78) 0.010	4.43 ± 1.38	0.26 (- 0.28-0.81) 0.685
	After 7 weeks	3.00 ± 1.45	0.96 (0.34-1.58) 0.002	3.73 ± 1.64	0.82 (-0.43-2.07) 0.313	2.61 ± 1.23	2.09 (1.60-2.57) < 0.001
Pain	Before intervention	18.68 ± 3.90	Reference	19.48 ± 4.34	Reference	16.84 ± 3.69	Reference
	After 3 weeks	13.88 ± 4.48	4.83 (3.40-6.25) < 0.001	14.96 ± 6.20	4.77 (2.91-6.64) < 0.001	16.48 ± 3.94	0.30 (- 0.59-1.20) > 0.999
	After 7 weeks	12.30 ± 4.84	6.17 (4.61-7.73) < 0.001	13.18 ± 5.66	6.00 (4.23-7.77) < 0.001	10.61 ± 4.91	6.17 (4.36-7.99) < 0.001
Physical function	Before intervention	38.44 ± 11.46	Reference	34.68 ± 10.41	Reference	31.20 ± 9.40	Reference
	After 3 weeks	33.20 ± 14.29	5.74 (3.42-8.06) < 0.001	26.40 ± 12.40	8.73 (5.42-12.04) < 0.001	28.48 ± 8.74	1.30 (0.48-2.13) 0.006
	After 7 weeks	30.74 ± 13.55	7.43 (4.64-10.23) < 0.001	24.18 ± 11.32	9.23 (5.08-13) < 0.001	20.00 ± 10.51	9.78 (7.55-12.01) < 0.001
Overall score	Before intervention	71.68 ± 17.70	Reference	69.20 ± 14.81	Reference	61.68 ± 12.19	Reference
	After 3 weeks	59.68 ± 20.30	12.48 (9.22-15.74)< 0.001	52.72 ± 18.92	17.04 (11.17-22.92)< 0.001	58.91 ± 12.21	1.87 (0.30-3.44) 0.016
	After 7 weeks	54.30 ± 20.36	16.83 (12.54-21.11)< 0.001	49.86 ± 18.51	17.59 (10.50-24.69)< 0.001	40.61 ± 16.83	20.17 (16.75-23.60) < 0.001

Note. ESWT: Extracorporeal shockwave therapy; PT: Physiotherapy; WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index; MD: Mean difference; CI: Confidence interval; SD: Standard deviation; VAS: Visual analogue scale.

Discussion

In the past 20-25 years, ESWT had shown positive therapeutic effects in the treatment of several common musculoskeletal problems (18). Furthermore, it was approved by the U.S. Food and Drug Administration (FDA) for the treatment of plantar fasciitis in 2000 and the lateral epicondylitis of the elbow in 2003 (19). ESWT has recently been used to reduce pain, physical impairments, and KOA progression with few reported complications (3). This study was performed to compare the efficacy of ESWT with conventional physical therapy.

According to the findings of the present study, either ESWT combined with exercise, physical modalities combined with exercise, or exercise alone would improve patients knee pain (evaluated by VAS), functional condition (evaluated by WOMAC), and mobility (evaluated by TUG) after the third week and their improving effect was preserved toward 7 weeks of treatment. Moreover, significant improvements were observed in knee ROM throughout the study only in patients receiving ESWT. In the third week of evaluation, there was no difference between ESWT and PT and both were superior to exercise-only treatment. Although the medium-term effect (7 weeks after the intervention) of PT and exercise was similar, EWST seemed to be the method of choice for reducing patients' knee pain in longer terms.

Additionally, ESWT has a therapeutic effect on knee pain and function in patients suffering from KOA. Zhao et al (1) reported that ESWT was more effective than a placebo in reducing pain during the 12-week treatment (P<0.01). In another study, Lizis et al (3) reported that ESWT was a better modality for decreasing knee pain

Table 3. The Between-group Analysis of Outcome Measures by the Treatment Group 3 Weeks After Intervention Initiation

Variable		Group			*P* Value		
		ESWT (n = 23)	PT (n = 22)	Exercise (n = 22)	ESWT vs. Exercise	PT vs. Exercise	ESWT vs. PT
		Mean ± SD	Mean ± SD	Mean ± SD			
VAS	Improvement	2.24 ± 1.05	2.40 ± 1.08	0.65 ± 0.71	< 0.001	< 0.001	> 0.999
	Percentage	31.94%	33.25%	10.20%			
WOMAC, mean ± SD							
Symptoms		1.28 ± 1.24	2.64 ± 2.61	0.01 ± 0.52	< 0.001	< 0.001	0.457
Knee stiffness		0.68 ± 1.07	1.04 ± 1.37	0.26 ± 1.01	0.411	0.039	0.920
Pain		4.80 ± 2.72	4.52 ± 3.53	0.30 ± 1.66	< 0.001	< 0.001	> 0.999
Physical function		5.24 ± 4.52	8.28 ± 6.00	1.30 ± 1.52	0.002	< 0.001	0.529
Overall score		12.00 ± 6.10	16.48 ± 10.44	1.87 ± 2.91	< 0.001	< 0.001	0.930
TUG (s), mean ± SD		1.64 ± 0.75	1.35 ± 1.27	0.40 ± 0.60	0.011	< 0.001	0.608
Knee flexion ROM (°), mean ± SD		6.12 ± 4.15	5.80 ± 6.72	-0.22 ± 2.37	< 0.001	0.001	0.605
Knee extension ROM (°), mean ± SD		3.00 ± 2.89	0.40 ± 2.00	0.00 ± 0.00	< 0.001	< 0.001	< 0.001

Note. ESWT: Extracorporeal shockwave therapy; PT: Physiotherapy; WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index; TUG: Timed up and go test; ROM: Range of Motion; SD: Standard deviation; VAS: Visual analogue scale.

Table 4. The Between-group Analysis of Outcome Measures by the Treatment Group 7 Weeks After Intervention Initiation

Variable		Group			*P* Value		
		ESWT (n = 23)	PT (n = 22)	Exercise (n = 22)	ESWT vs. Exercise	PT vs. Exercise	ESWT vs. PT
		Mean ± SD	Mean ± SD	Mean ± SD			
VAS	Improvement	3.35 ± 1.27	2.18 ± 1.10	1.70 ± 0.70	< 0.001	0.373	0.008
	Percentage	50.42 %	30.31%	28.26 %			
WOMAC, mean ± SD							
Symptoms		2.26 ± 1.91	1.55 ± 2.81	2.13 ± 1.22	0.982	0.952	0.752
Knee stiffness		0.96 ± 1.15	0.82 ± 2.26	2.09 ± 0.90	0.004	0.058	0.910
Pain		6.17 ± 2.89	6.00 ± 3.19	6.17 ± 3.37	0.995	0.998	0.999
Physical function		7.43 ± 5.17	9.23 ± 7.48	9.78 ± 4.12	0.509	0.996	0.895
Overall score		16.90 ± 8.36	18.55 ± 12.35	19.85 ± 6.55	0.690	0.968	0.927
TUG (s), mean ± SD		2.64 ± 1.04	2.08 ± 1.53	1.87 ± 0.97	0.100	0.978	0.371
Knee flexion ROM (°), mean ± SD		7.09 ± 4.97	5.45 ± 7.39	1.74 ± 5.56	0.001	0.092	0.510
Knee extension ROM (°), mean ± SD		4.13 ± 4.17	0.45 ± 2.13	1.30 ± 3.44	0.004	0.937	< 0.001

Note. ESWT: Extracorporeal shockwave therapy; PT: Physiotherapy; WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index; TUG: Timed up and go test; ROM: Range of Motion; SD: Standard deviation; VAS: Visual analogue scale.

compared to US in 5-week treatment. Of patients in the ESWT group, 80% reported ≥ 30% improvements in pain while 50% reported the same result in the US group. Shenouda (6) found that ESWT was more effective in reducing knee pain compared the exercise alone (4.26 ± 1.46 improvement compared to 1.733 ± 0.73). Contrarily, in the study by Imamura et al (20), radial ESWT led to a statistically significant improvement in the mean pain sub-score of WOMAC for pain while not in patients' VAS. It should be noted that this study evaluated patients with severe KOA compared to our study. In addition, patients received ESWT with a different protocol and lower total energy (3 sessions, each one week apart, 2,000 impulses per session, and positive EFD of 0.10-0.16 mJ/mm^2).

Although the pain-relieving mechanism of ESWT is not precisely known, several hypotheses have been made in this regard. For instance, Ochiai et al (21) found that ESWT reduced the level of calcitonin gene-related peptide (CGRP) within dorsal root ganglia (DRG) in a rat model of KOA. It was also reported that ESWT application could lead to a reduction in the substance P level in the target tissue and DRG (22, 23). Both substance P and CGRP are important neuropeptides in nociceptive pathways and contribute to the joint nociceptive inputs (24). In addition, the depletion of substance P from C-fibers could lead to selective involvement of sensory unmyelinated nerve fibers while not affecting larger myelinated nerve fibers (25). Another hypothesized theory is the gate-control effect induced by ESWT due to overstimulating the axons and thus raising the pain threshold (26). Other potential mechanisms, which are responsible for pain-alleviating effect of ESWT on KOA by ESWT mostly based on animal studies, include decreased levels of nitric oxide which could lead to reduced progression of KOA, improved subchondral bone remodeling, decreased cartilage degradation, reduced chondrocyte apoptosis, and local secretion of endorphins (10, 27-29).

In addition to the pain-relieving effect, ESWT seems to

Table 5. HSCRP Alteration Between Treatment Groups 7 Weeks After the Intervention

HSCRP		Group		
		ESWT	PT	Exercise
		n (%)	n (%)	n (%)
Before treatment	Positive	2 (8.0)	4 (16.0)	3 (12.0)
	Negative	23 (92.0)	21 (84.0)	22 (88.0)
After 7 weeks	Positive	0 (0.0)	0 (0.0)	2 (9.1)
	Negative	23 (100.0)	22 (100.0)	20 (90.9)
P-value		0.159	0.046	0.564

Note. HSCRP: High sensitivity C-reactive protein; ESWT: Extracorporeal shockwave therapy; PT: Physiotherapy.

be an effective agent for improving knee ROM in patients with KOA. Based on the findings of our study, significant knee ROM improvements throughout the entire course of the study were observed only in patients receiving ESWT. In the study by Shenouda (6), ESWT was the most effective method for increasing knee ROM joint with $P < 0.0001$ compared to mobilization and exercise only. Similarly, Chen et al (8) compared ESWT, US, and exercise and represented that only US and ESWT improved knee ROM after treatment, and only ESWT resulted in immediate improvement of ROM after each treatment. The analgesic and anti-inflammatory and tissue regeneration effect of ESWT could be responsible for a better improvement in knee ROM (6).

Patients' physical function (evaluated by WOMAC) and mobility (evaluated by TUG) improved after ESWT. Other studies demonstrated better knee functional improvements via receiving ESWT compared to the US, placebo, or exercise-only treatments (1,3,6,8). For example, Lizis et al (3) concluded that patients with KOA can achieve significantly better physical function (evaluated by WOMAC and KOOS) via the application of ESWT rather than the US. Comparing ESWT with laser therapy, Li et al (5) found that ESWT a greater therapeutic effect evaluated by WOMAC total, and its sub-scores at weeks 6 ($P < 0.05$) and 12 ($P \leq 0.01$) after treatment. In a recent study (30), there was no significant difference between ESWT and hyaluronic injection regarding WOMAC, Lequesne index, 40-m fast-paced walk test, and stair-climb test 1 month and 3 months after treatment ($P > 0.05$). The mechanisms of improvement in the function of patients with KOA after receiving ESWT seem to be multifactorial. For instance, Arno et al (31) reported that improved function after ESWT could be due to the analgesic effect, increased perfusion in ischemic tissues, the stimulation of growth factors (including vascular endothelial growth factor, proliferating cell nuclear antigen, endothelial nitric oxide synthase, and BMP-2) and healing process, and decreased inflammation. In another study, Wang et al (32) concluded that ESWT could facilitate angiogenesis and osteogenesis in rats, thus leading to an improvement in subchondral bone remodeling. This improvement was associated with a chondroprotective effect that could prevent the initiation of KOA in rats. In addition, Kang et al reported that ESWT has the potential to shorten the natural course of KOA due to a notable reduction in the bone marrow edema of the affected knee, observed via patients' MRI ($P < 0.01$).

Moreover, Kim et al (33) evaluate the dose-related effects of ESWT for KOA and found that ESWT with medium-energy application (1000 shocks/session, EFD = 0.093 mJ/mm^2) showed a greater pain relief effect (evaluated by VAS) and better functional outcomes compared to the low-energy group (1000 shocks/session, EFD = 0.040 mJ/mm^2). Based on the findings of another study, the effects of ESWT on the musculoskeletal system were dose-dependent, and further energy applied to patients resulted in a better effect (20). The reason could be that higher energy intensity drastically reduced more unmyelinated sensory nerve fibers, and thus had a greater pain-alleviating effect (33). On the other hand, EFD applied at >0.50 mJ/mm^2 was associated with degenerative changes in the hyaline cartilage of the rats (34). In addition, excessive increases in the applied energy could result in a corresponding increase in patient's pain and discomfort after the ESWT session. This requires local anesthesia administration, which could lead to a reduction in the efficacy of the ESWT (35). Therefore, it seems shockwave with medium intensity (EFD = 0.08–0.28 mJ/mm^2), according to (33), is the most suitable protocol for KOA patients. In the present study, the shockwave was applied with a medium intensity of EFD = 0.18 mJ/mm^2.

In summary, participants receiving ESWT combined with exercise reported continuous improvements in pain and functional status which was not found in other groups. This correlates with the point that the effects of ESWT not only focus on the immediate pain and impairment reduction, as well as ROM improvement and mobility but also on the reconditioning of the treated tissue for a better medium-term function.

Despite the apparent strength of this study, as the first one to assess the effect of ESWT on Iranian patients suffering from KOA, it is subject to some limitations. The main limitation was the small patient population and a limited follow-up period (7 weeks). Only a certain number of shocks, frequency, and type of ESWT were used in this study. Accordingly, further studies with a larger population and longer follow-ups are required to fully understand ESWT therapeutic effects on KOA. Finally, it is recommended that different ESWT protocols (i.e., radial or focused ESWT with different EFDs) are evaluated to achieve more reliable results.

Conclusions

Although PT and ESWT seem to be more effective than exercise alone in the short-term treatment of patients suffering from KOA, medium intensity ESWT is superior to PT and exercise in the medium-term rehabilitation

of these patients since it results in better pain-relieving and knee ROM. Further, ESWT combined with exercise not only could improve patient's pain, impairment, and mobility in the early phase of treatment but also could affect their medium-term function due to its tissue reconditioning effect. Thus, ESWT could be recommended as an effective addition for the treatment of KOA.

Conflict of Interests

None declared

Financial Support

None.

Acknowledgments

We would like to thank the Physical Medicine and Rehabilitation Research Center, Imam Reza hospital and Clinical Research Developmental Unit, Shohada hospital, Tabriz University of Medical Sciences.

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