Extracorporeal Shock Wave Treatment for Delayed Union and Nonunion Fractures: A Systematic Review

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Objectives: Nonunions after bone fractures are usually treated surgically with risk of infections and failure of osteosynthesis. A noninvasive alternative is extracorporeal shock wave treatment (ESWT), which potentially stimulates bone regeneration. Therefore this review investigates whether ESWT is an effective and safe treatment for delayed unions and nonunions.

Data Sources: Embase.com, MEDLINE ovid, Cochrane, Web of Science, PubMed publisher, and Google Scholar were systematically searched.

Study Selection: Inclusion criteria included studies with patients with delayed union or nonunion treated with ESWT; inclusion of ≥10 patients; and follow-up period ≥6 weeks.

Data Extraction: Assessment for risk of bias was conducted by 2 authors using the Cochrane tool. Union rates and adverse events were extracted from the studies.

Data Synthesis: Two RCTs and 28 nonrandomized studies were included. One RCT was assessed at medium risk of bias and reported similar union rates between ESWT-treated patients (71%) and surgery-treated patients (74%). The remaining 29 studies were at high risk of bias due to poor description of randomization (n = 1), nonrandomized allocation to control groups (n = 2), or absence of control groups (n = 26). The average union rate after ESWT in delayed unions was 86%, in nonunions 73%, and in nonunions after surgery 81%. Only minor adverse events were reported after ESWT.

Conclusions: ESWT seems to be effective for the treatment of delayed unions and nonunions. However, the quality of most studies is poor. Therefore, we strongly encourage conducting well-designed RCTs to prove the effectiveness of ESWT and potentially improve the treatment of nonunions because ESWT might be as effective as surgery but safer.

Key Words: Extracorporeal shock wave, nonunion, delayed union, bony union, union rates, adverse events

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

(*J Orthop Trauma* 2019;33:97–103)

INTRODUCTION

Delayed unions and nonunions are failures of bony healing after fractures, osteotomies, or arthrodesis. In practice, a wide variety exists in the exact definition of delayed unions and nonunions depending on fracture site and criteria used for the assessment of bony union.[1] In this review, we define delayed unions as fractures that do not show radiological union 3 months after a fracture and nonunions as fractures that do not show radiological union 6 months after a fracture.

Literature shows that 3%–5% of all fractures evolve into a nonunion, with highest nonunions rates reported in fractures of the scaphoid (16%), tibia (14%), and femur (14%).[2,3] Patients with nonunions suffer from pain and decreased function, which affects a patient's daily routines and decreases their quality of life.[4,5]

At present, most nonunions are treated with surgery, which is considered to be the "golden standard."[6] Surgical treatment options of nonunions are overall quite successful, with union rates reported between 74% and 95%.[7–10] However, complications can occur such as infection (5%), neurovascular damage (7%), or implant-related problems requiring an additional surgery (5%).[7,11,12] Alternatively to surgery, patients could be treated noninvasively, which could reduce the risk of these complications.

A noninvasive treatment for delayed unions and nonunions is extracorporeal shock wave treatment (ESWT). ESWT is a well-known treatment for fragmentation of kidney stones, but over the past decades, ESWT has been increasingly used for bone growth stimulation. In 1991, Valchanou and Michailov[13] used ESWT for the treatment of delayed unions and nonunions and reported bony union in 70 of 82 fractures without any complications. Subsequently to these promising results, more studies have been published in which ESWT was used for delayed union and nonunion treatment.

Bone healing after ESWT might be stimulated because of an increase in neovascularization and an upregulation of angiogenic and osteogenic growth factors.[14] Animal studies reported an increase in several growth factors after ESWT, which are important in bone regeneration (VEGF, TGF-beta

Accepted for publication October 9, 2018.
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The authors report no conflict of interest.
Presented as a poster at the International Society for Medical Shockwave Treatment Congress, San Sebastian, Spain, 20th until 24th of June 2017.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jorthotrauma.com).
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DOI: 10.1097/BOT.0000000000001361

1, and BMPs).[15,16] Also, it has been show that ESWT leads to an increased differentiation of bone marrow stem cells toward osteoprogenitor cells[17] and thickening of the cambium layer of the periosteum by proliferation of osteoprogenitor cells.[18] Although the exact working mechanisms of ESWT is still unclear, it has been hypothesized that the biological responses after ESWT are triggered by mechanotransduction, a process in which cells transform mechanical stimuli into biochemical signals.[19] During ESWT, pressure waves are generated by a piezoelectric, electromagnetic, or electrohydraulic mechanism. The created pressure waves are characterized by a fast pressure rise, exposing tissue cells to shear and tensile forces. These forces might cause liberation of messengers from the extracellular matrix, which can activate genes in the cell nucleus, which induces an upregulation of growth factors.[6,19]

In 2010, Zelle et al[20] published a systematic review concerning the treatment of delayed unions and nonunions with ESWT. They reported that treatment of delayed unions and nonunions with ESWT was successful in approximately 75% of the fractures. However, this conclusion was based on 10 cohort studies, which provided a poor level of evidence, and a risk of bias assessment was not performed. Presently, the clinical application of ESWT for delayed unions and nonunions has not widely spread, although more studies have been published since the review by Zelle et al.[20] Therefore, the aim of this systematic review is to provide a comprehensive overview of the currently available literature concerning the effectiveness and safeness of ESWT in the clinical treatment of delayed unions and nonunions.

METHOD

The protocol of this systematic review was prospectively registered in the International prospective register of systematic reviews (http://www.crd.york.ac.uk/prospero/; registration number CRD42016046120).

Eligibility Criteria

For this review, we included studies that treated delayed unions or nonunions with ESWT. See Table 1 for a full-overview of all eligibility criteria.

TABLE 1. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Patients with a delayed union or nonunion who are treated with ESWT	Follow-up period <6 weeks
Skeletally mature patients	Less than 10 patients
An outcome measure quantifying bony union (x-ray or CT) should be reported	
Full text available in English, Spanish, German, or Dutch	
Peer-reviewed study	
Randomized controlled trials and prospective and retrospective cohort studies	

Literature Search

Six databases were systematically searched on the 10th of August 2017. The databases that were searched were Embase.com, MEDLINE ovid, Cochrane, Web of Science, PubMed publisher, and Google Scholar. The search strategy that was used for the search in Medline Ovid (See **Table, Supplemental Digital Content 1**, http://links.lww.com/JOT/A578, for the search strategy for Medline Ovid). was adapted for the search in the other databases. Also, reference lists of eligible articles were checked for eligible articles that were missed by our search strategy.

Study Selection

Articles that were found by multiple databases were deduplicated. The articles were then included or excluded based on the eligibility criteria. Articles were first screened based on title and abstract. Eligible articles were again judged based on the full text. Both selection rounds were independently performed by 2 reviewers (A.W. and O.P.v.d.J.). After each selection round, the reviewers compared their selected articles, and disagreements were discussed and resolved by a consensus. A third reviewer (D.E.M.) was asked in case of an unsolved disagreement.

Risk of Bias Assessment

Risk of bias assessment was independently performed by 2 reviewers (A.W. and D.E.M.), using the Cochrane Risk of Bias tool for RCTs.[21] This tool contains 6 items, which can be scored as low, high, or unclear risk of bias. The 6 items concern random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, handling of incomplete outcome data, and selective outcome reporting. Discrepancies between the reviewers were discussed and resolved by a consensus. Afterward, studies were classified as being at low, moderate, or high risk of bias. Studies were at low risk of bias if all 6 items were scored as low risk of bias. Moderate risk of bias was defined as ≥4 items scored as low risk of bias. Studies were at high risk of bias if <4 items were scored as low risk of bias.

Data Extraction

A data extraction sheet was established by the reviewers (A.W., O.P.v.d.J., and D.E.M.) for accurate data extraction. Data that were extracted are general characteristics of the participants including fracture sites according to the OTA/AO classification,[22] general characteristics of the ESWT, union rates, and adverse events. Data were extracted from the studies by 1 reviewer (A.W.), who also completed a full check of the extracted data after the data extraction was completed.

Primary Outcome

Our primary outcome is the union rate 6 months after ESWT. In studies that only reported absolute numbers of bony union, union rates were calculated. If the union rate after 6 months was not reported, union rate was reported as has been conducted in the study (eg, union rate and average healing time).

The results of the studies will be presented based on the outcome of the risk of bias assessment (low risk of bias, moderate risk of bias, and high risk of bias).

Secondary Outcome

Our secondary outcome is the safety of ESWT. The number of adverse events and the kind of adverse events were extracted from the studies. Adverse events were graded based on the adapted Clavien-Dindo classification.[23,24] The Clavien-Dindo classification is a tool established in general surgery to grade the severity of complications after surgery. In this tool, adverse events are graded from 1 to 5, in which grade 1 indicates any deviation from the normal postoperative course without the need for any additional interventions, and grade 5 being the most serious, indicating the death of a patient.

RESULTS

Literature Search

The search resulted in 2780 studies, but after deduplication, 1868 studies remained for screening. The screening based on title and abstract resulted in 73 potentially eligible studies. After reading the full texts of those studies, 30 studies were found to be eligible. Screening of the reference lists of those articles did not result in any additional studies, and therefore 30 studies were included in this review (Fig. 1).

Risk of Bias Assessment

All 30 studies were assessed for risk of bias. After initial assessment, 173 of the 180 items were given the same score by both reviewers, and discrepancies were resolved by a consensus. The results of the risk of bias assessment per study are shown in **Supplemental Digital Content 2** (see **Table**, http://links.lww.com/JOT/A579). None of the studies was classified as being at low risk of bias. One study was classified as being at moderate risk of bias.[8] Twenty-nine studies were classified as being at high risk of bias.[9,10,13,25–50]

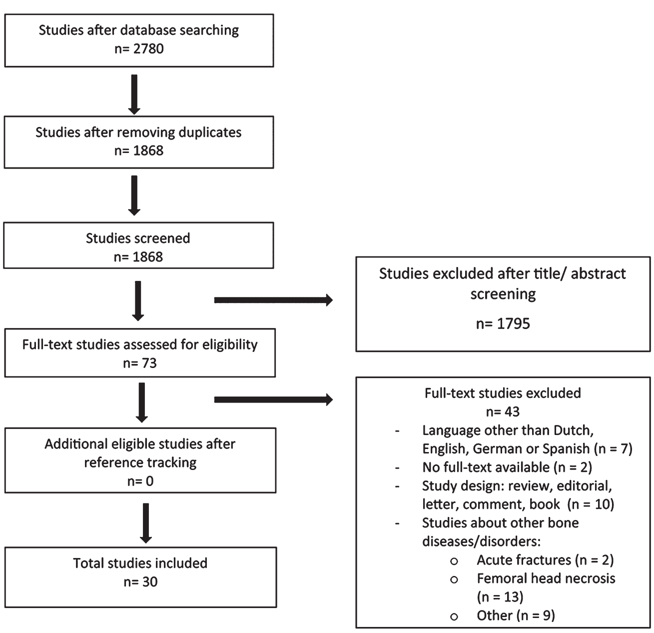

FIGURE 1. Flow chart of study selection.

General Characteristics of Included Studies

Studies at Moderate Risk of Bias

In the RCT of Cacchio et al,[8] 126 patients with nonunions of the long bones were randomly assigned to ESWT group 1, ESWT group 2, or to the surgical treatment group. Patients in ESWT group 1 were treated with an energy flux density of 0.40 mJ/mm^2 and patients in ESWT group 2 with an energy flux density of 0.70 mJ/mm^2. The general characteristics of this RCT are shown in **Supplemental Digital Content 3** (see **Table Part A**, http://links.lww.com/JOT/A580).

Studies at High Risk of Bias

From the 29 studies with a high risk of bias, 1 study was an RCT. In this RCT, 63 patients with nonunions of the long bones were randomly assigned to ESWT combined with transplantation of autologous human bone mesenchymal stems cells (hBMSCs) or only ESWT (see **Table Part A, Supplemental Digital Content 3**, http://links.lww.com/JOT/A580).[48]

Two studies at high risk of bias were retrospective nonrandomized trials.[9,10] Both studies compared patients with nonunions who were treated with ESWT with a surgery-treated control group. The general characteristics of the patients and ESWT are shown in **Supplemental Digital Content 3** (see **Table Part A**, http://links.lww.com/JOT/A580).

The remaining 26 studies were cohort studies without a control group; see **Supplemental Digital Content 3** (see **Table Part B**, http://links.lww.com/JOT/A580) for the general characteristics of the patients and of the ESWT. Nineteen of those studies treated nonunions in which the fracture was older than 6 months.[25–31,35,36,38,39,41–44,46,47,49,50] Five of them also reported data on the treatment of delayed unions[29,38,43,44,49]; however, Everding et al[49] were excluded from the results because they treated <10 delayed unions. Seven studies did not report how they defined delayed unions or nonunions.[13,32–34,37,40,45]

Of the 26 studies, 11 studies collected data prospectively,[25,26,28,30,31,36–38,39,44,47] 5 studies retrospectively,[34,35,41,42,49] and 10 studies did not report if data were collected prospectively or retrospectively.[13,27,29,32,33,40,43,45,46,50]

The general design of the cohort studies was that patients with delayed unions or nonunions were treated with ESWT and were followed over time to see whether bony union did occur.

Primary Outcome: Bony Union

Studies at Moderate Risk of Bias

The union rates reported by Cacchio et al[8] after 6 months were 70% for ESWT group 1, 71% for ESWT group 2%, and 74% for the surgical group. Union rates were not significantly different between the groups ($\chi^2 = 0.08$; $P = 0.95$).

Studies at High Risk of Bias

The RCT of Zhai et al[48] reported callus formation after 6 months in 55% of the patients who only received ESWT and in 63% of the patients in the hBMSCs + ESWT group.

In the nonrandomized trials, Notarnicola et al[10] reported union rates at 6 months of 79% in the ESWT group and 78%

in the surgical group. Union rates between the 2 groups were not significantly different ($\chi^2 = 0.01$; $P = 0.89$). Furia et al[9] reported union rates of 91% in the ESWT group and 90% in the surgical group after 6 months. No statistical analysis was performed in this study.

The union rates that were reported in the 26 cohort studies are shown in Figure 2 and vary between 39% and 100%.

The overall union rates of all studies at high risk of bias are presented in Table 2.

Secondary Outcome: Adverse Events

Cacchio et al,[8] Notarnicola et al,[10] and Furia et al[9] compared adverse events between ESWT-treated patients and surgery-treated patients. The absolute number of complications is shown in Table 3 and the overall complication rates in **Supplemental Digital Content 4** (see **Figure**, http://links.lww.com/JOT/A581). The RCT of Zhai et al[48] did not register adverse events.

Of the 26 included cohort studies, 23 studies registered adverse events after ESWT,[13,25–37,39,41–47,49] treating a total of 2027 delayed unions and nonunions. Eight studies reported that no adverse events occurred after ESWT.[13,32,34,36,41,42,45,47] Fifteen studies reported adverse events such as petechiae, local edema, and hematomas,[25–31,33,35,37,39,43,44,46,49] which are all grade 1 complications.

DISCUSSION

In this systematic review, the effectiveness of ESWT in delayed unions and nonunions was examined. The study by Cacchio et al[8] showed that ESWT is as effective as surgical treatment for patients with long bone nonunions, with unions rates between 71% and 74% after 6 months.[8] Next to this study, 2 more studies were published, in which ESWT was compared with a surgery-treated control group. In concordance with the findings of Cacchio et al,[8] both studies did find similar union rates between ESWT-treated patients and surgery-treated patients.[9,10] The results of these studies seem to indicate that ESWT is as effective as surgery in the treatment of nonunions. The RCT of Zhai et al[48] showed that hBMSCs transplantation with ESWT is more effective than ESWT alone, which shows that ESWT might be more effective with a combined treatment. These promising results are further supported by the included cohort studies, which together treated more than 2000 delayed unions and nonunions and reported similar union rates as after surgery.

However, although we were able to identify 30 studies concerning this topic, the overall quality of those studies was poor because of high risks of bias within the studies. The RCT of Cacchio et al[8] was at moderate risk of bias, and the results should therefore be interpreted with caution. The remaining 29 studies were all assessed as high risk of bias because of missing control groups or nonrandomized allocation to control groups, no blinding of the outcome assessors and participants, and unclear handling of incomplete data. Therefore, it is unadvisable to draw strong conclusions from these study results.

In addition to effectiveness, we also aimed at investigating the safety of ESWT for nonunions. Twenty-six of the 30 studies addressed adverse events, treating together more than 2000 delayed unions and nonunions. None of those studies reported any serious adverse events after ESWT,

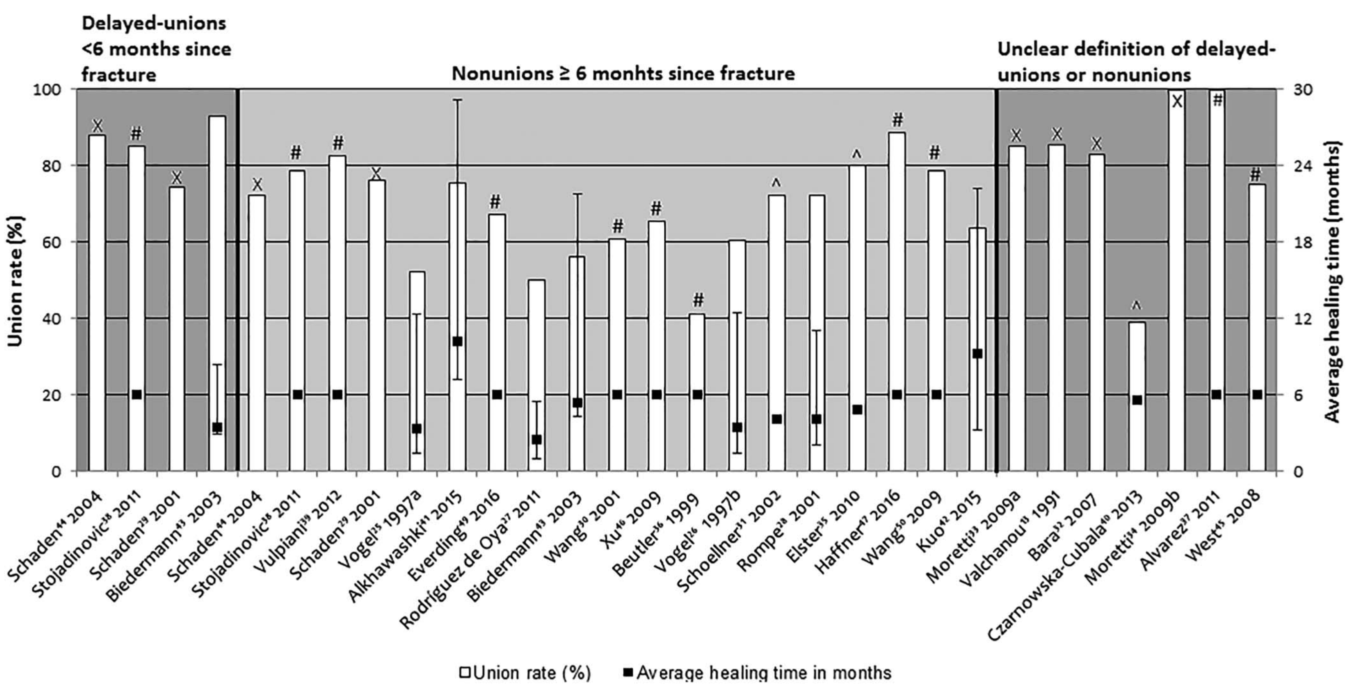

FIGURE 2. Union rates on the left x-axis and average healing times in months on the right x-axis reported in the 26 cohort studies. Error bars indicate the ranges in time to union after ESWT; #study determined union rates at a fixed point of 6 months after ESWT; Xstudy did not report average union time; ^study did not report range in union time.

TABLE 2. Overall Union Rates of Studies at High Risk of Bias

	Union Rate	Total No. Treated Patients
Delayed unions treated with ESWT	86	314
Nonunions treated with ESWT	73	1782
Nonunions treated with surgery	81	80
Nonunions treated with hBMSCs and ESWT	62.5	32

whereas severe adverse events were reported after surgery. None of the adverse events reported after ESWT needed further treatment. Based on these results, it seems that ESWT is a safer treatment option for delayed unions and nonunions than surgery.

Zelle et al[20] published a systematic review on the effectiveness of ESWT in 2010 based on 10 studies. They suggested that approximately 75% of delayed unions or nonunions could be treated successfully with ESWT, but the level of evidence is rather low because all 10 studies were cohort studies.[20] Since the review by Zelle et al,[20] multiple studies have been published on the effectiveness of ESWT.[9,27,35,37–42] However, even after the conduction of those studies, the level of evidence remains low.

This review encountered some challenges and limitations. First, because RCTs are the golden standard to prove the effectiveness of a treatment, we decided to perform the risk of bias assessment with a tool for RCTs. However, our search resulted in only 2 RCTs, and therefore all nonrandomized and cohort studies were judged as high risk of bias. However, we believe that by using this tool, the lack of well-performed RCTs is clearly pointed out. It is argued that nonunions are a biological endpoint in which no further bone healing will occur and that therefore a control group is not necessary to prove the effectiveness of ESWT. However, no clear consensus does exist when this biological endpoint is reached. Marsh[51] showed that in patients with nonunions at 6 months, 50% experienced spontaneous fracture healing within the next 4 months. Biedermann et al[43] compared these results with the results of several studies that applied ESWT and concluded that ESWT does not seem to accelerate bone union compared with natural fracture healing in nonunions. Thus, the cohort studies without a control group might wrongly attribute the natural fracture healing process to ESWT, even after 6 months of nonunion.[43]

Second, there was a lot of heterogeneity within and between the studies. Most studies included in this review included patients with fractures of different bones and with different types of delayed unions and nonunions. Furthermore, studies used different energy settings for ESWT and differed in the number of shock waves applied to a fracture and the number of ESWT sessions that were conducted. Also, the type of anesthesia differed between the studies (ranging from no anesthesia at all to general anesthesia), which might influence the effectiveness of ESWT.[52] Overall, because of the heterogeneity between the studies and the poor quality of the studies, combining the results in a meta-analysis would not have empowered our conclusion. More research should be performed with homogeneous groups and shock wave parameters to be able to make recommendations about optimal shock wave parameters for particular fractured bones.

Last, some of the included studies were published by the same research groups.[25,26,30,33,34,50] Looking at the results of those studies, it seems that some participants might have been included in the analysis of more than 1 publication. Therefore, this review might overestimate the actual amount of subjects who have been treated with ESWT.

In conclusion, the union rates that have been presented in this review after ESWT were comparable to union rates after surgery, and no serious adverse events have been reported after ESWT. Therefore, it seems that ESWT is as effective as surgery for the treatment of delayed unions and nonunions with less severe complications. However, the quality of the studies was poor, and therefore the evidence for the effectiveness of ESWT for the treatment of delayed unions and nonunions is weak. We therefore hope that in the near future, high-quality RCTs will be conducted on the effect of ESWT in nonunions. These studies are essential to potentially implement ESWT into standard care.

TABLE 3. Absolute Number of Complications Classified by the Adapted Clavien-Dindo Classification

	ESWT				Surgery			
		No. Complications				No. Complications		
	No. Patients	Grade 1	Grade 2	Grade 3	No. Patients	Grade 1	Grade 2	Grade 3
Cacchio et al[8]	84	23*	0	0	42	1†	0	2‡
Notarnicol et al[10]	58	0	0	0	60	0	0	0
Furia et al[9]	23	1§	0	0	20	1¶	1‖	9#
Overall	165	24	0	0	122	2	1	11

*Hematomas.
†Nerve neuropraxia.
‡Wound infections requiring surgical debridement and antibiotics.
§Mild petechiae.
¶Superficial cellulitis.
‖Refracture requiring 5 weeks of immobilization in a walking boot.
#Hardware removal due to symptoms related to hardware.

ACKNOWLEDGMENTS

The authors thank Wichor Bramer, Biomedical information specialist at the Erasmus MC, for his help with the systematic search of the databases.

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