



## Extracorporeal shockwave therapy (ESWT) ameliorates healing of tibial fracture non-union unresponsive to conventional therapy



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### ARTICLE INFO

#### Article history:

Accepted 11 April 2016

#### Keywords:

Non-union

Pseudarthrosis

Tibia

Extracorporeal shockwave therapy

ESWT

### ABSTRACT

Tibial non-unions are common cause of demanding revision surgeries and are associated with a significant impact on patients' quality of life and health care costs. Extracorporeal shockwave therapy (ESWT) has been shown to improve osseous healing *in vitro* and *in vivo*. The main objective of present study was to evaluate the efficacy of ESWT in healing of tibial non-unions unresponsive to previous surgical and non-surgical measures. A retrospective multivariate analysis of a prospective open, single-centre, clinical trial of tibia non-union was conducted. 56 patients with 58 eligible fractures who met the FDA criteria were included. All patients received 3000–4000 impulses of electrohydraulic shockwaves at an energy flux density of 0.4 mJ/mm<sup>2</sup> (–6 dB). On average patients underwent 1.9 times ( $\pm 1.3$  SD) surgical interventions prior to ESWT displaying the rather negatively selected cohort and its limited therapy responsiveness. In 88.5% of patients receiving ESWT complete bone healing was observed after six months irrespective of underlying pathology. The multivariate analysis showed that time of application is important for therapy success. Patients achieving healing received ESWT earlier: mean number of days between last surgical intervention and ESWT (healed – 355.1 days  $\pm 167.4$  SD vs. not healed – 836.7 days  $\pm 383.0$  SD;  $p < 0.0001$ ). ESWT proved to be a safe, effective and non-invasive treatment modality in tibial non-unions recalcitrant to standard therapies. The procedure is well tolerated, time-saving, lacking side effects, with potential to significantly decrease health care costs. Thus, in our view, ESWT should be considered the treatment of first choice in established tibial non-unions.

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### Introduction

Non-unions of the tibia are a common cause for challenging revision surgery in traumatology. Reaching an incidence of almost one-third of long bone fractures, tibia is the most commonly fractured among this entity and with a 2.5% combined prevalence also the most frequent long bone non-union [1–4]. Definition of tibia non-unions is still controversial and frequently discussed in the literature. Authors used many different classifications to

distinguish delayed osseous healing from non-unions which significantly hampers the outcome comparisons between different studies.

According to the definition of worldwide recognised agencies, including but not limited to The Food and Drug Administration [5], a non-union is evident, when a fracture fails to demonstrate cortical continuity despite operative and non-operative interventions over a period of nine or more months and fails to demonstrate any radiographic signs towards osseous healing within the last three months of the follow up. This broad definition of non-union, found in contemporary, peer reviewed literature, as well as some health insurance agencies, is criticised because of an arbitrary cut off time point that fails to take into account any biological and clinical relevant aspects of bone healing. These include the degree

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of soft tissue damage, fragment alignment, vascularity, and quality of the remaining bone stock. Acknowledging this criticism, we applied the current and generally accepted definition of non-unions for this study, in the absence of a more precise characterisation.

Non-unions are a remarkable burden to both individuals and their families as well as healthcare system and government. Patients' inability to walk significantly impairs their quality of life, affects their working capacity and everyday activities. Moreover, the socio-economic burden to healthcare system, of tibia non-unions is significant, reaching over \$50,000 per patient in accumulated costs (direct and indirect costs) [6]. Due to discrepancies in direct and indirect costs reported to the relevant health care systems, however, makes comparative analysis of expenses in different countries difficult to conceive. Nonetheless, in sequence to relieve patients and the community in an equal amount there is a compelling necessity in effective and economic treatment modalities.

The causes of non-unions have been shown to be multifactorial including local conditions, such as fracture morphology (closed versus open, single versus comminuted), local changes in homeostasis such as inadequate blood supply, periosteal stripping, fracture distraction and trauma-associated enveloping soft tissue damage and systemic factors such as infection, smoking or inadequate calorie intake which all may contribute to an unfavourable outcome. Additionally, failure to sufficiently immobilize the fracture is important contributing factor in the development of tibia non-unions [1,7–11].

Given that non-unions typically have lost the endogenous potential to heal without further intervention, many surgical treatment options were introduced to achieve bony union in a timely manner. Available techniques consist of intramedullary nailing, exchange reamed nailing, and compression plating to address fracture stability and autologous bone grafting as an adjunct osteoinductive and -conductive mean. Furthermore, external fixation systems (e.g. Illizarov technique) are feasible treatment options [12]. However, the invasiveness inherent to each surgical intervention potentially complicates healing and therefore may negatively interfere with outcome. In particular, the high incidence of donor site morbidity after autologous bone graft harvesting (e.g. from the iliac crest) considerably affects patients' quality of life [13]. In order to avoid surgical related complications several semi- or non-invasive treatment alternatives were investigated. Recombinant osteogenic growth factors such as bone morphogenetic proteins (BMP) [14–16], low intensity pulsed ultrasound (LIPUS) [17–20] or the application of pulsed electromagnetic fields (PEMF) [20–23] have either shown inconsistent results or an unreasonable cost to benefit ratio.

Extracorporeal shock wave therapy (ESWT) has shown to be a promising approach to successfully treat non-unions (and other musculoskeletal diseases), reaching success rates equal to surgery, but with a significantly better functional short term outcome [2,24–30]. Moreover, ESWT is completely lacking serious adverse events [26,28,30]. Other than the clinical efficacy of extracorporeal shockwave application, extended basic research activities exhibit essential cellular and molecular mechanism potentially involved in ESWT. Via a mechanism known as mechanotransduction [31] shockwaves are transduced into biochemical signals affecting multiple endogenous pathways. To illustrate, ATP triggered ERK1/2 pathway activation improves cell proliferation and wound healing [32,33], and modulation of the inflammatory process via TLR3 [34] and other molecular signals [35,36] seem to accelerate wound healing. Biological responses induced by ESWT include angio- and lymphogenesis [36–43]; recruitment, proliferation and differentiation of endogenous stem cells [42,44–47]; osteogenesis [48–53]. All of these are essentially involved in the initiation of the healing

response, thus implicating ESWT as a highly effective modality due to its multisided target systems.

The main objective of the present research was to further investigate the clinical potential of ESWT in the treatment of tibia non-unions. Here, we conducted a retrospective analysis of a prospective open clinical trial of 56 patients, with 58 eligible fractures (irrespective of the aetiology of the fractures) using success of healing at six months post treatment as the primary outcome.

## Material and methods

We conducted a retrospective multi-variant analysis of an open prospective, single armed clinical study to investigate the effectiveness of ESWT in the treatment of tibial non-unions. The study was approved by the institutional (AUVA) ethical committee, Vienna, Austria.

### Definitions

According to the definition of non-union, in our local institution as well as worldwide recognised agencies including but not limited to The Food and Drug Administration, United States Department of Health and Human Services Technology Assessment of bone growth stimulating devices, non-union is established when a [1] fracture fails to demonstrate cortical continuity despite operative and non-operative interventions for a period of 9 or more months; and, [2] fracture fails to demonstrate any sign of healing on radiographic assessment of the fracture in the following 3 months. According to this definition, a non-union fracture will NOT heal on its own without further therapeutic intervention. In the absence of a more precise definition, we applied the current and generally accepted definition of non-union for this study. Therefore, the inclusion criteria for this study included patients with fractures of the tibia that had failed to respond to any previous treatment for a period exceeding 9 months after trauma, and lacking radiological signs of osseous healing for the following period of 3 months, who were referred to the AUVA-Trauma Center by attending orthopaedic surgeons for consideration of alternative treatment.

The primary endpoint for this study is healing of the tibia non-union at 6 months after enrolment and ESWT. Successful healing was defined clinically as healing with painless full weight bearing and radiologically as re-establishment of cortical continuity of at least 3 of 4 cortices.

### Demographics

During the period of September 2005 to December 2009, 56 patients suffering from 58 tibial non-unions who were referred to the AUVA Trauma Center Meidling, Vienna, Austria, and met the FDA criteria for non-unions and eligibility criteria. Patients provided informed written consent to participate in the study prior to enrollment. Patients of both genders ageing between 15 and 85 years old at the time of initial presentation for ESWT were included in the study. After enrollment, patients received ESWT according to a pre-determined schedule and were followed-up for a minimum period of 6 months.

### Assessment of tibia non-union

All initial fractures occurred as a consequence of non-surgical trauma. Fracture non-union was clinically defined as a painful weight bearing as well as pressure soreness over the fracture. Radiologically, non-unions were characterised by absence of restitution of cortical continuity of at least 3 of 4 cortices. In almost all cases an additional CT-scan was performed to precisely evaluate

the non-union. Taking into account anatomical location of the fracture, tibia non-unions were grouped as metaphyseal or diaphyseal. We radiographically assessed underlying pathophysiological processes correlated with fracture healing, and grouped fractures into one of the three pathological categories: [1] atrophic/oligotrophic, non-union that showed diminished callus formation or osteopenia; [2] hypertrophic, non-unions that had seemingly well perfused, viable bone ends but inadequate mechanical stability; and [3] infected, non-unions that showed signs of infection in either clinical, laboratory or radiologic assessment of the patient.

#### Patient demographics and fracture details

Patient's demographical information such as [1] age, [2] gender, [3] primary presentation, [4] involved tibial segment, [5] number of previous orthopaedic surgeries, [6] presence of external fixators and [7] type of fixation were recorded (Table 1). Additionally, we documented [8] time periods from injury and/or last surgery to ESWT, [9] number of treatments as well as treatment characteristics, [10] *in situ* implants (due to their possible interaction with shockwaves), [11] concomitant interventions, [12] immobilisation and [13] additional measures, such as weight bearing (Table 2).

Patients were followed for a period of 6 months and assessed for complete healing of the tibia non-union, the primary endpoint of

the study. We additionally evaluated effectiveness of the ESWT at intermediate time point 3 months after the first ESWT. Complete healing was assessed on the basis of clinical and radiological data collected during the follow-up.

#### Extracorporeal shockwave treatment

All treatments were conducted under general or regional anaesthesia (spinal block) using the electrohydraulic shockwave device OrthoGold280 (MTS Medical UG, Constance, Germany). Patients were positioned in supine orientation on the operating table. Once anaesthesia was initiated, the extremity was fixated in flexed hip and 90° knee flexion. Visualisation of non-union was done under fluoroscopic projection in the anterior–posterior and lateral view. Thereafter, the non-union gap was marked on the skin with a surgical marker concomitant with the axis of the tibia. ESWT trajectory was selected in a manner that neurovascular structures were out of the focus. Sterile coupling gel (Aquasonic 100; Parker Laboratories, Fairfield, New Jersey) was applied to the marked areas and the therapy head positioned accurately. In cases of complementary surgery the surgical site was draped aseptically. Special care was taken to avoid air bubble formation within the coupling gel to avoid energy losses due to different impedances between air and gel. Correct focusing of the fracture site was confirmed by manually manipulating therapy applicator head. All treatments were performed with an energy flux density of 0.4 mJ/mm<sup>2</sup> (−6 dB), a frequency of 4 Hz, and application of 3000–4000 impulses. Shockwaves were equally applied from at least 2 different directions (range 2–4). In cases of extramedullary implants, ESWT was applied sparing those implants in order to assure full energy delivery at the fracture site. Mean intervention time was 23 ± 8 min. After removal of the residual coupling gel, alterations at the application site were recorded according to the study protocol. During the shockwave treatment and follow-up period, we did not observe any major adverse events related to the treatment and no systemic complications (cardiac, respiratory). No progress of the already established infections due to shockwave treatment and no *de novo* infections attributable to treatment were observed.

#### Post intervention measures

Almost all patients were provided with a plaster cast immobilisation between 4 and 12 weeks after injury along with partial or no weight bearing based on fracture location, stability, tibial axis alignment and presence of infection. In the selected cases where cast immobilisation was not possible (e.g. comorbidities, age, and disorder of contralateral leg) patients were instructed to avoid full weight bearing (completely or partially) for 3–6 weeks. All patients were provided with crutches and received low molecular heparin to prevent potentially thrombo-embolic events due to plaster cast fixation and weight unloading. Patients without concomitant surgery were all discharged one day after ESWT.

#### Statistical analysis

Study relevant data were recorded using study specific data sheets and collected using the Microsoft<sup>®</sup> Office Access 2010 databank software. Data summary and manipulation was performed using Microsoft<sup>®</sup> Office Excel 2010 software (Microsoft Corporation, USA). Final statistical analysis of the data was performed using JMP software (Version, 9.0; SAS Institute Inc., USA). Categorical factors and their associations were studied using Fisher exact test (for small expected values) and Pearson  $\chi^2$  test as

**Table 1**  
Patients demographics, fracture details, and postinterventional measures (continued).

Characteristic	Healed-46 (88.46%)	Not healed-6 (11.54%)	p-Value
Age			
Mean [years]	46 (50.34 ± 14.6)	6 (38.66 ± 6.2)	0.073
Gender			
Male	35 (76.09%)	5 (83.33%)	0.682
Female	11 (23.91%)	1 (16.67%)	
Tibia location			
Methaphysis	13 (28.26%)	3 (50%)	0.357
Diaphysis	33 (71.74%)	3 (50%)	
Fracture type			
Open	20 (43.48%)	5 (83.3%)	0.094
Closed	26 (56.52%)	1 (16.7%)	
Pathology			
Hypertrophic	17 (36.96%)	1 (16.67%)	0.551
Oligo-/a-trophic	14 (30.43%)	2 (33.33%)	
Infected	15 (32.61%)	3 (50.00%)	
Primary immobilisation			
Yes	19 (41.30%)	3 (50.00%)	0.689
No	27 (58.70%)	3 (50.00%)	
Intramedullar stabilisation			
Yes	22 (47.83%)	24 (52.17%)	0.210
No	1 (16.6%)	5 (83.33%)	
Extramedullar stabilisation			
Yes	18 (39.13%)	28 (60.87%)	0.382
No	4 (66.67%)	2 (33.33%)	
External fixator			
Yes	11 (23.91%)	35 (76.09%)	0.632
No	2 (33.33%)	4 (66.67%)	
Cancellous bone			
Yes	6 (13.04%)	3 (50%)	0.057
No	40 (86.96%)	3 (50%)	
No. of cancellous bone grafts			
Mean	46 (0.152 ± 0.06)	6 (0.50 ± 0.17)	0.071
Number of previous orthopaedic operations			
Mean	46 (1.74 ± 1.41)	6 (1.5 ± 0.57)	0.696

**Table 2**  
Patients demographics, fracture details, and post-interventional measures (continued).

Characteristic	Healed – n = 46 (88.46%)	Not healed – n = 6 (11.54%)	p-Value
Time from injury to first ESWT			
Mean [days]	46 (446.24 ± 244.15)	6 (687.667 ± 526.75)	0.057
Time from last orthopaedic surgery to first ESWT			
Mean [days]	46 (355.065 ± 167.38)	6 (836.667 ± 382.98)	<0.0001
Time from injury to last orthopaedic surgery			
Mean [days]	46 (91.17 ± 162.0)	6 (94.5 ± 91.43)	0.424
Number of ESWT <i>cat</i>			
1	32 (69.57%)	3 (50.00%)	0.379
2 and more	14 (31.43%)	3 (50.00%)	
Number of ESWT <i>cont</i>			
Mean	46 (1.45 ± 0.78)	6 (1.5 ± 0.55)	0.896
Hardware <i>in situ</i>			
Yes	36 (78.26%)	3 (50.00%)	0.157
No	10 (21.74%)	3 (50.00%)	
Type of hardware			
Intramedullary nail	12 (33.33%)	0 (0%)	0.723
Plates	5 (13.89%)	1 (33.33%)	
Plate + screws	8 (22.22%)	1 (33.33%)	
Screws	2 (5.56%)	0 (0%)	
Unreamed tibial nail	9 (25.00%)	1 (33.33%)	
Additional surgery			
Yes	7 (13.22%)	0 (0%)	0.580
No	39 (84.78%)	6 (100%)	
Immobilisation			
Yes	29 (63.04%)	5 (83.33%)	0.651
No	17 (36.96%)	1 (16.67%)	
Type of immobilisation after ESWT			
Cast or orthosis up to 6 weeks	20 (41.67%)	2 (50.00%)	0.235
Cast or orthosis 6+ weeks	9 (18.75%)	3 (33.33%)	
None	17 (35.42%)	1 (16.67%)	
Additional measure			
Yes	45 (97.83%)	5 (83.33%)	0.219
No	1 (2.17%)	1 (16.67%)	
Type of additional measure			
No or partial weight bearing up to 3 weeks	16 (34.04%)	2 (40.00%)	0.235
No or partial weight bearing 4+ weeks	30 (63.83%)	2 (40.00%)	
None	1 (2.13%)	1 (20.00%)	

appropriate. For statistical analysis of the continuous variables, we performed analysis of variance. Data are presented as mean  $\pm$  standard deviation (SD). Results were considered statistically significant when the “*p*” value was lower than 0.05 ( $p < 0.05$ ).

## Results

### Demographics

The study population consisted of 56 individuals with 58 eligible fractures that were referred to a single trauma centre (AUVA-Trauma Center Meidling, Vienna). Six patients with six fractures of interest were excluded from further analysis due to incomplete data during the 6 month follow-up, thus analysis of 52 non-unions are presented.

According to the study protocol a minimal lag of nine months (range 272–1702 days) between initial trauma and the first ESWT was applied for the entire study population. Mean time between trauma and ESWT for the analysed patient population was  $474.1 \pm 293.0$  days. Mean time from the last surgical intervention and ESWT was  $410.6 \pm 251.5$  days (range 98–1458 days). The patient population consisted of 76% males and 24% females with a mean age of  $47.7 \pm 15.1$  years (range 16–82 years).

### Non-union analysis

Subgroup analysis of the non-union site revealed that nearly one-third were metaphyseal (30.8%) and the remainder were diaphyseal (69.2%). Two patients suffered from two level fractures in which one patient had 2 fractures at the diaphyseal level and the other bi-level fracture being both meta- and diaphyseal. The distribution of hypertrophic, oligotrophic/atrophic and infected non-unions was almost equal ( $n = 18$ , 34.6%;  $n = 18$ , 34.6%; and  $n = 16$ , 31.8%, respectively).

In cases of osteosynthetic supply previous to ESWT (whether initially at the time of fracture or within a surgical revision surgery) intramedullary stabilisation was present in 23 patients whereas 24 patients had some type of extramedullary stabilisations at the time of shockwave treatment.

### Co-morbidities

In our cohort only 6 patients suffered from diabetes. Interestingly, all of these non-unions resulted in bony consolidation although half of them had to be treated twice. At study inclusion 8 patients reported to smoke. One-third ( $n = 2$ ) of the patients with non-unions which failed to heal after ESWT were smokers ( $p = 0.226$ ). Further relevant co-morbidities found in the

study cohort include hypertension, coronary heart disease ( $\pm$  stent implantation), cardiac infarction, osteoporosis, peroneal nerve lesion, and cortisol therapy due to either peripheral chronic polyarthritis (PCP) or chronic bronchial asthma. However, only the long-term cortisol treatment in a patient suffering from PCP resulted in a refractory non-union whereas all others showed healing in response to ESWT.

#### *Surgical interventions and extracorporeal shockwave treatment*

Patients were referred to ESWT because they failed to respond to either surgical or non-surgical (conservative) standard orthopaedic treatment. Only 9.6% ( $n = 5$ ) of the fresh fractures were treated conservatively and had no further surgical intervention until presentation to ESWT. The vast majority ( $n = 47$ ; 90%) of the patient population had one ( $n = 25$ ) or more previous orthopaedic surgeries (mean  $1.9 \pm 1.3$ ; range 1–7) prior to ESWT. In fact, 12 patients had one, 5 received two, and 3 were subjected to 3 revisional surgeries. One patient even ended up in 5 and another one in 6 surgical interventions beforehand ESWT. Interestingly, only 42% were initially instructed to immobilize the affected limb. According to our compiled medical history, 10 patients had additional surgery previous to ESWT during the consecutive follow-up after trauma, being flap surgery in 4 cases, osteotomy of the fibula in 2 patients, and dynamisation, negative pressure wound therapy, implantation of antimicrobial beads and arthroscopy in one case each.

Fractures with concomitant soft tissue trauma (open fractures) were initially present in 21 cases (40.4%) graded from I to III according to the classification of Gustilo and Anderson [54]. The relatively low healing rate 80.9% ( $n = 17$ ) of this sub-category at 6 months after ESWT generally reflects the challenging management of open tibial fractures. This result becomes even clearer looking at the 5 initially open fracture cases ending up in persistent non-union (out of 6) despite ESWT.

Three quarters of patients ( $n = 39$ ) had some type of implant *in situ* during shockwave treatment. Of those, 56.4% ( $n = 22$ ) had an intramedullary nail, 35.9% ( $n = 14$ ) had plates and screws, 5.1% ( $n = 2$ ) had screws only, and one fracture (2.6%) was treated with Prevot nails which was additionally stabilised with a plate.

The majority of patients ( $n = 35$  corresponding to 67.3%) received only one ESWT. Of those patients who received multiple shockwave treatments (17 patients; 32.7%), 62.5% ( $n = 11$ ) were treated twice, 31.3% ( $n = 5$ ) underwent ESWT three times and one patient (6.2%) received four treatments. Non-unions which were treated more than once were diagnosed not healed after 6 months following ESWT by X-ray or/and CT scan. In most cases these patients refused a surgical revision and were therefore offered a further ESWT. Patients who received 2 treatments still showed healing in 73% ( $n = 8$ ), and those receiving 3 or 4 treatments healed in 100% clearly showing the feasibility and efficacy of multiple applications.

Concomitant with ESWT, seven patients (13.5%) had additional surgery related to the same limb at the same time, predominantly dynamisation of the intramedullary nail achieved by selective screw removal. In all cases, surgery was done prior to ESWT and the wound was covered with a sterile drape (Opsite, Smith & Nephew, Hamburg, Germany). Thereafter, sterile gel was administered on top of the drape and extracorporeal shockwave treatment was performed in the same manner as in the other cases without additional surgery. No further intervention except immobilisation was implemented.

Once extracorporeal shockwave therapy was completed, 65.4% of all patients ( $n = 34$ ) were provided with a plaster cast from 4 to 12 weeks with weight unloading for a minimum of 3 weeks (range 3–6 weeks). The residuary part was introduced for either no weight

bearing between 3 and 6 weeks ( $n = 15$ ; 28.8%) or partial loading for 4 weeks ( $n = 3$ ; 5.8%).

#### *Healing rate*

The primary goal of the conducted study was to evaluate success of the ESWT to induce healing in the tibial non-unions. Clinical and radiological evaluation of shockwave treated non-unions 3 months following ESWT revealed that already at 3 months after ESWT, 71.1% of the fractures showed signs of bony healing. Contrary to them, 23.1% were judged as not healed and 5.8% demonstrated inconclusive radiological appearance, hence categorised as uncertain at this time point. However, examination of the treated non-unions 6 months after ESWT evidenced successful healing in 88.5% (46 patients) (Fig. 1). Interestingly, 7 non-unions previously (3 months) ascertained as not healed progressed to healed fracture at the 6 months follow up. All 3 non-unions categorised as uncertain at 3 months after inclusion achieved bony consolidation 6 months following ESWT.

Regarding the different etiologies analyses showed a comparable distribution in numbers of healed *versus* not healed tibial non-unions irrespective of the underlying aetiology. Hypertrophic non-unions healed in 94% following ESWT whereas 87% oligo-/atrophic non-unions and 83% of infected non-unions completely healed.

One way analysis of variance showed marginal statistically significant differences ( $p = 0.056$ ) in mean number of days between trauma and ESWT between patients with positive and negative outcome,  $446.2 \pm 244.2$  and  $687.7 \pm 526.8$ , respectively. Importantly, we found strong statistical correlation between healing outcome and time period between last surgery and date of first ESWT. Mean number of days for patients that showed complete healing was  $355.1 \pm 167.4$  and  $836.7 \pm 383.0$  for patients who did not heal after 6 months follow up ( $p < 0.0001$ ).

Surprisingly, prior autologous cancellous bone grafting had a significant negative impact on the success of ESWT. Even though this result reached statistical significance, interpretation of these results has to be done with caution due to the small number of patients (from the entire patient population, only 17.3% ( $n = 9$  patients) had cancellous bone grafting).

#### **Discussion**

The primary objective of our study was to evaluate efficacy of extracorporeal shockwave treatment in tibia non-unions six months after conduction. Our results show that complete, full weight bearing with no pain was achieved in 88.5% of the patients who initially failed to respond to one or more previous surgical and non-surgical interventions. Importantly, herein we found strong correlation between the timing of application and complete fracture healing suggesting that ESWT should be applied earlier in the treatment schedule in order to achieve shorter healing time and faster return to normal everyday activities of the patients.

Surgical treatment, can reach a healing rate of up to 86–94% [29]. However, surgical interventions are accompanied with inherent risk of infection and surgical complications that can affect ultimate goal, complete healing. Therefore, any treatment should be at least in the same range of efficacy to prove its efficacy and to have better risk-to-benefit ratio in order to be competitive with the revisional surgery.

The current literature, comparing ESWT with surgical treatment shows an equivalent outcome between the two methods yet exhibiting less short term complications in the ESWT groups [55]. In accordance to that, our present study revealed no major side effects of the treatment and patients tolerated ESWT well. If no other intervention was needed, patients left our clinic the following day, giving ESWT advantage over the other treatment



**Fig. 1.** A 47-year-old male who was injured during work by a truck and suffered from a polytrauma including a 3rd degree open 2 level fracture of the left tibia (A). He was initially treated with an intramedullary nail (B) as well as wound revision followed by negative pressure wound therapy. Wound was then covered by a meshed autologous split thickness skin graft. Mobilisation was performed with partial weight bearing initially when full weight bearing. The radiological FU revealed delayed osseous healing on both levels and dynamisation was performed (C). While the distal fracture healed the proximal fracture persisted over 9 months (D). ESWT was performed accompanied with no weight bearing for 6 weeks. The FU X-rays showed progressive healing of the proximal non-union with bony consolidation 6 month after ESWT (E).

options in terms of hospital stay and associated costs, as well as lower risk to benefit ratio. We achieved a healing rate of 88.5% excluding six patients lost to follow-up. If these six patients were included in the study as not healed, we would still have achieved a high healing rate of 79.3%, matching the results of surgical intervention. Previously published studies using ESWT in non-unions, achieved a healing rate ranging from 52% to 91% [2,26,28,56,57]. We have also recently shown that ESWT is a feasible method to treat tibial non-unions as complete healing was evident in 80.2% (138/172 non-unions) [2].

Three months after ESWT, our healing rate already reached 71.1%. Another 23.1% of fractures were judged as not healed and 5.8% were considered uncertain at this time point. Beutler et al. [58], pointed out that 3 months follow up will be sufficient to conclude success of ESWT and in case of failure at three month only little time is lost for further treatment including revision surgery. As in our study the healing rate increased with further follow-up, we strongly believe in a follow-up of six months to finally determine osseous healing.

According to the definition of Weber and Czech [59] we also differentiated between atrophic/oligotrophic and hypertrophic non-unions. Generally, atrophic non-unions perform worse [60,56], acknowledging the caveat that atrophic/avascular non-union might not be avascular, as shown by Reed [61]. Furthermore, infections are a major contributor to delayed and non-healing of tibial fractures. Interestingly, in our patient population, we saw no significant difference in outcome among the currently differentiated types of non-union (atrophic/oligotrophic, hypertrophic and infected). Our results suggest that classification and identification of these subtypes, which is clinically challenging, might be unnecessary for ESWT. Our results are supported by the experimental results of Gollwitzer et al. [65] showing bactericidal effects of ESWT in the rabbit model of osteomyelitis. However, effects of the ESWT on the

infected fractures/wounds are yet to be fully elucidated. In general, the diaphysis is more prone to develop a non-union than the metaphysis, which can be confirmed in our patient population (81.25% in the metaphysis and 91.66% in the diaphysis). Regardless of the fracture location, application of the ESWT showed equal success rate.

According to our data there was generally no association between number of preceding surgeries, as a potential predictor of severe cases of non-unions and ultimate outcome of the fracture and ESWT. However, we did observe strong statistical correlation between time of ESWT application and last surgical procedure. In the patients that received ESWT within one year after the last surgery we observed a 100% healing rate (data not shown). Therefore we conclude that a longer period between surgical intervention and ESWT, negatively affects osseous healing after ESWT.

The ESWT is not the only minimal invasive therapeutic option available to treat non-unions. Peer-reviewed publications exist for low-intensity pulsed ultrasound (LIPUS) and pulsed electromagnetic field therapy (PEMF). While Gryphon et al. in a Cochrane review reported some beneficial effects of PEMF [62], other studies, investigating LIPUS in non-unions, reported healing rates of up to 75% with an average ultrasound treatment duration for all treated cases of 188 days (ranging from 52 to 739 days) applied once daily for 20 min [63,64] comparing to a 89% healing rate in our study. In contrast to PEMF and LIPUS, ESWT is only applied once in most of the cases with more favourable success rates, probably due to better patient compliance. The long treatment schedule of LIPUS and PEMF significantly affects their feasibility, as it requires far more adherence and significantly affects patient's everyday activities. In contrast 66% ( $n = 38/58$ ) of our study population received only one ESWT, 22% ( $n = 13/58$ ) where treated twice, 10% ( $n = 6/58$ ) three times and 2% ( $n = 1/58$ ) four times, including the

six patients lost to follow up. Xu et al. [56] concluded that a second ESWT is not indicated if there is no radiological evidence towards osseous healing unless there are contraindications for surgery. Our own data only partially supports this, showing a 60% healing rate after a single ESWT, yet cases with multiple ESWT's (29%) still showed osseous healing even after several months after primary ESWT application. Looking closely at our results this might also be a reason for multiple prior operations, since we saw some correlation between the number of operations and the number of applied ESWT.

Limitation to the current, and all other studies concerning non-union, is its actual definition. Although not uniformly agreed on, our use of the 9-month criterion for defining non-union was based on several factors. The local treatment practice guidelines in the standardised healthcare system in Austria limit the non-operative management of non-union to 6 months, therefore limiting our referral population to this time point. In addition, the 9-month definition of non-union has been adopted by some regulatory bodies and provides further substantiation of the 9-month defining threshold used by our group. Finally, as a result of the nature of our referral population, the antecedent treatment course was not controlled for but followed national standards of practice focused on surgical intervention and/or immobilisation of the long-bone non-union.

Other limitations of this study include those inherent to retrospective, non-randomised study designs; however, its primary limitation is the lack of a control group to distinguish the effect of immobilisation from the shock wave treatment itself. Due to the retrospective nature of the study is the loss of 6 patients to follow-up. Although these patients were demographically similar to the remaining 52 patients, bias can be introduced in the statistical analysis, bias that might be avoided by a prospective study design. In order to overcome some of the limitations of this study, mainly its retrospective design, we are currently conducting another, open, prospective clinical trial. We do recognize limitations of this study design; however, it is our opinion a control group with no further treatment is unethical and therefore not included.

In the current peer-reviewed literature there is no consensus concerning treatment parameters such as energy flux densities, different devices, applications and frequencies to treat musculoskeletal disorders, making it difficult to draw correlations between different studies and ultimately to compare success rates of ESWT for particular indications. Essentially, there is an urgent need for generally accepted guidelines for ESWT in various indications to allow better comparison of studies.

In conclusion, extracorporeal shockwave therapy is effective, safe, with virtually no negative side effects for the treatment of tibial non-unions. It is equally successful to surgical revision regardless of the underlying pathophysiological processes or location. It is a non-invasive, well tolerated treatment option for patients suffering tibial non-unions, which is easy to perform, inexpensive to use and virtually does not affect patient's everyday activities. Based on our findings we would strongly recommend ESWT application even before non-union has fully developed according to the used definition.

## Conflicts of interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or

professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

## Author contribution

RM, WS, VA, and AS worked out the concept and design of the study. NH, DS, PS, and RM performed data processing and analysis. VA and AS carried out the statistical analysis. NH, DS, PS, and RM wrote the manuscript which was proof-read and revised by WS, VA, and AS. All authors have read and approved the final manuscript.

## References

- [1] Phieffer LS, Goulet JA. Delayed unions of the tibia. *J Bone Joint Surg Am* 2006;88(1):206–16.
- [2] Elster EA, Stojadinovic A, Forsberg J, Shawen S, Andersen RC, Schaden W. Extracorporeal shock wave therapy for nonunion of the tibia. *J Orthop Trauma* 2010;24(3):133–41.
- [3] Court-Brown CM, Rimmer S, Prakash U, McQueen MM. The epidemiology of open long bone fractures. *Injury* 1998;29(7):529–34.
- [4] Chua W, Murphy D, Siow W, Kagda F, Thambiah J. Epidemiological analysis of outcomes in 323 open tibial diaphyseal fractures: a nine-year experience. *Singap Med J* 2012;53(6):385–9.
- [5] Taylor JC. Delayed union and nonunion of fractures, vol. 8. 1992;p. 1287–345.
- [6] Antonova E, Le TK, Burge R, Mershon J. Tibia shaft fractures: costly burden of nonunions. *BMC Musculoskelet Disord* 2013;14:42.
- [7] Connolly JF. Common avoidable problems in nonunions. *Clin Orthop Relat Res* 1985;194:226–35.
- [8] Smith TK. Prevention of complications in orthopedic surgery secondary to nutritional depletion. *Clin Orthop Relat Res* 1987;222:91–7.
- [9] Schmitz MA, Finnegan M, Natarajan R, Champine J. Effect of smoking on tibial shaft fracture healing. *Clin Orthop Relat Res* 1999;365:184–200.
- [10] Cierny III G, Byrd HS, Jones RE. Primary versus delayed soft tissue coverage for severe open tibial fractures. A comparison of results. *Clin Orthop Relat Res* 1983;178:54–63.
- [11] Adams CI, Keating JF, Court-Brown CM. Cigarette smoking and open tibial fractures. *Injury* 2001;32(1):61–5.
- [12] Hak DJ. Management of aseptic tibial nonunion. *J Am Acad Orthop Surg* 2011;19(9):563–73.
- [13] Becker ST, Warnke PH, Behrens E, Wiltfang J. Morbidity after iliac crest bone graft harvesting over an anterior versus posterior approach. *J Oral Maxillofac Surg* 2011;69(1):48–53.
- [14] Kanakaris NK, Calori GM, Verdonk R, Burssens P, De BP, Capanna R, et al. Application of BMP-7 to tibial non-unions: a 3-year multicenter experience. *Injury* 2008;39(Suppl. 2):S83–90.
- [15] Pecina M, Haspl M, Jelic M, Vukicevic S. Repair of a resistant tibial non-union with a recombinant bone morphogenetic protein-7 (rh-BMP-7). *Int Orthop* 2003;27(5):320–1.
- [16] Kanakaris NK, Paliobeis C, Nlanidakis N, Giannoudis PV. Biological enhancement of tibial diaphyseal aseptic non-unions: the efficacy of autologous bone grafting, BMPs and reaming by-products. *Injury* 2007;38(Suppl. 2):S65–75.
- [17] Nolte PA, van der KA, Patka P, Janssen IM, Ryaby JP, Albers GH. Low-intensity pulsed ultrasound in the treatment of nonunions. *J Trauma* 2001;51(4):693–702.
- [18] Gebauer D, Mayr E, Orthner E, Ryaby JP. Low-intensity pulsed ultrasound: effects on nonunions. *Ultrasound Med Biol* 2005;31(10):1391–402.
- [19] Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. *J Bone Joint Surg Am* 1994;76(1):26–34.
- [20] Nelson FR, Brighton CT, Ryaby J, Simon BJ, Nielson JH, Lorich DG, et al. Use of physical forces in bone healing. *J Am Acad Orthop Surg* 2003;11(5):344–54.
- [21] Heckman JD, Ingram AJ, Loyd RD, Luck Jr JV, Mayer PW. Nonunion treatment with pulsed electromagnetic fields. *Clin Orthop Relat Res* 1981;161:58–66.
- [22] Garland DE, Moses B, Salyer W. Long-term follow-up of fracture nonunions treated with PEMFs. *Contemp Orthop* 1991;22(3):295–302.
- [23] Delima DF, Tanna DD. Role of pulsed electromagnetic fields in recalcitrant non-unions. *J Postgrad Med* 1989;35(1):43–8.
- [24] Wang CJ. Extracorporeal shockwave therapy in musculoskeletal disorders. *J Orthop Surg Res* 2012;7:11.
- [25] Wang CJ, Chen HS, Chen CE, Yang KD. Treatment of nonunions of long bone fractures with shock waves. *Clin Orthop Relat Res* 2001;387:95–101.
- [26] Furia JP, Juliano PJ, Wade AM, Schaden W, Mittermayr R. Shock wave therapy compared with intramedullary screw fixation for nonunion of proximal fifth metatarsal metaphyseal–diaphyseal fractures. *J Bone Joint Surg Am* 2010;92(4):846–54.
- [27] Furia JP, Rompe JD, Cacchio A, Maffulli N. Shock wave therapy as a treatment of nonunions, avascular necrosis, and delayed healing of stress fractures. *Foot Ankle Clin* 2010;15(4):651–62.
- [28] Cacchio A, Giordano L, Colafarina O, Rompe JD, Tavernese E, Ioppolo F, et al. Extracorporeal shock-wave therapy compared with surgery for hypertrophic long-bone nonunions. *J Bone Joint Surg Am* 2009;91(11):2589–97.

- [29] Birnbaum K, Wirtz DC, Siebert CH, Heller KD. Use of extracorporeal shock-wave therapy (ESWT) in the treatment of non-unions. A review of the literature. *Arch Orthop Trauma Surg* 2002;122(6):324–30.
- [30] Schaden W, Fischer A, Sailler A. Extracorporeal shock wave therapy of non-union or delayed osseous union. *Clin Orthop Relat Res* 2001;387:90–4.
- [31] Huang C, Holfeld J, Schaden W, Orgill D, Ogawa R. Mechanotherapy: revisiting physical therapy and recruiting mechanobiology for a new era in medicine. *Trends Mol Med* 2013;19(9):555–64.
- [32] Weihs AM, Fuchs C, Teuschl AH, Hartinger J, Slezak P, Mittermayr R, et al. Shock wave treatment enhances cell proliferation and improves wound healing by ATP release-coupled extracellular signal-regulated kinase (ERK) activation. *J Biol Chem* 2014;289(39):27090–104.
- [33] Yu T, Junger WG, Yuan C, Jin A, Zhao Y, Zheng X, et al. Shockwaves increase T-cell proliferation and IL-2 expression through ATP release, P2X7 receptors, and FAK activation. *Am J Physiol Cell Physiol* 2010;298(3):C457–64.
- [34] Holfeld J, Tepekoylu C, Kozaryn R, Urbschat A, Zacharowski K, Grimm M, et al. Shockwave therapy differentially stimulates endothelial cells: implications on the control of inflammation via toll-like receptor 3. *Inflammation* 2014;37(1):65–70.
- [35] Davis TA, Stojadinovic A, Anam K, Amare M, Naik S, Peoples GE, et al. Extracorporeal shock wave therapy suppresses the early proinflammatory immune response to a severe cutaneous burn injury. *Int Wound J* 2009;6(1):11–21.
- [36] Stojadinovic A, Elster EA, Anam K, Tadaki D, Amare M, Zins S, et al. Angiogenic response to extracorporeal shock wave treatment in murine skin isografts. *Angiogenesis* 2008;11(4):369–80.
- [37] Nishida T, Shimokawa H, Oi K, Tatewaki H, Uwatoku T, Abe K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. *Circulation* 2004;110(19):3055–61.
- [38] Zimpfer D, Aharinejad S, Holfeld J, Thomas A, Dumfarth J, Rosenhek R, et al. Direct epicardial shock wave therapy improves ventricular function and induces angiogenesis in ischemic heart failure. *J Thorac Cardiovasc Surg* 2009;137(4):963–70.
- [39] Mittermayr R, Hartinger J, Antonic V, Meinel A, Pfeifer S, Stojadinovic A, et al. Extracorporeal shock wave therapy (ESWT) minimizes ischemic tissue necrosis irrespective of application time and promotes tissue revascularization by stimulating angiogenesis. *Ann Surg* 2011;253(5):1024–32.
- [40] Mittermayr R, Antonic V, Hartinger J, Kaufmann H, Redl H, Teot L, et al. Extracorporeal shock wave therapy (ESWT) for wound healing: technology, mechanisms, and clinical efficacy. *Wound Repair Regen* 2012;20(4):456–65.
- [41] Ha CH, Kim S, Chung J, An SH, Kwon K. Extracorporeal shock wave stimulates expression of the angiogenic genes via mechanosensory complex in endothelial cells: mimetic effect of fluid shear stress in endothelial cells. *Int J Cardiol* 2013;168(4):4168–77.
- [42] Tepekoylu C, Wang FS, Kozaryn R, brecht-Schgoer K, Theurl M, Schaden W, et al. Shock wave treatment induces angiogenesis and mobilizes endogenous CD31/CD34-positive endothelial cells in a hindlimb ischemia model: implications for angiogenesis and vasculogenesis. *J Thorac Cardiovasc Surg* 2013;146(4):971–8.
- [43] Kim IG, Lee JY, Lee DS, Kwon JY, Hwang JH. Extracorporeal shock wave therapy combined with vascular endothelial growth factor-C hydrogel for lymphangiogenesis. *J Vasc Res* 2013;50(2):124–33.
- [44] Zhao Y, Wang J, Wang M, Sun P, Chen J, Jin X, et al. Activation of bone marrow-derived mesenchymal stromal cells – a new mechanism of defocused low-energy shock wave in regenerative medicine. *Cytotherapy* 2013;15(12):1449–57.
- [45] Schuh CM, Heher P, Weihs AM, Banerjee A, Fuchs C, Gabriel C, et al. In vitro extracorporeal shock wave treatment enhances stemness and preserves multipotency of rat and human adipose-derived stem cells. *Cytotherapy* 2014.
- [46] Aicher A, Heeschen C, Sasaki K, Urbich C, Zeiher AM, Dimmeler S. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia. *Circulation* 2006;114(25):2823–30.
- [47] Suhr F, Delhase Y, Bungartz G, Schmidt A, Pfannkuche K, Bloch W. Cell biological effects of mechanical stimulations generated by focused extracorporeal shock wave applications on cultured human bone marrow stromal cells. *Stem Cell Res* 2013;11(2):951–64.
- [48] Kearney CJ, Hsu HP, Spector M. The use of extracorporeal shock wave-stimulated periosteal cells for orthotopic bone generation. *Tissue Eng Part A* 2012;18(13–14):1500–8.
- [49] Moretti B, Notarnicola A, Moretti L, Patella S, Tato I, Patella V. Bone healing induced by ESWT. *Clin Cases Miner Bone Metab* 2009;6(2):155–8.
- [50] Tamma R, dell'Endice S, Notarnicola A, Moretti L, Patella S, Patella V, et al. Extracorporeal shock waves stimulate osteoblast activities. *Ultrasound Med Biol* 2009;35(12):2093–100.
- [51] Sun D, Junger WG, Yuan C, Zhang W, Bao Y, Qin D, et al. Shockwaves induce osteogenic differentiation of human mesenchymal stem cells through ATP release and activation of P2X7 receptors. *Stem Cells* 2013;31(6):1170–80.
- [52] Wang CJ, Yang YJ, Huang CC. The effects of shockwave on systemic concentrations of nitric oxide level, angiogenesis and osteogenesis factors in hip necrosis. *Rheumatol Int* 2011;31(7):871–7.
- [53] Yin TC, Wang CJ, Yang KD, Wang FS, Sun YC. Shockwaves enhance the osteogenic gene expression in marrow stromal cells from hips with osteonecrosis. *Chang Gung Med J* 2011;34(4):367–74.
- [54] Gustilo RB, Merkow RL, Templeman D. The management of open fractures. *J Bone Joint Surg Am* 1990;72(2):299–304.
- [55] Schaden W, Mittermayr R, Haffner N, Smolen D, Gerdesmeyer L, Wang CJ. Extracorporeal shockwave therapy (ESWT) – first choice treatment of fracture non-unions. *Int J Surg* 2015;24(Pt B):179–83.
- [56] Xu ZH, Jiang Q, Chen DY, Xiong J, Shi DQ, Yuan T, et al. Extracorporeal shock wave treatment in nonunions of long bone fractures. *Int Orthop* 2009;33(3):789–93.
- [57] Wang CJ, Yang KD, Ko JY, Huang CC, Huang HY, Wang FS. The effects of shockwave on bone healing and systemic concentrations of nitric oxide (NO), TGF-beta1, VEGF and BMP-2 in long bone non-unions. *Nitric Oxide* 2009;20(4):298–303.
- [58] Beutler S, Regel G, Pape HC, Machtens S, Weinberg AM, Kreimeke I, et al. [Extracorporeal shock wave therapy for delayed union of long bone fractures – preliminary results of a prospective cohort study]. *Unfallchirurg* 1999;102(11):839–47.
- [59] Weber BG, Cech O. Pseudarthrosis: pathology, biomechanics, therapy, results; 1976.
- [60] Vulpiani MC, Vetrano M, Conforti F, Minutolo L, Trischitta D, Furia JP, et al. Effects of extracorporeal shock wave therapy on fracture nonunions. *Am J Orthop (Belle Mead NJ)* 2012;41(9):E122–7.
- [61] Reed AA, Joyner CJ, Brownlow HC, Simpson AH. Human atrophic fracture non-unions are not avascular. *J Orthop Res* 2002;20(3):593–9.
- [62] Griffin XL, Costa ML, Parsons N, Smith N. Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults. *Cochrane Database Syst Rev* 2011;4. CD008471.
- [63] Jingushi S, Mizuno K, Matsushita T, Itoman M. Low-intensity pulsed ultrasound treatment for postoperative delayed union or nonunion of long bone fractures. *J Orthop Sci* 2007;12(1):35–41.
- [64] Rutten S, Nolte PA, Korstjens CM, van Duin MA, Klein-Nulend J. Low-intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula. *Bone* 2008;43(2):348–54.
- [65] Gollwitzer H, Roessner M, Langer R, Gloeck T, Diehl P, Horn C, et al. Safety and effectiveness of extracorporeal shockwave therapy: results of a rabbit model of chronic osteomyelitis. *Ultrasound Med Biol* 2009;35(4):595–602.