2023

Does Extracorporeal Shock Wave Therapy (ESWT) Reduce Pain in Patients Diagnosed with Kellgren-Lawrence Grades II or III Knee Osteoarthritis Compared to Placebo ESWT?

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Does Extracorporeal Shock Wave Therapy (ESWT) Reduce Pain in Patients Diagnosed with Kellgren-Lawrence Grades II or III Knee Osteoarthritis Compared to Placebo ESWT?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2022

ABSTRACT

Objective: The objective of this selective EBM review is to determine "Does extracorporeal shock wave therapy (ESWT) reduce pain in patients diagnosed with Kellgren-Lawrence grades II or III knee osteoarthritis compared to placebo ESWT?"

Study Design: A systematic review of three randomized controlled trials (RCTs) published in peer-reviewed journals between 2013-2020

Data Sources: All articles were published in peer reviewed journals and researched using AltHealthWatch, AMED, CINAHL, MEDLINE and Rehabilitation and Sports Medicine Sources within EBSCOhost and PubMed. Studies were selected based on how well they answered the clinical question and if they discussed patient-oriented outcomes.

Outcome Measured: A reduction in knee pain was the outcome measured in all three studies using the 10-cm Visual Analog Scale (VAS) at 12 weeks after intervention. The mean change from baseline was calculated after obtaining VAS at 12 weeks.

Results: In the Zhang et al. RCT, ESWT had a small treatment effect due to a 1.8-point difference but provided a statistically significant reduction in pain due to p-values <0.001 when compared to the control group. The same was demonstrated in the study's within-analysis due to a point difference of 1.6 plus a significant p-value <0.001 and narrow CI of 0.896-1.775 in placebo and 2.485-3.461 in ESWT groups. In the Uysal et al. RCT, ESWT had a small treatment effect due to a 1.4- and 1.6-point difference during rest and activity between the ESWT and control groups. However, ESWT provided a statistically significant reduction in pain both at rest and during activity due to p-values being ≤ 0.001 when compared to the control group. In the Zhao et al. RCT, ESWT had a small treatment effect due to a 2.59-point difference but provided a statistically significant reduction in pain during activity due to p-values being $<0.001$when compared to the control group.

Conclusion: The results found in all studies demonstrated that ESWT does reduce pain in adult men and women with Kellgren-Lawrence grades II and III knee osteoarthritis but the treatment effect is small. Future studies should explore efficacy of various ESWT regimens/doses, all severities of Kellgren-Lawrence scale, and compare ESWT with current knee osteoarthritis treatment modalities.

Key Words: knee, osteoarthritis, shock wave therapy

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease most commonly affecting the knee that occurs when structures within the joint begin to breakdown due to the high use and stress applied. The development of knee OA is due to activation of chondrocytes to repair damaged cartilage and activation of inflammatory mediators which contribute to cartilage erosion and consequently loss of function.[1] This process of breakdown leads to narrowed joint spaces which cause significant disability and symptoms such as pain, stiffness, swelling and decreased range of motion.[2]

Osteoarthritis is the most common form of arthritis in adults and is the leading cause of disability in the US.[3] Based upon the most recent research, in 2020, it was estimated that there were around 654 million individuals worldwide ≥ 40 y.o. who have knee OA.[4] Additionally in 2020, the annual incidence of knee OA in individuals ≥ 20 y.o. was estimated to be 86 million worldwide with the incidence in the United States being 130 per 10,000 person-years.[4] It is estimated that the number of individuals with knee OA will likely increase due to aging and the increasing prevalence of obesity.[3] Due to the high occurrence of OA in individuals, a large financial and healthcare burden has resulted. In 2015 lifetime direct medical costs due to knee OA ranged from $1,800-$12,400 (discounted) depending on treatment modality.[5] The exact number of healthcare visits have not been identified, but it is estimated that individuals diagnosed with knee OA spend 50% of their life between treatments while waiting for total knee arthroplasty (TKA) after failing all other non-surgical options.[5]

Osteoarthritis currently has few effective treatments, none of which have been proven to delay disease progression.[3] Current treatment modalities range from non-pharmalogical, medications, and surgery. Treatment is usually approached by beginning with non-pharmalogical

options and progressing to medications depending on tolerability and efficacy of each. Current non-pharmalogical regimens are to encourage weight loss, physical therapy, relieving joints with braces, splits or crutches, acupuncture and transcutaneous electrical nerve stimulation (TENS).[2-3] Initiation of medications start with oral acetaminophen and progresses as needed to topical and oral non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoid injections such as methylprednisolone or triamcinolone, lubrication injections such as hyaluronic acid, and opioids as a last resort medication option.[2-3] If medications fail, surgery via total knee arthroplasty is typically reserved as the last treatment effort due to its substantial health costs, invasiveness, and burden yet it is also the only current cure for knee OA.[3-4]

Extracorporeal shock wave therapy (ESWT) is a treatment modality that has been researched to determine its efficacy in treating certain musculoskeletal disorders and where its placement is in treatment regimens. ESWT has been recommended as effective treatment including in pain reduction in numerous musculoskeletal disorders such as multiple tendinopathies and plantar fasciitis[6] leading to the clinical question on whether this would have the same outcome for knee OA. ESWT works by promoting neovascularization, bone healing, anti-inflammatory properties and by producing a chondroprotective effect.[6] This paper evaluates three randomized controlled trials (RCTs), assessing the efficacy of extracorporeal shock wave therapy (ESWT) in reducing pain in patients suffering from knee osteoarthritis.

OBJECTIVE

The objective of this selective EBM review is to determine "Does extracorporeal shock wave therapy (ESWT) reduce pain in patients diagnosed with Kellgren-Lawrence grades II or III knee osteoarthritis compared to placebo ESWT?"

METHODS

Resources for this selective EBM review were chosen based on their relevance towards the clinical question as well as their incorporation of discussing patient-oriented outcomes related to the clinical question. All studies chosen were peer-reviewed journals written in the English language and were researched using the databases AltHealthWatch, MEDLINE, AMED, CINHAL, and Rehabilitation and Sports Medicine sources within EBSCOhost and PubMed. All three studies included were randomized, placebo-controlled trials published in the years 2013, 2019 and 2020 found using the key words knee, osteoarthritis and shock wave therapy. Inclusion criteria consisted of primary research studies published from 2011 to present comparing ESWT and sham-ESWT as placebo which included both men and women older than 45 years old. Exclusion criteria included studies from 2010 or older comparing ESWT against other treatments rather than a sham-ESWT and any secondary research.

The populations focused upon within the chosen studies were adult men and women diagnosed with KL grade II or III knee OA. Knee osteoarthritis can be classified based on the Kellgren-Lawrence (KL) Scale which is divided into 5 levels ranging from 0 to 4[3], with grades II and III being the focus of this systematic review. Grade II is defined as the presence of clear bone tissue and possible stenosis of the joint space while grade III is defined as the presence of moderate multiple bone tissue, clear narrowing of the joint space, slight sclerosis, and possible bone deformity.[3] Among all three studies the intervention groups received ESWT and were compared among a placebo group receiving a sham-ESWT but all differed slightly in the doses of ESWT received which is specified in table 1. To have consistency across all three studies only the outcome of pain is discussed in this review. Table 1 demonstrates the demographics and characteristics of the three RCTs discussed in this review. Statistical analysis used for all three studies included mean change from baseline and p-values with Zhong et al. additionally using

confidence intervals. Uysal et al. specifically conducted analysis at rest and with activity, Zhao et al. conducted analysis upon movement and Zhong et al. did not specify.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Zhong[7] 2019	RCT	63	Mean age was 62.8 ± 7.9 years of age	Men and women with > 6-month history of symptoms of knee OA classified as Kellgren-Lawrence grades II or II via ACR[1] Criteria and radiographic criteria	Joint replacements, intra-articular injection history, surgery, ESWT, loss of independent walking ability, or any major concomitant diseases possibly interfering with participation in the trial.	3 (2 in ESWT group and 1 in placebo group)	2000 pulses of ESWT at 8 Hz frequency and 2.5 bars vs 2000 pulses of sham-ESWT at 8 Hz frequency and 0.2 bar x4 weeks each. Addition of simple home exercise programs 3x/day
Uysal[8] 2020	RCT	104	50-70 years of age	Men and women 50-70 years of age diagnosed with knee OA via ACR[1] and classified as Kellgren-Lawrence grade II or III.	Secondary OA, severe chronic illness, poor general health status, knee replacement, prior malignancy, previous intra-articular injections (corticosteroid, hyaluronic acid) within previous 6 months	Not specified	ESWT at 2000 shocks at 10 Hz at 2-3 bars vs sham-ESWT at 0 shocks, 10 Hz frequency at 0.1 bar x3 weeks each. Addition of use of hot packs x40 min plus a home exercise program for 30 min qd x3 weeks
Zhao[9] 2013	RCT	70	≥ 45 years of age	Patients ≥ 45 y.o. with diagnosis of knee (OA) via ACR[1] criteria and classified as Kellgren and Lawrence grade II or III with knee pain > 3 months	History of spinal stenosis, evidence of neurologic disease by history or physical exam, secondary causes of arthritis, history of surgical intervention/intra-articular injection within 6 months and CI to MRI or radiography.	9 (4 in ESWT groups and 5 in placebo)	ESWT of 4000 pulses at 6 Hz frequency at 0.25 mJ/mm^2 vs sham-ESWT of 4000 pulses at 6 Hz frequency at 0 mJ/mm^2 x4 weeks each.

[1]ACR – American College of Rheumatology

OUTCOME MEASURED

All three RCTs measured the outcome of reduction in knee pain via the 10-cm Visual Analog Scale (VAS). The VAS is a sensory pain rating scale with scores ranging from 0-10. At the endpoints of the scale, a score of 10 indicates the worst possible pain whereas a 0 indicates

no pain[7,9]. VAS scores analyzed in this review were those obtained at 12 weeks after intervention and were compared with VAS scores from baseline before intervention to obtain the mean change from baseline for both the experimental and placebo groups. In addition, the difference of means was calculated for all three studies for this review to determine the treatment effect between the placebo and ESWT groups.

RESULTS

All three studies included adult men and women diagnosed with KL grades II and III knee OA and evaluated ESWT and its effect on pain reduction compared to placebo. Zhong et al. conducted a RCT including those who specifically had pain on most days with a pain intensity greater than 4-cm on a 10-cm VAS. Participants were randomized into the ESWT or placebo group by a computer-generated random numbers list conducted by an independent researcher not involved with the treatment outcome measurement.[7] Once a week for 4 weeks, the ESWT group received 2000 pulses of ESWT at 8 Hz frequency and 2.5 bars while the placebo group received 2000 pulses of sham-ESWT at 8 Hz frequency and 0.2 bars.[7] All physical therapists, radiologists and statisticians were also kept blind of group assignment.[7] Additionally, both groups were educated on a simple home exercise program consisting of a single knee extensor muscle strengthening activity repeated ten times for three groups per day and was supervised over the phone once every 3 days for 4 weeks.[7]

Knee pain intensity was evaluated by a blinded investigator, at baseline and at 12 weeks after intervention using the 10-cm VAS.[7] Two participants were lost in the ESWT group due to refusal to continue and inability to contact as well as one participant being lost in the placebo group due to inability to contact.[7] This resulted in 32 individuals who received ESWT and 31 who received placebo.[7] As seen in table 2, those who received ESWT exhibited a decrease in

mean pain values from a baseline value of 5.3 ± 0.8 to a week 12 value of 2.3 ± 1.2, resulting in a mean change from baseline of 3.[7] Those in the placebo group exhibited a decrease in mean pain values from a baseline of 5.5 ± 1.1 to a week 12 value of 4.3 ± 1.1 resulting in a mean change from baseline of 1.2 (Table 2).[7] Based on a p-value of <0.001, ESWT had a clinically significant effect in reducing more pain compared to the placebo group however, there was a 1.8 point difference indicating that ESWT had a small treatment effect when considering the 10-cm VAS (Table 2).[7]

Additionally, Zhong et al. completed a within-subject analysis comparing the placebo and ESWT groups for pain reduction to account for potential unaccounted differences among participants.[7] The placebo group had a mean difference from baseline to week 12 of 1.335 ± 0.215 with a p-value of <0.001 and a 95% CI of 0.896-1.775 while the ESWT group had a mean difference of 2.973 ± 0.239 with a p-value of <0.001 and a CI of 2.485-3.461 (Table 3).[7] Using the within-subject analysis there was still a 1.6-point difference between both groups indicating a small treatment effect however, the p-values were still significant and the CI between the placebo and ESWT groups were narrow and not overlapping.

Table 2. 10-cm VAS Pain Intensity Mean Scores from Baseline to Week 12 (Zhong et al.[7])

	Baseline (Mean ± SD)	**Week 12** (Mean ± SD)	**Mean change from baseline**	**P-value**	**Difference of the means** (calculated)
ESWT group	5.3 ± 0.8	2.3 ± 1.2	3	<0.001	1.8
Placebo group	5.5 ± 1.1	4.3 ± 1.1	1.2		

Table 3. Within-subject analysis of 10-cm VAS Pain intensity Mean Scores from Baseline to Week 12 (Zhong et al.[7])

	Baseline to Week 12 difference of mean (Mean ± SD)	**Difference of the means** (calculated)	**P-value**	**95 % Confidence Interval (**CI)
ESWT group	1.335 ± 0.215	1.6	<0.001	0.896-1.775
Placebo	2.973 ± 0.239		<0.001	2.485-3.461

Uysal et al. performed a single-blind RCT specifically including participants ranging from 50-70 y.o. who were admitted to their outpatient clinic. Participants were randomly assigned to either the ESWT group or sham-ESWT group by using block randomization.[8] Once a week for 3 weeks, the ESWT group received 2000 shocks at 10 Hz frequency at 2-3 bars while the sham-ESWT received 0 shocks at 10 Hz frequency at 0.1 bar.[8] Participants in both groups also received an addition of hot packs for 40 minutes, transcutaneous electrical nerve stimulation for 30 minutes and a home-based exercise program for 30 minutes per day for 3 weeks.[8]

Evaluations of pain were done at baseline and at 3 months both at rest and with activity, using the 10-cm VAS. Evaluations were conducted by a physiatrist who was blind to the treatments the groups received.[8] A total of 52 participants received ESWT and 52 participants received sham-ESWT but this study did not specify if any were lost.[8] Those who received ESWT had a decrease in mean pain values at rest from a baseline value of 4.5 ± 2.0 to a 3 month value of 1.0 ± 0.8 resulting in a mean change from baseline of 3.5 (Table 4).[8] There was also a decrease in mean pain values during activity for those who received ESWT from a baseline value of 7.4 ± 0.7 to a 3 month value of 2.9 ± 1.4 resulting in a mean change from baseline of 4.5 (Table 5).[8] Those who received sham-ESWT had a decrease in mean pain values at rest from a baseline value of 4.0 ± 1.0 to a 3 month value of 1.9 ± 1.3 resulting in a mean change in baseline of 2.1 (Table 4).[8] There was also a decrease in mean pain values during activity for the sham-ESWT from a baseline value of 7.3 ± 1.0 to a 3 month value of 4.4 ± 1.8 resulting in a mean change in baseline of 2.9 (Table 5).[8] Based on the 1.4 point difference at rest and a 1.6 point difference during activity between the two groups, ESWT has a small treatment effect, however the p-value was 0.001 at rest and <0.001 during activity indicating that ESWT had a clinically significant effect reducing knee pain in both activity levels.[8]

Table 4. 10-cm VAS Mean Pain Scores from Baseline to Week 12 - At Rest (Uysal et al.[8])

	At Rest				
	Baseline (Mean ± SD)	**Month 3** (Mean ± SD)	**Mean change from baseline**	**P-value**	**Difference of the means** (calculated)
ESWT group	4.5 ± 2.0	1.0 ± 0.8	3.5	0.001	1.4
Sham-ESWT group	4.0 ± 1.0	1.9 ± 1.3	2.1		

Table 5. 10-cm VAS Mean Pain Scores from Baseline to Week 12 - Activity (Uysal et al.[8])

	During Activity				
	Baseline (Mean ± SD)	**Month 3** (Mean ± SD)	**Mean change from baseline**	**P-value**	**Difference of the means** (calculated)
ESWT group	7.4 ± 0.7	2.9 ± 1.4	4.5	<0.001	1.6
Sham-ESWT group	7.3 ± 1.0	4.4 ± 1.8	2.9		

Zhao et al. performed a RCT specifically including participants ≥45 y.o. who had knee pain for the previous 3 months. A block randomization list was generated by a simple computerized random number generator which was used by an independent researcher not involved in the intervention or data assessment, who further assigned individuals to the ESWT or placebo group according to randomization of odd and even numbers.[9] Once a week for 4 weeks, the ESWT group received a total of 4000 pulses at 6 Hz frequency at 0.25 mJ/mm^2 while the placebo group received a total of 4000 pulses at 6 Hz frequency at 0 mJ/mm^2.[9] Additional physical activity was recommended for 48 hours after but not required.[9]

Evaluations of knee pain were conducted at baseline and at 12 weeks using a 10-cm VAS by a physician who was not involved in the selection and treatment of patients.[9] Five participants withdrew from the placebo group, two due to increased pain and three due to lack of efficacy resulting in 31 participants who completed the trial.[9] Four participants withdrew from the ESWT group, two due to loss of follow up and two from lack of efficacy resulting in 30 participants who completed the trial.[9] To account for those loss from the trial, the study analyzed data using an intention-to-treat analysis.[9] Those in the ESWT group showed a decrease in mean pain values

from a baseline value of 7.56 to a week 12 value of 3.83 resulting in a mean change in baseline of 3.73 (Table 6).[9] Those in the placebo group showed a decrease in mean pain values from a baseline value of 7.55 from baseline to a week 12 value of 6.41, resulting in a mean change in baseline of 1.14 (Table 6).[9] Based on a 2.59 difference between the two groups the treatment effect is small considering a 10-cm VAS. Nonetheless, the p-value is <0.001 indicating that ESWT had a clinically significant effect in reducing knee pain compared to the placebo group.

Table 6. 10-cm VAS Pain Intensity Mean Scores from Baseline to Week 12 (Zhao et al.[9])

	Baseline (Mean)	**Week 12** (Mean)	**Mean change from baseline**	**P-value**	**Difference of the means** (calculated)
ESWT group	7.56	3.83	3.73	<0.001	2.59
Placebo group	7.55	6.41	1.14		

DISCUSSION

Osteoarthritis has many current treatment options available however few are effective. One of the most effective treatments, such as TKA, can be invasive and very costly resulting in delay to treatment. This consequently leaves many individuals having to live with the debilitating pain associated with knee OA.[1] The same was demonstrated for chronic tendinopathies, for once conservative measures failed, the only option left was expensive surgeries.[10] However, ESWT has been shown to be effective in treating these tendinopathies as well as being less costly.[6,10] Few side effects have been noted in treatment with ESWT such as pain during application, petechial bleeding or hematoma formation in the skin due to high doses and slight reddening of the skin.[10] This explains why all three studies focused on using lower doses of ESWT.

The purpose of this study was to determine if ESWT can reduce pain in adult men and women with KL grade II or III knee OA. Among the three articles, ESWT provided a clinically significant decrease in pain due to significant p-values ≤ 0.001.[7-9] Even though ESWT showed this clinically significant pain reduction, it also demonstrated a small treatment effect based on

the calculated difference of means, between the placebo and ESWT groups, being on the lower spectrum when considering the 10-cm VAS. Zhong et al. provided an additional benefit in which they conducted a within-subject analysis to account for any undetected differences between the groups. With this analysis, the CI were narrow and without overlaps between the placebo and ESWT groups.[7] This indicates that there is a 95% confidence that the best possible pain reduction in the placebo group would not reach the high levels of pain reduction that could be received in the ESWT group even when at its lowest values.[7] However, with this within-subject analysis, the difference of means between both groups was still small when considering the 10-cm VAS, still indicating a small treatment effect. Uysal et al. also provided an additional benefit of analyzing pain reduction at rest and during activity. Results were shown to be statistically significant at rest and during activity due to p-values <0.001 showing that ESWT could have benefits during both activity levels.[8]

It is important to consider the various methodology of how ESWT was given, as well as which doses were used among the three articles and whether that could play a role in how well ESWT decreased pain. All three studies used lower doses of ESWT to prevent some of the side effects that are seen with higher doses yet, the exact doses, regimens and treatment duration differed (Table 2).[7-9] It is possible pain reduction responds better to certain doses, specific amounts of pulses and for a specific duration. Zhong et al. and Uysal et al. both included additional treatments for both placebo and ESWT groups while Zao et al. did not require this. It could be possible these additional treatment modalities could have had an impact on the outcomes. Uysal et al. and Zhao et al. did not follow up on whether individuals completed their activities also contributing to this possible impact. An additional limitation shared among all three articles is that data only applies to those with KL grade II or III knee OA and does not

evaluate whether ESWT would be effective in more severe, late, or less severe, early OA.[7-9] Specifically, Zhong et al. did not perform a worst-case analysis or intention-to-treat analysis for the patients that were lost to follow up. In addition, this study presented conflicting data when stating five participants were lost to follow up but only recording three that were lost in the flow diagram.[7] This decreases validity due to being unsure of how these participants were included in the analysis of the data and resulting in skepticism on how many were lost and if any participants were not accounted for. Yet when calculating for five losses, there was still only an 8% loss which is valid. Lastly, even though Zhao et al. performed randomization and used independent researchers, blinding was not achieved among the evaluator, technologist who performed ESWT or the independent researcher who distributed groups resulting in a potential for bias.

CONCLUSION

All three randomized control trials discussed in this systematic review demonstrated that ESWT does reduce pain in adult men and women diagnosed with KL grades II and III knee OA but, the treatment effect associated with it is small based on a 10-cm VAS. Future research should focus on comparing different doses of ESWT to determine if there is an effective dose range due to all three studies using different ESWT regimens. This would allow the benefit of knowing which dose can be harmful for knee OA and which are most effective to allow for the greatest optimization of pain reduction. Zhao et al. reported in their conclusions that ESWT could be a good option as an alternative treatment before considering surgery. Based off this and the smaller but clinically significant treatment effect displayed by the data, future research should focus on comparing ESWT to other treatment modalities for knee OA to determine its place in management and if it compares to the treatments already used today. Additionally, since the three studies only focused on KL grades II and III, ESWT should be studied across all

severities within the KL scale to determine if there is a level where ESWT is no longer effective as well as most beneficial. Lastly, future research should include double blinding when evaluating for pain reduction by making evaluators, those involved in randomization, those giving interventions or participants unaware of group assignment and intervention received. By increasing the number of studies that include double blinding this would allow for more trust in the data due to less potential for bias to cause a possible effect on the results. Additional studies should also be sure to account for all of those lost to follow up such as performing intention to treat analysis or worst-case analysis. This would increase validity of the results by introducing more clarity on how those who were lost were included in the data and whether it was due to the intervention of ESWT or not.

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