Extracorporeal shock wave treatment for delayed-union and nonunion fractures; a systematic review

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Abstract

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; follow-up period ≥6 weeks.

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

Data synthesis: Two RCT's and 28 non-randomized 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), non-randomized 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 RCT's to prove the effectiveness of ESWT, and potentially improve the treatment of nonunions as ESWT might be as effective as surgery but safer.

Level of Evidence: Therapeutic Level II

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 three months after a fracture, and nonunions as fractures that do not show radiological union six 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]

Currently 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% to 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 therapy (ESWT). ESWT is a well-known treatment for fragmentation of kidney stones, but over the last decades ESWT has been increasingly used for bone growth stimulation. In 1991 Valchanou and Michailov used ESWT for the treatment of delayed-unions and nonunions and reported bony union in 70 of 82 fractures without any complications.[13] 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 due to an increase in neovascularization and an upregulation of angiogenic and osteogenic growth factors.[14] Animal studies reported an increase of several growth factors after ESWT, which are important in bone regeneration (VEGF, TGF-beta 1 and BMP's).[15, 16] Also, it has been show that ESWT leads to an increased differentiation of bone marrow stem cells towards 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 ten 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 of 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 nonunion with ESWT. See table 1 for a full-overview of all eligibility criteria.

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 of Medline Ovid is presented in table 2, and was adapted for the search of 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 full-text. Both selection rounds were independently performed by two reviewers (AW and OJ). After each selection round the reviewers compared their selected articles, and disagreements were discussed and resolved by consensus. A third reviewer (DM) was asked in case of an unsolved disagreement.

Risk of bias assessment

Risk of bias assessment was independently performed by two reviewers (AW and DM), using the Cochrane Risk of Bias tool for RCT's.[21] This tool contains six items, which can be scored as low, high or unclear risk of bias. The six 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 consensus. Afterwards, 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 (AW, OJ, DM) for accurate data extraction. Data that were extracted are general characteristics of the participants including fracture sites according to the OTA classification[22], general characteristics of the ESWT, union rates and adverse events. Data were extracted from the studies by one reviewer (AW), 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 six months after ESWT. In studies that only reported absolute numbers of bony union, union rates were calculated. If the union rate after six months was not reported, union rate was reported as has been done in the study (e.g. 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 1-5, in which grade 1 indicates any deviation from normal postoperative course without the need for any additional interventions, and grade 5 is 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 eligibly 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 (figure 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 consensus. The results of the risk of bias assessment per study are shown in table 3. 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]

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, 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 table 4a.

Studies at high risk of bias

From the 29 studies with a high risk of bias, one study was a RCT. In this RCT, 63 patients with nonunions of the long bones were randomly assigned to ESWT combined with transplantation of human autologous bone mesenchymal stems cells (hBMSCs) or only ESWT (table 4a).[48]
Two studies at high risk of bias were retrospective non-randomized trials.[9, 10] Both studies compared patients with nonunions that were treated with ESWT, with a surgery-treated control group. The general characteristics of the patients and ESWT-treatment are shown in table 4a.

The remaining 26 studies were cohort studies without a control group, see table 4b for the general characteristics of the patients and of the ESWT-treatment. Nineteen of those studies treated nonunions in which the fracture was older than six 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] was excluded from the results as 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, ten studies collected data prospectively,[25, 26, 28, 30, 31, 36, 38, 39, 44, 47] five studies retrospectively, [34, 35, 41, 42, 49] and ten 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 six 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 (X^2=0.08; p=0.95).

Studies at high risk of bias

The RCT of Zhai et al. [48] reported callus formation after six months in 55% of the patients who only received ESWT, and in 63% of the patients in the hBMSCs + ESWT group.
In the non-randomized trials, Notarnicola et al.[10] reported union rates at six months of 79% in the ESWT group and 78% in the surgical group. Union rates between the two groups were not significantly different (X^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 six months. No statistical analysis was done in this study.
The union rates that were reported in the 26 cohort studies, are shown in figure 2, and vary between 39%-100%.
The overall union rates of all studies at high risk of bias are presented in table 5.

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 are shown in table 6 and the overall complication rates in figure 3. 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 hematoma's,[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 of 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 six months.[8] Next to this study, two more studies were published, in which ESWT treatment was compared to 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, due to 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, due to missing control groups or non-randomized 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 to investigate the safety of ESWT treatment for nonunions. Twenty-three of the 30 studies addressed adverse events, treating together more than 1500 delayed-unions and nonunions. None of those studies reported any serious adverse events after ESWT, 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 that evidence is rather low because all ten studies were cohort studies[20]. Since the review of 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. Firstly, as RCT's are the golden standard to prove the effectiveness of a treatment, we decided to perform the risk of bias assessment with a tool for RCT's. However, our search resulted in only two RCT's, and therefore all non-randomized and cohort studies were judged as high risk of bias. However, we believe that by using this tool, the lack of well performed RCT's is clearly pointed out. It is argued that nonunions are a biological end-point 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 et al.[51] showed that in patients with nonunions at six months, 50% experienced spontaneous fracture healing within the next four months. Biederman 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 to natural fracture healing in nonunions. Thus, the cohort studies without control group might wrongly attribute the natural fracture healing process to ESWT, even after six months of nonunion.[43]
Secondly, 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, differed in the number of shock waves applied to a fracture and the number of ESWT sessions that were done. Also, the type of anaesthesia differed between the studies (ranging from no anesthesia at all to general anesthesia) which might influence the effectiveness of ESWT[52]. Overall, due to 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 done with homogeneous groups and shock wave parameters to be able to make recommendations about optimal shock wave parameters for particular fractured bones.
Lastly, 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 one publication. Therefore, this review might overestimate the actual amount of subjects that 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 treatment of delayed-unions and nonunions is weak. We therefore hope that in the near future high quality RCT's will be conducted on the effect of ESWT in nonunions. These studies are essential to potentially implement ESWT into standard care.

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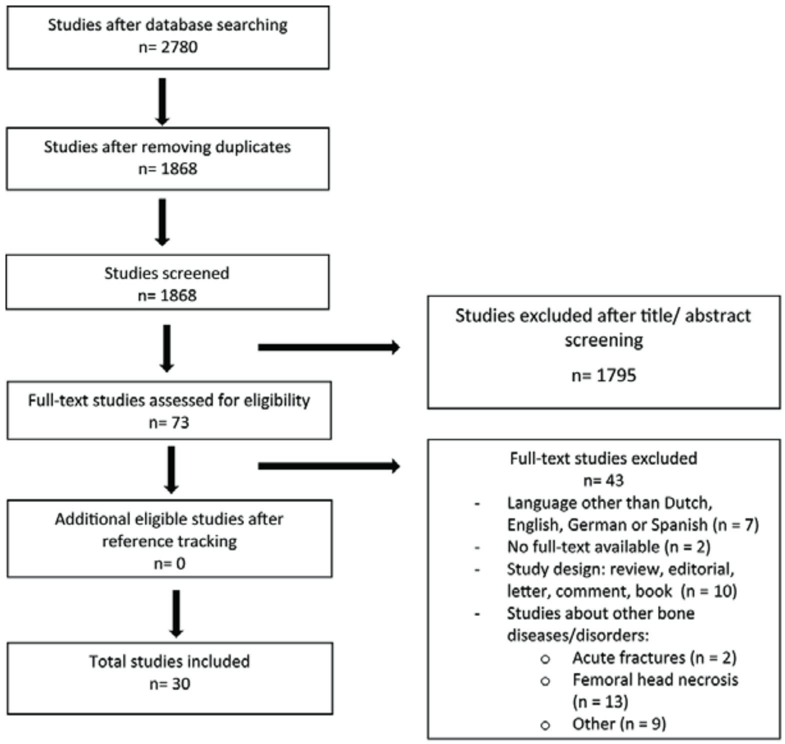

Figure 1. Flow chart of study selection

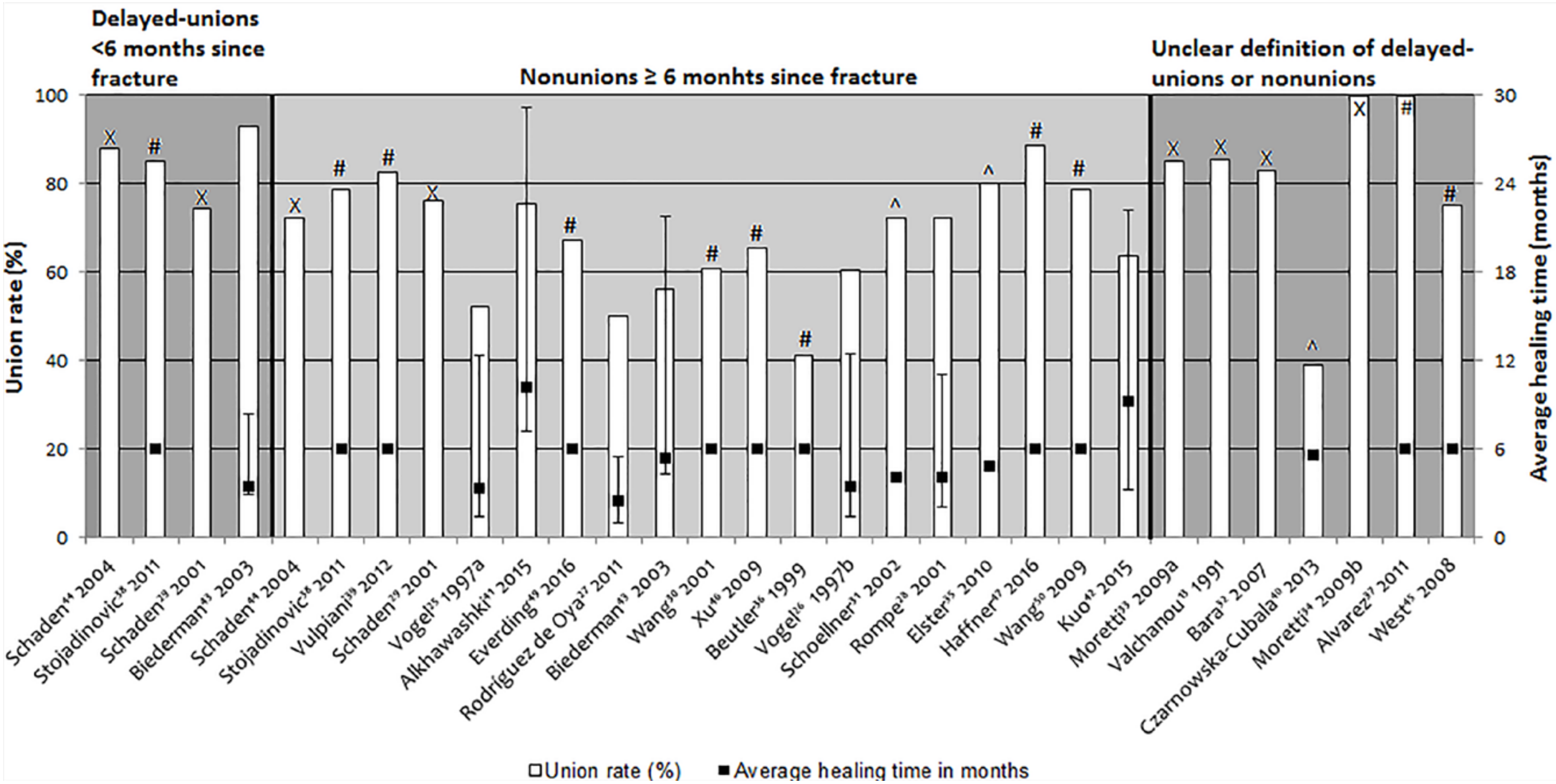

Figure 2. Union rates on the left x-axis and average healing times in months on the right x-axis reported in the 26 cohort studies. Error bars indicate the ranges in time to union after ESWT; # = study determined union rates at a fixed point of 6 months after ESWT; X = study did not report average union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

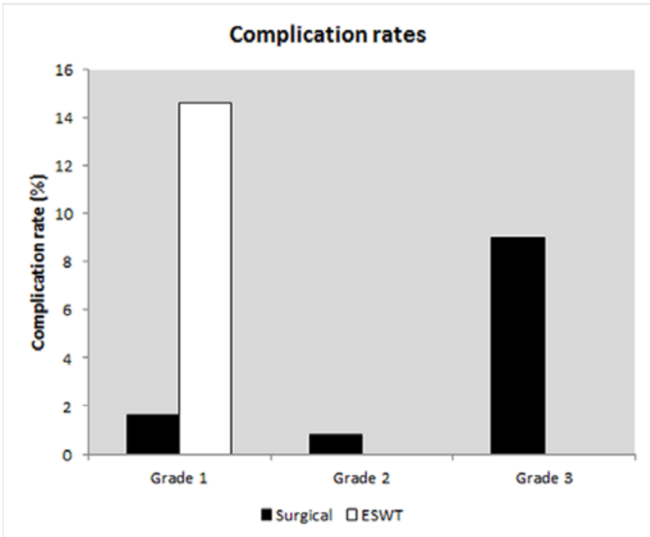

Figure 3. Overall complication rates based on the reported complications in the studies of Cacchio et al.[8], Notarnicola et al.[10], and Furia et al.[9], classified by the adapted Clavien-Dindo classification[23].

Table 1. Eligibility criteria

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

Table 2. Search strategy for Medline

("High-Energy Shock Waves"/ OR (((shock OR pressure*) AND wave*) OR shockwave* OR eswt OR orthotrip*)) AND (exp "Bone and Bones"/ OR exp "Bone Development"/ OR exp "Bone Remodeling"/ OR exp "Fractures, Bone"/ OR "Fracture Healing"/ OR "Bone Density"/ OR exp "Bone Diseases"/ OR (bone OR bones OR fracture* OR nonunion OR ((non OR delay*) ADJ3 (union*)) OR osteo* OR osseous OR intraosseous OR (avascular* ADJ3 necro*) OR skelet* OR pseudarthrit* OR pseudoarthrit* OR (pseud* ADJ arthrit*)).ab,ti.) NOT (exp animals/ NOT humans/)

Table 3. Results of risk of bias assessment of the individual studies with scores per item.

	Items of the Cochrane Risk of Bias tool for RCT's						Overall risk of bias
	1	**2**	**3**	**4**	**5**	**6**	
Cacchio[8] 2009	+	+	-	+	+	?	Moderate risk of bias
Zhai[49] 2016	?	?	-	?	+	?	High risk of bias
Notarnicola[10] 2010	-	-	-	-	?	?	High risk of bias
Furia[9] 2010	-	-	-	-	+	?	High risk of bias
Schaden[45] 2004	-	-	-	-	?	?	High risk of bias
Stojadinovic[39] 2011	-	-	-	-	?	?	High risk of bias
Schaden[29] 2001	-	-	-	-	?	?	High risk of bias
Everding[50] 2016	-	-	-	-	+	?	High risk of bias
Biederman[44] 2003	-	-	-	-	-	?	High risk of bias
Vulpiani[40] 2012	-	-	-	-	?	?	High risk of bias
Vogel[25] 1997a	-	-	-	-	?	?	High risk of bias
Alkhawashki[42] 2015	-	-	-	-	?	?	High risk of bias
Rodríguez de Oya[27] 2011	-	-	-	-	?	?	High risk of bias
Wang[30] 2001	-	-	-	-	-	?	High risk of bias
Xu[47] 2009	-	-	-	-	-	?	High risk of bias
Beutler[37] 1999	-	-	-	-	?	?	High risk of bias
Vogel[26] 1997b	-	-	-	-	?	?	High risk of bias
Schoellner[31]2002	-	-	-	-	?	?	High risk of bias
Rompe[28] 2001	-	-	-	-	?	?	High risk of bias
Elster[36]2010	-	-	-	-	-	?	High risk of bias
Haffner[48] 2016	-	-	-	-	-	?	High risk of bias
Wang[51]2009	-	-	-	-	?	?	High risk of bias
Kuo[43] 2015	-	-	-	-	?	?	High risk of bias
Moretti[34] 2009a	-	-	-	-	?	?	High risk of bias
Valchanou[13] 1991	-	-	-	-	?	?	High risk of bias
Bara[32] 2007	-	-	-	-	-	?	High risk of bias
Czarnowska-Cubala[31] 2013	-	-	-	-	?	?	High risk of bias
Moretti[34] 2009b	-	-	-	-	?	?	High risk of bias
Alvarez[38] 2011	-	-	-	-	-	?	High risk of bias
West[46] 2008	-	-	-	-	?	?	High risk of bias

1= Random sequence generation; 2 = Allocation concealment; 3= Blinding of participants and personnel; 4= Blinding of outcome assessment; 5= Incomplete outcome data; 6= Selective reporting; + = low risk of bias; - = high risk of bias; ? = unclear risk of bias

Table 4a. Characteristics of included controlled trials

		Number of fractures	Age in years (range)	Males in percen-tages	Fracture sites	Average months of non-union before ESWT (range)	Percentage previously infected nonunions	Type of nonunion in percentages			Type of anesthe-sia	Treatment
								Hyper-thropic	Atro-phic	Oligo-tropic		
Randomized controlled trial												
Cacchio[8] 2009	Intervention 1	42	42.8 (NR)	76	Long bones of the upper and lower extremities	11.5 (NR)	NR	71	29	0	R	ESWT (4x 4000 shocks at 0,40 mJ/mm²)
	Intervention 2	42	43.1 (NR))	74		10.8 (NR)		74	26	0	R	ESWT (4x 4000 shocks at 0,70 mJ/mm²)
	Control	42	42.5 (NR)	71		10.2 (NR)		74	26	0	G	Surgical revision with fixation (locked intramedullary nail ± autogenous bone graft or external fixator)
Zhai[48] 2016	Intervention	32	39,6 (23 - 50)	56	Shaft of the long bones	13,4 (9 -20)	NR	91	90	NR	NR	Transplantation of autologous hBMSC + 4-5x ESWT (mean of 2900 shock waves at average 23 kV)
	Control	31	38,1 (20 – 49)	58		12,9 (9 –19)		90	10	NR	NR	4-5x ESWT (mean of 2900 shock waves at average 23 kV)
Non-randomized controlled trials												
Notarnico-la [10] 2010	Intervention	58	33,2 (16-65)	91	Scaphoid	14,8 (9-36)	NR		NR		NR	ESWT (3x 4000 shocks at 0,05-0,12 mJ/mm²)
	Control	60	33,1 (16-65)	87		15,8 (9-40)					NR	Surgery according to the Matti-Russe method
Furia[9] 2010	Intervention	23	42,7 (17-78)	57	Proximal metaphyseal-diaphyseal part of the fifth metatarsal	10,4 (6-39)	NR		NR		G (n=15), R (n=6), L (n=2)	ESWT (2000-4000 shocks at 0.35 mJ/mm²)
	Control	20	40,8 (19-78)	40		6,2 (4-13)					NR	Intramedullary screw fixation

Table 4b. General characteristics of the included cohort studies

	Number of fractures	Age in years (range)	Males in percentage	Fracture sites	Average months of non-union before ESWT (range)	Percentage previously infected nonunions	Type of nonunion in percentages: Hyperthropic	Atrophic	Oligotrophic	Type of anesthesia	Number of shocks applied	Energy density in mJ/mm²
Studies with delayed-unions (<6 months since fracture) and nonunions (≥ 6 months since fracture)												
Schaden[44] 2004	DU: 152 NU: 445	44 (10-90)	68	Upper + lower extremities	16,1 (NR)	10	39	61		G, R or L	2000-4000	0,38
Stojadinovic[38] 2011	DU: 120 NU: 229	48 (15-91)	67	Upper + lower extremities	NR	NR	NR	NR	NR	G or R	NR	NR
Schaden[29] 2001	DU: 35 NU: 80	43 (10-86))	64	Upper + lower extremities	NR	19	NR	NR	NR	G (n=60) R (n=51) L (n=4)	1000-12.000	0,25-0,40
Everding[49] 2016	DU:9[a] NU: 33	43 (18-74)	72	Upper + lower extremities	DU: 4,3 (3,5-5) NU:17,3 (6-48)	NR	52	48	NR	NR	3000	0,36
Biederman[43] 2003	DU: 16 NU: 57	42 (NR)	53	Long bones: 58; others 12	DU: 5 (0,2-5) NU: 19 (6-74)	NR	DU: 86 NU: 61	DU: 14 NU: 39	NR	G (n=46), L (n=39)	1-2x 2900 (mean)	23 kV
Studies with nonunions (≥ 6 months since fracture)												
Vulpiani[39] 2012	143	41 (14-81)	64	Upper + lower extremities	14,1 (6-84)	NR	10	17	73	L (n=17) NA (n=126)	3-5x 2500-3000	0,25-0,84
Vogel[25] 1997a	52	37 (12-81)	62	Upper + lower extremities	13 (6-51)	15	NR	NR	NR	R (n=51) NR (n=1)	3000	0,6
Alkhawashki[41] 2015	49	34 (14-70)	80	Upper + lower extremities	11,9 (6-60)	Excluded	NR	NR	NR	NR	1-3x 2000-4000	26 kV
Rodríguez de Oya[27] 2001	20	42 (26-62)	63	Upper + lower extremities	17 (6-42)	NR	25	30	45	G or R	3500 – 10.000	0,3-0,4
Wang[30] 2001	72	39 (15-74)	73	Long bones of the upper + lower extremities	NR (NR)	NR	53	18	29	G or R	1000-6000	0,47-0,62
Xu[46] 2009	69	38 (22-72)	64	Long bones of the upper + lower extremities	12,5 (6-84)	NR	84	16	NR	R or L	3000-10.000	0,56-0,62
Beutler[36] 1999	27	35 (19-72)	NR	Long bones of the upper + lower extremities	9 (6-16)	NR	59	41	NR	NA(n=24) NR (n=1)	2x 2000	18 kV
Vogel[26] 1997b	48	38 (12-81)	52	Lower extremities	12 (6-48)	17	NR	NR	NR	R (n=47)	3000	0,6

										NR (n=1)		
Schoellner[31] 2002	43	39 (18-74)	53	Long bones of the lower extremities	13 (9-51)	NR	NR	NR	NR	R	3000	0,6
Rompe[28] 2001	43	40 (18-74)	53	Long bones of the lower extremities	11 (9-36)	NR	NR	NR	NR	R	3000	0,6
Elster[35] 2010	192	45 (16-90)	73	Tibia	16,8 (NR)	21	38	41	NR	G or R	1-4x 2000-12.000	0,38-0,40
Haffner[47] 2016	58	48 (16-82)	76	Tibia	15,6 (9-56)	31,8	34,6	34,6		G or R	3000-4000	0,4
Wang[50] 2009	42	35 (16-68)	52	Diaphysis of the long bones of the lower extremities	15,0 (6-48)	NR	83	17	NR	G	6000	0,62
Kuo[42] 2015	22	30 (18-45)	59	Femoral shaft	10,5 (6-16)	NR	0	100	0	G or R	3000	0,58
Studies with undefined definition of delayed-union and nonunion												
Moretti[33] 2009a	204	NR (NR)	NR	Upper + lower extremities	NR (NR)	NR	NR	NR	NR	NR	4000	0,22-1,10
Valchanou[13] 1991	82	28 (9-76)	90	Upper + lower extremities	20,2 (NR)	NR	NR	NR	NR	R	1000 – 4000	1000 – 1700 bars
Bara[32] 2007	81	NR (12-89)	68	Upper +lower extremities	8 (4-204)	NR	NR	NR	NR	NA	1500-3000	500 bars
Czarnowska-Cubala[40] 2013	31	47 (21-72)	65	Long bones of the upper + lower extremities	NR (NR)	NR	NR	NR	NR	NR	3000	300 bars
Moretti[34] 2009b	10	NR (20-29)	100	Lower extremities	NR (NR)	NR	NR	NR	NR	NA	3x 4000	0,09-0,17
Alvarez[37] 2011	34	50 (16-75)	22	Proximal metatarsal or zone 2/3 of the fifth metatarsal	6,8 (2,3-192,2)	NR	NR	NR	NR	G or R	2000	0,22-0,51
West[45] 2008	28	48 (16-75)	21	Proximal metatarsal or zone 2/3 of the fifth metatarsal	13,3 (2,3-19,2)	NR	NR	NR	NR	G with regional block	2000	24 kV

DU: Delayed-union; NU: Nonunion; NR: Not reported; G: General anesthesia; R: Regional anesthesia; L: Local anesthesia; NA: No anesthesia; a: excluded from results due to <10 patients

Table 5. Overall union rates of studies at high risk of bias

	Union rate (%)	Total number of treated patients
Delayed-unions treated with ESWT	86	314
Nonunions treated with ESWT	73	1782
Nonunions treated with surgery	81	80
Nonunions treated with hBMSC's and ESWT	62,5	32

Table 6. Absolute number of complications classified by the adapted Clavien-Dindo classification

	ESWT				Surgery			
	Number of patients	**Number of complications**			**Number of patients**	**Number of complications**		
		Grade 1	Grade 2	Grade 3		Grade 1	Grade 2	Grade 3
Cacchio[8] 2009	84	23[1]	0	0	42	1[2]	0	2[3]
Notarnicol[10] 2010	58	0	0	0	60	0	0	0
Furia[9] 2010	23	1[4]	0	0	20	1[5]	1[6]	9[7]
Overall	165	24	0	0	122	2	1	11

1. hematomas; 2. nerve neuropraxia; 3. wound infections requiring surgical debridement and antibiotics; 4. mild petechiae; 5. superficial cellulitis; 6. refracture requiring five weeks of immobilization in a walking boot; 7. hardware removal due to symptoms related to hardware