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Extracoporeal shockwave treatment decreases pain, functional limitations and medial collateral ligament thickness in subjects aged 50-70 years with knee osteoarthritis

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ABSTRACT

BACKGROUND

Pain from knee and hip osteoarthritis (OA) can have a significant impact on the physical function and quality of life of affected individuals worldwide. The objective of this study was to evaluate the effect of extracorporeal shockwave therapy (ESWT) on pain, flexibility, function, and medial collateral ligament (MCL) thickness in knee osteoarthritis (KOA).

METHODS

A study of quasi experimental design was performed involving 15 subjects aged 50 – 70 years with Kellgren-Lawrence grade 2-3 KOA. All subjects were evaluated regarding baseline -pain using visual analogue scale (VAS), range of motion (ROM), functional outcome using Western Ontario and McMaster Universities Arthritis Index (WOMAC), and MCL size. Extracorporeal shock wave therapy was given 3 times, at baseline, and 4 and 8 weeks after intervention. All subjects were given 4000 shocks at intensities of 1.5 – 4 Bar (raised gradually) per session. The shocks were given in the supine position, knee flexed 90°, without topical anesthetic. Statistical analyses were conducted using a dependent t-test.

RESULTS

After 8 weeks of intervention, ESWT significantly improved pain score ($p<0.01$), WOMAC ($p<0.01$) and MCL thickness ($p<0.01$) in patients with OA of the knee. However, there was no significant difference in knee ROM, both for degree of flexion and extension ($p>0.05$).

CONCLUSION

The use of ESWT for treatment of knee OA had a beneficial effect on pain relief, function outcome and MCL thickness. However, there remains a lack of clarity regarding the frequency and dosage levels of ESWT required to achieve maximum improvement.

Keyword: Knee osteoarthritis, quasi-experimental, extracorporeal shockwave therapy, medial collateral ligament

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INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis (inflammation of the joints) and the most common cause of disability worldwide, mainly due to pain, as the main symptom of this disease. Osteoarthritis occurs most often in the weight bearing joints such as the knees and hips. The diagnosis of OA of the knee can be confirmed based on clinical and/or radiological findings. The economic burden caused by OA is quite impactful, including the costs that are related to management, environmental and lifestyle modifications, and also decreased work productivity.[1]

The number of patients with knee OA (KOA) in the US has multiplied twice as much compared to the mid-20th century.[2] Approximately 13% of women and 10% of men aged 60 years or older have symptomatic OA. In Indonesia, the prevalence of OA that has been diagnosed radiologically reaches 15.5% in men and 12.7% in women aged 40-60 years.[3] Also at the outpatient clinic of the Medical Rehabilitation Department, Cipto Mangunkusumo Hospital, Indonesia, the number of patients with KOA in 2016 reached 1,018 patients (15.2% of the total number of outpatients in the musculoskeletal division).[4] The proportion of people with symptomatic KOA increases with age and their body mass index (BMI).[2]

Osteoarthritis is a disease of multifactorial etiology, including local and systemic factors. Increasing age, female, overweight and obesity, history of knee injury, muscle weakness, and joint hyperlaxity are risk factors for OA.[5] To date, there is no therapy that can cure OA. Management is primarily aimed at controlling/ relieving pain, improving motion and joint function and improving quality of life. Optimal management of OA includes pharmacological and non-pharmacological management. Joint replacement surgery is reserved for patients with severe degrees of OA that do not respond to conservative treatment.[6]

Extracorporeal shock wave therapy (ESWT) has been widely used for the management of musculoskeletal abnormalities and pain. The curative effect of ESWT has been demonstrated in plantar fasciitis, calcified tendinitis of the shoulder, epicondylitis, patellar and Achilles tendinopathy, non-union and malunion fractures of long bones, and avascular necrosis of the femoral head.[7] Extracorporeal shock wave therapy is a non-invasive treatment modality that has a low complication rate, can be performed in the outpatient setting, and has a relatively low cost compared to other conservative therapies and surgery.[8]

The principle of ESWT is the production of pressure waves by electrohydraulic, electromagnetic, piezoelectric, or pneumatic sources. These waves work on both liquids and solid matter. The shock wave energy focused on one area is defined as energy flux density (EFD) which is recorded in mJ per unit area (mm^2).[5] Based on the energy flux density, ESWT is classified into low dose (<0.08 mJ/mm^2), moderate dose (0.08-0.28 mJ/mm^2), and high dose (>0.28-0.60 mJ/mm^2).[9]

Several animal studies have shown improvement in motor dysfunction and decrease in pain in OA.[10] Extracorporeal shockwave therapy has been increasingly used in patients suffering from KOA.[11-13] Observational research by Li et al.[11] demonstrated[12]better[13]improvement in KOA after 6 and 12 weeks of ESWT compared to laser therapy, measured using the numeric rating scale and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) as outcome parameters.

Imamura et al.[12] did a clinical test on radial ESWT in patients with grade 2 – 4 knee OA. Their study compared radial ESWT at doses of 0.1 – 0.16 mJ/mm^2 with sham radial ESWT. The study showed that the radial ESWT group had a significant difference only in the WOMAC pain component, therefore the authors considered that this dose is less effective to treat knee OA.[12]

Several studies reported varying results, but generally, the improvement in pain score and

functional score after being given ESWT is due to its regenerative effect on soft tissue and its pain reduction effect. Structural abnormalities in knee OA can occur not only in the cartilage but also in the ligaments that function as passive stabilizers of the knee. The medial collateral ligament (MCL) is a ligamentous structure that serves as the knee's main stabilizer against valgus stress. The MCL is also the most commonly injured knee ligament. Injuries to the MCL are most commonly the result of trauma; however, MCL injuries can also result from non-traumatic causes, e.g. degenerative diseases of the knee joint, particularly those involving the medial tibiofemoral compartment. Grade 1 MCL injury is characterized by edema around the MCL structure and involves disruption of a few fibers resulting in localized tenderness but no instability.[14] The difference of this study with the previous study lies in the changes in MCL features in knee OA before and after receiving ESWT management. Therefore, the aim of this study was to evaluate the effect of ESWT on pain, flexibility, functional outcome, and MCL thickness in KOA subjects.

METHODS

Research design

A study of quasi experimental design was conducted in Cipto Mangunkusumo Hospital, Jakarta from October 2019 – February 2020.

Research subjects

A total of 15 KOA male and female subjects aged 50-70 years were recruited into the study. The inclusion criteria of this study were: i) knee pain with VAS 31 - 69 mm; ii) diagnosed with primary knee OA of Kellgren-Lawrence (KL) grade 2 and 3 with MCL size > 5.6 mm that was confirmed by ultrasound examination; iii) sedentary level of physical activity; iv) could understand and follow instructions and v) willing to participate in this study and had signed informed consent after given information regarding the study. The exclusion criteria of this study were: i) had a history of total knee replacement (TKR) surgery; ii) genu varus / valgus >15°; iii) had existing tumor or infection or signs of acute inflammation in the knee and the surrounding tissue; iv) had conditions that cause a tendency to bleed (including taking anticoagulants; v) requiring invasive management; and vi) received injection therapy in the knee in the last 6 months. The sample size was calculated using mean difference formula within paired group of differences in WOMAC scores of 15 points with standard deviation of 20 points (data from a preliminary study). Assuming a significance level of 5% and a test power of 80%, we calculated that we needed a minimum
of 15 participants.

Data collection

All subjects fulfilling the inclusion criteria would be given complete oral and written information about the study by the principal researcher, who was also to collect the basic data. These consisted of age, gender, occupation, body weight, height, diagnosis of knee osteoarthritis, baseline VAS score, baseline ROM using a goniometer, baseline functional score using the WOMAC questionnaire, and baseline MCL thickness using knee ultrasonography examination.

Measurements

Body mass index was calculated from the subject's weight in kilograms and the height in meters squared. The diagnosis of knee OA was established using clinical criteria and radiological findings according to the American College of Rheumatology (ACR) criteria.

Intervention

The ESWT used was the BTL® radial ESWT type SWT-6000. The patient would be given ESWT in the supine position with the knee flexed at 90°, without topical anesthetics. The ESWT would be given at 2 of the most painful locations according to the patient. The dose was started from the lowest dose (1.5 bars) and

increased gradually to 4 bars in 8 levels, each consisting of 500 shocks for a total of 4.000 shocks. The ESWT probe was held stationary on a trigger point around the knee or at the patellofemoral and tibiofemoral borders of the target knee (if the patient was unable to point out the 2 most painful locations), we avoided a direct placement on the peroneal nerve or blood vessel. In order to limit the loss of shockwave energy at the interface, we used an aqueous gel, not containing any pharmacologically active substance as a coupling medium between the probe of the device and the skin, and it was applied in circular motions. Each treatment session did not exceed 30 minutes and was given once per week. Before receiving ESWT therapy, the patients were informed that there would be pain/ discomfort during therapy. The patients received the first ESWT therapy according to the protocol and were instructed to come back and undergo the second and third ESWT therapy respectively 7 and 14 days after the first to complete the therapy. Patients were also directed to come in weeks 1, 2, 4 and 8 for evaluation.

Outcome measures

One researcher performed all the evaluations at baseline (week 0) and after 1 (week 1), 2 (week 2), 4 (week 4), and 8 weeks (week 8). The following parameters were assessed during the evaluations:

- Pain using visual analogue scale (VAS): Scores were recorded by making a handwritten mark on a 10-cm line that represents a continuum between "no pain" and "worst pain.[15]
- Knee extension and flexion using range of motion (ROM) – the knee extension and flexion were measured in the prone starting position with lower limb extension in the hip and knee joint. The lateral femoral condyle was used as a landmark for the measurement of the knee extension and flexion. The central pivot of a goniometer was placed over the midpoint of the lateral joint margin, with the stationary arm of the goniometer aligned with the great trochanter. The moving arm of the goniometer was then aligned with the lateral malleolus. During the measurement we stabilized the joint at half the length of the thigh by a girdle. Each knee (in extension or flexion) was measured twice with an accuracy of 1 degree, and the higher angle was recorded for the statistical analysis. Knee flexion and extension ROM in degrees were measured bilaterally in the prone position. For this purpose, the lateral femoral condyle was used as a landmark for the measurement of knee flexion and extension. The central pivot of a universal goniometer was placed over the midpoint of the lateral joint margin, with the stationary arm aligned with the great trochanter. The moving arm was then aligned with the lateral malleolus, with the neutral position taken as zero. To measure knee flexion, the hip was initially at 0 degree of extension, abduction, and adduction. In order to avoid knee flexion, the examiner held the lower limb and stabilized the femur to prevent hip rotation, abduction or adduction. To measure knee extension, the lower limb was extended. The previous precautions were taken to prevent compensations (i.e. adduction, abduction, and rotation).
- Functional outcome using the WOMAC questionnaire, a disease-specific index of disability, that was used as a subjective measure of perceived health and physical function. The WOMAC questionnaire is a three-part questionnaire that can be completed by the subjects in approximately 10 minutes. It consists of 24 questions and probes clinically important symptoms in the areas of pain (5 questions), stiffness (2 questions), and physical function (17 questions) for patients with OA of the hip and/or knee. The patients answer the questions to describe their symptoms and difficulties from the past 3 days.[16]
- Medial collateral ligament (MCL) thickness was measured using knee ultrasonography.

For examination of the medial side of knee, the patient is in the supine position and is asked to do hip external rotation with knee flexion of 20° – 30°. The transducer is placed obliquely in the long-axis of the MCL. Mean thickness of normal MCL is 4.3mm (3.3mm – 5.6 mm).[17]

Data analysis

All data were analyzed using the Statistical Package for the Social Sciences software v.20.0 (IBM Corp). Univariate analysis was done to produce descriptive data. Numeric data were expressed as mean/median, and categoric data as proportion (%). The paired t test (for normal distribution) or Wilcoxon signed rank test (for non-normal distribution) was used to analyze the data. Two-sided p values of <.05 were regarded as the statistical significance levels.

Ethical clearance

This study protocol was approved by the Ethics Committee, Faculty of Medicine, Universitas Indonesia under no. 19-08-0947. All the patients gave their written informed consent to participate in the study.

RESULTS

During the study, 3 subjects resigned, 1 of them claimed to have increased pain in the knee, and 2 subjects were unable to follow up due to the Covid-19 pandemic. A total of 12 female subjects were analyzed (Figure 1).

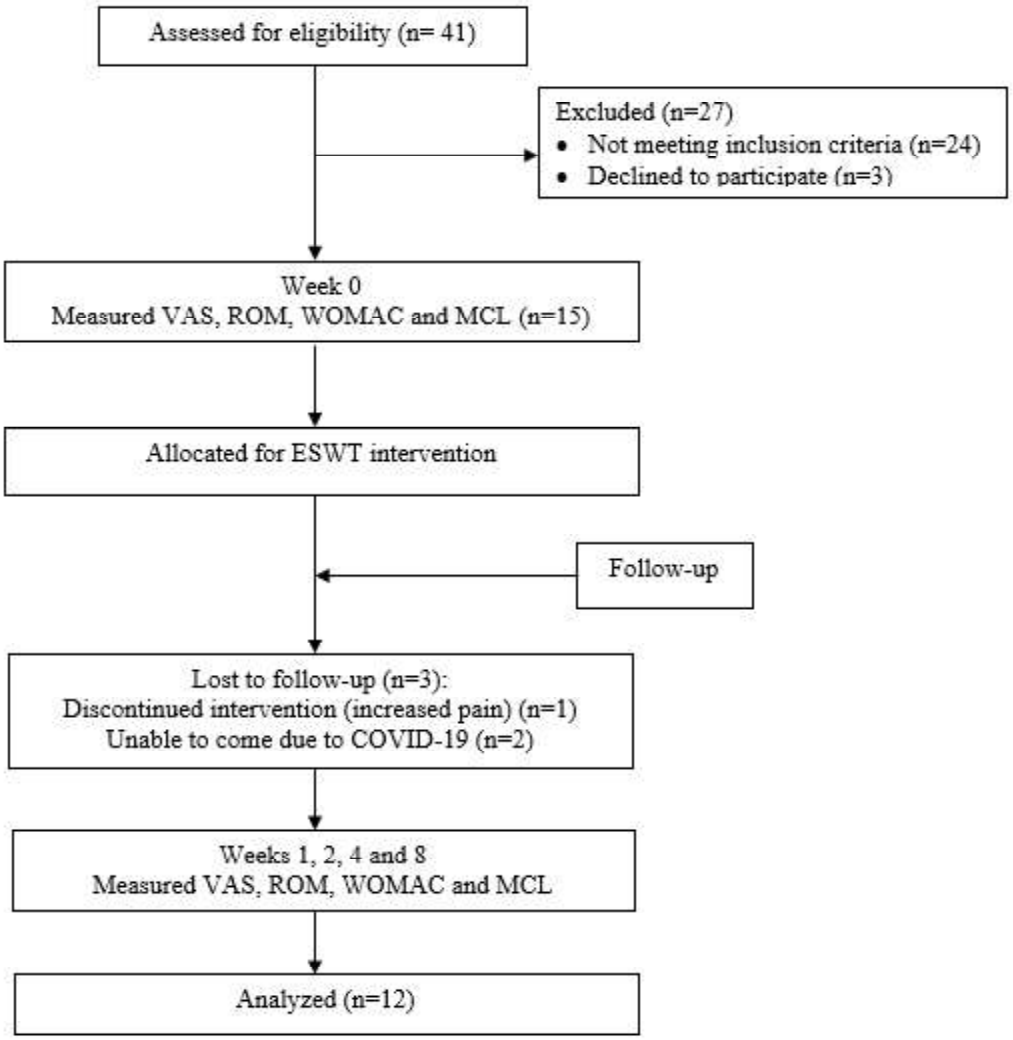

Figure 1. Recruitment and flow of participants through the trial

Table 1. Characteristics of the participants

Characteristics	Mean ± SD	n (%)
Age (years)	59.33 ± 4.33	
Age category (years)		
< 60		7 (58.33)
> 60		5 (41.67)
Gender		
Female		12 (100.0)
Male		0 (0.0)
Education		
Elementary-Middle School		3 (25.0)
Senior High School		6 (50.0)
Diploma		1 (8.34)
Bachelor		2 (16.67)
Profession		
Housewives		11 (91.66)
Government employees		1 (8.34)
BMI	28.34 ± 2.30	
KL grade		
2		4 (33.33)
3		8 (66.67)
VAS	51.09 ± 13.81	
Flexion degree	124.29 (120.1 – 130.2)	
Extension degree	-1.43 (-10.0 - 0.2)	
MCL	0.7 ± 0.16	
WOMAC total	37.50 ± 16.61	
WOMAC pain	9.0 ± 2.49	
WOMAC stiffness	2.75 ± 2.45	
WOMAC function	24.25 ± 11.83	
Comorbidity		
Hypertension		5 (41.67)
Diabetes		2 (16.67)
Hypercholesterolemia		5 (41.67)

Abbreviations: BMI: body mass index; KL: Kellgren-Lawrence; VAS: visual analog scale; MCL: medial collateral ligament; WOMAC: Western Ontario and McMaster Universities Arthritis Index

Mean age of subjects was 59.33 ± 4.33 years and mean BMI 28.58 ±2.30 kg/m^2, while knee OA had KL 2 on 5 knees (35.7%) and KL 3 on 9 knees (64.3%). The characteristics of the subjects are presented in Table 1.

After the subjects received the intervention, at the eighth week of follow up, there was a significant improvement in pain score ($p<0.001$), functional abilities ($p=0.007$), and MCL thickness ($p=0.001$). However, there was no significant difference in the stiffness ($p=0.317$), nor the WOMAC subscore for stiffness ($p>0.05$).

Paracetamol use was also evaluated in this study. There were 2 subjects (16.67%) who used paracetamol 3x1000 mg for 2 days in the first week, but then discontinued the drug because the pain had decreased.

DISCUSSION

Several studies have been done previously to observe the changes in patients with knee OA after being given the ESWT intervention, such as the observational study by Li et al. [11] who showed improvement in subjects with knee OA after receiving ESWT for 6 and 12 weeks compared with laser treatment, the changes being measured with the Numeric Rating Scale parameter and the Western Ontario and McMaster Universities Index (WOMAC).

Table 2. Mean (±SD) of within-group differences for pain, WOMAC, ROM and MCL outcome after intervention

Parameter	Time					Delta			
	Before (T0)	Week 1 (T1)	Week 2 (T2)	Week 4 (T3)	Week 8 (T4)	T1 - T0	T2 - T0	T3 - T0	T4 - T0
Pain Scoring (VAS)	51.09±13.81	43.24±15.84	37.48±17.13	34.83±18.78	29.33±19.95	7.85±6.82	13.61±10.24	16.64±13.17	21.76±13.73
						(p=0.001)*	(p<0.001)*	(p=0.001)*	(p<0.001)*
Flexion degree	124.29 (120, 130)	125 (120, 130)	124.29 (120, 130)	124.79 (120, 130)	123.93 (120, 130)	0.71 (0, 10)	0 (0)	0.5 (0, 5)	-0.36 (-5, 0)
						(p=0.317)**	(p=1.00)**	(p=0.180)**	(p=0.317)**
Extension degree	-1.43 (-10, 0)	-1.43 (-10, 0)	-1.43 (-10, 0)	-1.07 (-10, 0)	-1.07 (-10, 0)	0 (0)	0 (0)	0.36 (0, 5)	0.36 (0, 5)
						(p=1.00)**	(p=1.00)**	(p=0.317)**	(p=0.317)**
WOMAC total score	37.50±16.61	28.49±20.26		31.34±15.83	29.17±16.58	9.01±12.09		6.16±7.26	8.34±8.78
						(p=0.033)*		(p=0.013)*	(p=0.007)*
WOMAC pain score	9±2.49	8.17±3.19		7.42±2.68	6.58±2.61	0.83±1.70		1.58±1.00	2.42±1.24
						(p=0.117)*		(p<0.001)*	(p<0.001)*
WOMAC stiffness score	2.75±2.45	2.33±2.27		2.08 (0, 7)	1.83 (0, 6)	0.42±0.67		0.67(-2, 3)	0.92 (-2, 3)
						(p=0.053)*		(p=0.098)**	(p=0.059)**
WOMAC function Score	24.25±11.83	22.25±11.69		20.42±11.80	19.58±12.52	2±2.30		3.83±5.73	4.67±6.64
						(p=0.012)*		(p=0.041)*	(p=0.033)*
MCL thickness	7.73±1.59	7.68±1.77		6.76±1.38	6.8±1.75	0.05±1.11		0.971±1.21	0.93±1.27
						(p=0.869) *		(p=0.01) *	(p= 0.017) *

Abbreviations: BMI: body mass index; KL: Kellgren-Lawrence; VAS: visual analog scale; MCL: medial collateral ligament; WOMAC: Western Ontario and McMaster Universities Arthritis Index

Several other studies also compared the use of ESWT with another modality. Lee et al.[7] compared ESWT with hyaluronic acid injection and said that ESWT significantly improved the VAS and WOMAC, but did not differ significantly compared to hyaluronic acid injection in the first and third months. The study by Lizis et al. [13] compared ESWT with kinesiotherapy and showed that there was a significant difference in the WOMAC score of the ESWT group compared to the kinesiotherapy group. In this study, the ESWT dose used was the highest dose (0.4 mJ/mm^2) and no adverse effects were reported immediately from all subjects.

As noted previously, Imamura et al.[12] studied the administration of ESWT at doses of 0.1 – 0.16 mJ/mm^2 to patients with grade 2–4 knee OA as compared to sham ESWT and found that ESWT had only a significant effect on WOMAC. Therefore the investigators considered these doses to be less effective for treatment of knee OA. The clinical dose of ESWT is usually not more than 0.5 mJ/mm^2.

There is as yet no fixed recommended dose of ESWT for treating knee OA. The intervention given in our study followed the PEDro systematic recommendation, in which the treatment protocol of the optimum ESWT for a musculoskeletal problem consists of 3 sessions at one week intervals, with 2000 shocks per session with the highest EFD that the patients can tolerate.[1] However, because this research uses the interval method, the researchers used a larger number of total shocks to prevent the lack of shocks needed to affect knee OA. This is similar to the study by Zhao et al.[10] who compared the effect of ESWT to sham ESWT and showed that administration of 4000 shocks in one session with 0.25 mJ/mm^2 EFD did not show any adverse effect. Because Imamura et al.[12] found that doses of 0.1 – 0.16 mJ/mm^2 did not significantly improve knee OA, the initial EFD dose (0.15 mJ/mm^2) was considered to be less effective in producing the ESWT effects, and was only used as a warm-up.

The main symptoms of knee OA, such as pain and stiffness, will hinder the patient's daily activities and functional abilities. Eventually there is decreased use of the knee as a result of this pain in an attempt to avoid pain due to activity. The evaluation of the subject's function used the WOMAC questionnaire, which not only assesses the OA symptoms, such as pain and stiffness, but also evaluates the daily activities, such as climbing up and down stairs, squatting and walking. With the reduction in pain, the functional limitations are also expected to decrease.

Our study did not use any local anesthesia in the treatment area. This is in accordance with the PEDro systematic recommendation that reported decreased effectivity of the ESWT if the treatment area was given local anesthesia.[18] The molecular mechanism that causes the decreased effect has not been understood yet; however, there is ample evidence leading to the central role of the peripheral nervous system in mediating the cellular and molecular effects of the shockwave when applied to the musculoskeletal system. These effects might be inhibited by local anesthesia. Therefore, generally the shockwave application for the musculoskeletal system is recommended to be given without local anesthesia.

In the present study, VAS measurement was done in weeks 1, 2, 4, and 8, to observe the duration needed to effect a clinically significant decrease in the pain score. There was a statistically significant decrease in VAS in weeks 1, 2, 4 and 8, but a decrease in VAS that was considered clinically significant was only found in week 4, namely a reduction of 16.64 mm and a further reduction was seen in week 8 (21.76 mm). According to the study by Concoff et al.,[2] the decrease in moderate pain that is considered clinically significant is a reduction of 14–15 mm. This is similar to the study by Lee et al.[11] who reported a decrease in VAS score of 22.4 mm in week 12. In several other studies, a higher reduction in VAS score was reported, such as by Zhao et al.[8] and Li et al.,[11] who reported a

decrease in VAS score of 37.3 mm and 47 mm, respectively, in week 12. The differences between these studies could be caused by a different basic VAS score, which in the two previous studies was reported to be >70 mm. In addition, both studies did the follow up in week 12, therefore further studies with longer follow up periods might be needed to evaluate these differences.

The decreasing VAS pattern for 8 weeks of follow up showed that the VAS score at week 8 is the lowest VAS score. This agrees with the study by Xu et al.,[20] which showed that'the maximum effect of reducing pain in the treatment of knee OA with ESWT appeared in the eighth week.

Generally, the effectiveness of pain reduction after ESWT application can be divided into two, namely the short-term and the long-term analgesic effects. The short-term analgesic effect can be explained by the hyperstimulation theory, in which hyperstimulation of axons by pain stimuli can produce analgesic effects.[21] The pain sensations can be affected by the stimuli to the nervous system as mechanism to block the neuronal path against the pain signals. The increasing nociceptive impulse transmission at high frequency could prevent the pain transmission according to the 'gate control theory' and is started by the activation of the A-delta and C nerve fibers. The signals are transmitted through the type C nerve fibers to the posterior horn up to the periaqueductal gray (PAG) region and retransmitted to the posterior horn as inhibitors, causing pain signals to be ignored.[22] The myelin of A-delta nerve fibers inhibit the signal transmission from the C fibers. The memory of pain can be eliminated by this mechanism, so that normal movement can be restored, the neural and muscular compensation being no longer required. Thus, ESWT is able to break the vicious cycle of pain. For long-term analgesia, several studies have been done to explain the biological effects of ESWT on pain and concluded that some molecular and cellular changes, for example a reduction in the number of neurons that are responsible for substance P in the dorsal root ganglia, reduction in the calcitonin-gene related peptide (CGRP) of the dorsal root ganglia, and reducing the amount of unmyelinated nerve fibers after ESWT application.[21] Substance P is concentrated in the A-delta and C nerve fibers, then released to the nociceptive neurons in the central and peripheral sensory system after stimulation. Calcitonin-gene related peptide is the marker of that is typically related to the pain perception and appear simultaneously with P substance. In the activation of small diameter nerve fibers through local depolarization, axonal reflexes or dorsal root reflexes release CGRP and substance P.[23] Then both of the substances will act on the peripheral target cells such as mast cells, immune cells and vascular smooth muscle cells, which will lead to inflammation. This phenomenon is known as neurogenic inflammation. This chronic inflammation might affect the chronic pain of knee OA. The reduction in substance P has been proven to be able to reduce the inflammation of the experimental animal. Therefore, it can be hypothesized that the reduction in substance P of dorsal root ganglia plays an important role in mediating the long-term analgesic effects after ESWT application. Local selective unmyelinated neuronal damage also might play a role in the long-term analgesic effects.

In this study, there were no significant changes in the degree of knee flexion as well as knee extension after intervention, whether in the first, second, fourth, or eighth weeks. There was one subject who experienced limited knee flexion (90p) and two subjects who experienced limited knee extension (-10p), while the rest of the study subjects achieved the full ROM of flexion and extension. Because in most subjects the ROM of knee flexion and extension was already full, the changes seen after intervention could not exceed the full knee ROM. The subjects who experienced limited knee flexion and extension, also did not get improvement after intervention. All of the study subjects who has limited knee ROM had grade 3 knee OA.

The limitation of ROM in knee OA generally appears in advanced OA and might be caused by narrowing of the knee joint space caused by cartilage damage and changes in the knee alignment. In other pathological conditions, such as calcified rotator cuff tendinopathy that has ROM limitation due to soft tissue pathology, ESWT treatment has been shown to improve the ROM, such as in the study by Wijayanti et al.[24] According to this study, ESWT therapy has not been proven to affect the ROM of knee OA patients.

In the present study, it was found that the difference in WOMAC score in weeks 1, 4 and 8 of follow up was statistically significant with a decrease in week 4 by 6.16 points. This is similar to a study by Lee et al.[7] who reported a decrease in WOMAC score of about 7.14 points in the first month. However, there was a difference in the results of the eighth week of follow up between the present study and the others. In this study, the reduction in WOMAC score was only 8.34 points, while several previous studies reported a higher reduction in WOMAC score. The study by Lee et al.[7] reported a reduction of about 15.4 points during the twelfth week of follow up, with increasing reduction trends since the sixth week. The BMI score is a factor that plays a role in OA formation and progression and could be explained by the increased excessive load which might affect the degeneration of the cartilage. Meanwhile, the adipose tissue increases the release of pro-inflammatory cytokines, such as IL-6, IL-1, IL-8, TNF-alpha and IL-18, and decreases the regulator cytokines, such as IL-10. Therefore, very likely the subjects' nutrition status affected the ESWT treatment results. However, the researchers realize that more research is required to prove it.

The collateral ligament edema in one subject could be caused by trauma or secondary abnormalities of meniscus extrusion and osteoarthritis. Medial collateral ligament injury is marked by increased thickness, which can be examined by using musculoskeletal USG.[22]

In this study, there was a significant change in MCL thickness in the fourth and eighth weeks, with the greatest reduction in the eighth week (reduced by 0.93 mm). This might be related to a regenerative effect after ESWT treatment. The ESWT has been proven to be able to reduce the expression of inflammatory mediators (metalloproteinases and interleukin matrix). Therefore, ESWT can be considered to produce a regeneration effect and improve the musculoskeletal tissue, and not only a disintegration effect as expected before. Another study by Liao et al.[23] reported that ESWT has given mechanical stimuli conducted by wave sound, through mechanotransduction stimuli that are converted to sequences of biochemical signals that can enhance tissue regeneration. They also reported that there was increased production of protein, nitric oxide and growth factors, which increased neoangiogenesis, tenocyte and fibroblast proliferation, and collagen synthesis, which further increased tissue catabolism, healing and remodeling.[3] Acoustic cavitation is also formed due to the tensile phase of the shock wave. This cavitation effect is the second effect of ESWT, which is also increasing tissue regeneration by increased tissue permeability, and efficiently destroying the calcification deposits of the soft tissue.[22] The series of biological events mentioned before can support the use of ESWT to reduce pain, increase blood flow to the ischemic tissue, soften the calcified tissue, and release the adhesions, which will improve physical function and performance. A study by Cho et al.[6] has proven that there is increased vascularization in the medial knee area that is confirmed by musculoskeletal USG evaluation at the knee immediately after ESWT treatment.

The ESWT adverse effects are related to high doses. The adverse effects reported in previous studies were local bleeding (petechiae, hematoma), increased pain, arrhythmias, hypertension, and peripheral nerve paresthesia. In general, researchers have concluded that ESWT is a safe modality to treat knee OA.

However, studies with larger samples and more specific soft tissue involvement might be required to know about the increased pain after ESWT application in knee osteoarthritis patients.

The limitations of this study are its pre-post design and there were no control subjects to minimize other variables that may or may not interfere with the outcome measurement. Regardless, the results of this study may be used as baseline data and further study implementing randomized controlled trial design with larger sample size can be done to produce higher levels of evidence supporting the use of ESWT for knee osteoarthritis.

CONCLUSION

There was a significant difference in pain score, functional capacity, and MCL thickness after ESWT therapy, but there was no significant difference in flexibility after ESWT therapy. In general, ESWT is a safe modality to treat patients with knee OA.

CONFLICT OF INTEREST

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