An Original Study

Effects of Extracorporeal Shock Wave Therapy on Fracture Nonunions

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Abstract
The purpose of this study was to examine the effect of focused extracorporeal shock wave therapy (ESWT) on the treatment of nonunions. As part of a prospective study, we included 143 patients (average age, 41.4 years) with a diagnosis of nonunion (mean, 14.1 months; range, 6-84 months). High-energy shock wave treatment was applied using electromagnetic shock wave generators. The shock waves were applied in 3-5 sessions of 2500 to 3000 impulses each given at 0.25-0.84 mJ/mm^2, at intervals of 48-72 hours between sessions. A maximum of 3 cycles of treatment was given, at 3-month intervals. The patients were followed during a 12-month period until fracture healing or, in case of failure, until another therapy was adopted. Complete healing was observed in 80 of 143 cases (55.9%) at an average time of 7.6 months (range, 2-24 months). Partial healing occurred in 41 cases (28.7%) and no healing was observed in 22 cases (15.4%). Patients with trophic nonunions had a better success rate than patients with atrophic nonunions (*P*<.05). The results show ESWT is a safe and effective treatment for nonunions. ESWT is more effective for trophic nonunions than atrophic nonunions.

Delayed unions and nonunions of fractures are not uncommon. Management can be challenging. Both nonoperative and operative measures can be used to treat delayed unions and nonunions. The former usually involves prolonged immobilization in some type of cast or orthotic device. Low intensity pulsed ultrasound and pulsed electromagnetic fields have been reported to be effective treatments for these conditions.[1-3] Unfortunately, these techniques usually require time-consuming, daily treatment sessions, and for that reason are often poorly tolerated in the clinical setting.

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Surgical treatment remains the gold standard for treating delayed unions and nonunions. Success rates range from 80% to 95%.[4] Surgery usually entails some type of fracture site debridement, application of bone graft and/or growth factors followed by internal or external fixation. Although effective, surgery is invasive, expensive, and may be associated with significant morbidity. Time away from work and sport can vary and is usually significant.

With the advent of better devices and the desire for a less invasive approach, extracorporeal shock wave therapy (ESWT) has become another treatment for fracture nonunions. Basic scientific studies have suggested that ESWT has an osteogenic effect on treated bone and may potentiate fracture healing.[5-26] There are several clinical trials that support the use of ESWT as a method of treating delayed and nonunions.[27-39]

The purpose of this prospective trial was to examine the effect of ESWT on the treatment of nonunions.

Materials and Methods

This was a prospective cohort study and Institutional Review Board approval was obtained. Inclusion of patients was discussed with the local Ethical Committee and a randomized placebo-controlled study was not permitted.

Between January 2000 and September 2007, all patients with an established nonunion fracture who were treated at a tertiary referral center, where ESWT is typically performed, were considered for inclusion in this study. Patients were specifically referred and considered for the ESWT procedure. The ESWT procedures were performed by 1 of 5 staff physicians after written informed consent for the procedure was obtained. All of the physicians involved are qualified to administer ESWT treatment.

For the purposes of this trial, a nonunion was defined as a fracture that did not demonstrate cortical continuity on radiographs despite operative or nonoperative intervention for 6 months. Not all patients were treated operatively before the nonunion occurred. Nonunions were classified according to their radiographic appearance as trophic-hypertrophic (ie, abundant callus on radiographs but with apparent instability), oligotrophic (little callus), or atrophic (ie, no or little callus and resorption of the bone).[40]

Patients with an established nonunion fracture, who were treated with ESWT during the study period, were included in the study. Exclusion criteria included open

Figure 1. (A) Radiograph of the right scaphoid bone of a 22-year-old man showing nonunited fracture 8 months after the fracture. (B) Radiograph of the same scaphoid bone taken 6 months after shock wave treatment.

or neoplastic fractures, local infection, proximity to epiphyseal growth plate, a bone gap more than 0.5 cm, grossly unstable situations, and the presence of fixation devices in the fracture site which would interfere with the x-ray localization. Patients who were pregnant, had cardiac pacemakers, or were receiving anticoagulants or immunosuppressive therapy were also excluded. Overall, 18 patients were excluded from the study because they met exclusion criteria (3 neoplastic fractures, 5 local infections, 4 excessive cortical gaps, 3 unstable situations, 1 pregnant patient) or were unwilling to participate (n = 2).

There were 143 patients, 92 males and 51 females, with an average age of 41.4 years (range, 14-81 years) enrolled in the trial, including 143 nonunions (mean 14.1 months; range 6-84 months). There were 15 hypertrophic (10.5%), 104 oligotrophic (72.7%), and 24 atrophic (16.8%) nonunions. The distribution of bones involved is summarized in Table I.

All patients had a preoperative evaluation that included a complete medical history, a history of the present illness and a focused physical examination. All patients had anteroposterior, lateral and oblique radiographs performed at the initial evaluation. Magnetic resonance imaging, tomographic and scintigraphic studies were performed on a case-by-case basis (Table II).

Table I. Distribution of Bones Treated

Bones	No. (%)
Clavicle	6 (4.1)
Femur	24 (16.8)
Fibula	7 (4.9)
Humerus	25 (17.5)
Metatarsus	5 (3.5)
Radius	7 (4.9)
Scaphoid	17 (11.9)
Tibia	39 (27.3)
Ulna	13 (9.1)
Total	143

The shock wave treatment was applied using an electromagnetic shock wave generator (STORZ MEDICAL AG, Tägerwilen, Switzerland), with a penetration depth between 0 and 150 mm, and a focus diameter of 4 mm. Only procedures performed for scaphoid nonunions were conducted using local anesthesia. All other ESWT procedures were performed without general or regional anesthesia. The procedure is reasonably well tolerated due to the characteristics of the device and to the protocol followed.

Shock waves were constantly focused on the fracture gap and on the adjacent cortical structures with x-ray localization and in-line ultrasound. The total number of shocks was divided equally along the proximal and distal margins of the nonunion. If shock wave-altering implants (soundproof material) was present at the fracture point, the shock wave direction was selected in such a way that the implants did not shield the energy from the fracture site.

Each treatment cycle included 3 to 5 sessions with 2500 to 3000 impulses each given at 0.25-0.84 mJ/mm^2, at intervals of 48-72 hours between sessions. The number of shock waves and the power at the focus point varied according to the bones involved and to the type of nonunion. Lower energy protocols were used for short bones while higher protocols were reserved to long or multiple bones, or more severe fractures. A maximum of 3 cycles of treatment was given, at 3-month intervals. Another cycle of treatment was prescribed in those patients in whom complete healing was not achieved in the first and second follow-up evaluations. Ninety-six patients received 1 cycle of treatment, 39 patients received 2 cycles, and 8 patients received 3 cycles.

After ESWT treatment, in those cases where osteosynthesis devices were absent or provided inadequate fracture fixation, immobilization was required to achieve the full stabilization of nonunion. Immobilization was then used in 77 patients (25 cases with plaster cast and 52 cases with splints). Partial and progressive weight-

Table II. Pretreatment Diagnostic Imaging Procedures

Diagnostic Procedures	Hypertrophic Nonunion (15)	Oligotrophic Nonunion (104)	Atrophic Nonunion (24)
X-ray, no. (%)	15 (100)	104 (100)	24 (100)
MRI, no. (%)	2 (13.3)	61 (58.6)	-
TC Scan, no. (%)	4 (23.7)	23 (22.1)	12 (50)
Bone Schintigraphy, no. (%)	-	37 (35.6)	19 (79.2)

bearing with crutches was prescribed for patients with fractures of the lower extremities and a sling to support fractures of the upper extremities. The immobilization time was selected individually, depending on the type and localization of the fracture, and varied from 4 to 8 weeks. Sixty-six patients with stable fractures, with or without internal fixation, received no additional external immobilization.

The patients were followed-up for 12 months until fracture healing or, in case it did not heal, until another therapy was adopted. All post-procedure radiographs were assessed by a different, independent orthopaedic surgeon. A nonunion was deemed healed when 4 cortices (2 on the anteroposterior radiograph and 2 on the lateral radiograph) were bridged or if no gap could be detected using conventional tomography.[33] After review of the post-procedure radiographs, fractures were determined to be either completely healed (ie, bridging callus on 4 cortices), partially healed (ie, incomplete bone callus formation, not requiring further treatment) or not healed.

The statistical analysis was performed with the Student's t-test and Mann-Whitney U test using SPSS 15.0 software package, with $P<.05$ statistical significance.

Results

The distribution of the bones treated is summarized in Table I. The mean age, duration of symptoms and length of follow-up for the entire group were 41.4 years (range, 14-81; standard deviation [SD], 15.4), 14.1 months (range, 6-84; SD, 12.9), and 8.9 months (range, 3-12; SD, 2.7) respectively.

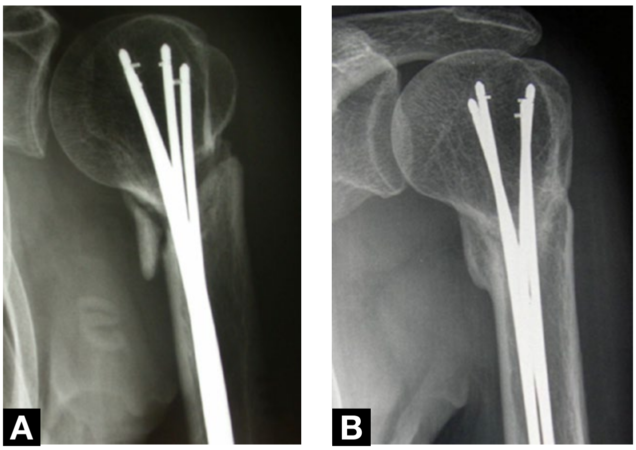

Figure 2. (A) Radiograph of the left humerus of a 46-year-old female showing nonunited fracture 7 months after the fracture. (B) Radiograph of the same humerus taken 7 months after shock wave treatment.

Table III summarizes the number of fractures healed at 3, 6, 9, and 12 months after treatment. Figure 3 represents a flow chart of the trial until the last follow-up at 12 months from baseline.

The data as reported in Table III show that during the 12 months follow-up period, for the entire cohort, 80 of the 143 nonunions (55.9%) ultimately healed after ESWT at an average time of 7.6 months (range, 2-24 months; SD, 16.3), 41 were partially healed (28.7%), and 22 had no healing (15.4%).

Fifty-three of the 131 patients with partially healed or not healed fracture 3 months after treatment were prescribed a second cycle of ESWT (40.5%); 6 patients declined additional treatment. Of those patients who elected to have a second cycle of treatment (n = 47), 3 (6.4%) were completely healed 3 months after the second cycle, 31 (65.9%) were partially healed and 13 (27.7%) had no healing.

Eight of the patients who were either partially healed or had no healing 6 months after treatment, and who showed no improvement after 2 cycles of treatment, elected to have a third cycle. Among these patients, 2 (25%) were completely healed 12 months after treatment, 2 (25%) were partially healed and 4 (50%) had no healing. In our study, no lasting adverse events and only minor complications such as transient soft tissue swelling or smaller subcutaneous bleeding were observed.

Subgroup Analysis

Table III summarizes the number, mean age, duration of symptoms, number of fractures completely healed, partially healed and not healed at 3, 6, 9, and 12 months after treatment.

The number of hypertrophic and oligotrophic nonunions completely healed and partially healed at all follow-up time points (3, 6, 9, and 12 months after treatment) were each greater than the corresponding number of atrophic nonunions completely healed and partially healed ($P<.05$ for each subgroup analysis).

Overall, 13 of the 119 nonunions (10.9%) classified as either hypertrophic or oligotrophic did not heal after ESWT, and 9 of the 24 atrophic nonunions (37.5%) did not heal after ESWT. Furthermore, no significant differences were observed between results obtained in the upper extremity nonunions (68 cases) and those

Table III. Patient Characteristics and Results at 3, 6, 9, and 12 Months Posttreatment for the Entire Group

3 months posttreatment	All patients	Hypertrophic	Oligotrophic	Atrophic
Cases, no. (%)	143	15 (10.5)	104 (72.7)	24 (16.8)
Age, mean (SD)	41.4 (15.4)	41.9 (16.3)	41.6 (16.1)	40 (11.8)
Duration of nonunion, mean (SD)	14.1 (12.9)	20.2 (22.7)	11.9 (9.2)	20.2 (15.8)
Results, no. (%)				
Healed	12 (8.4)	1 (6.7)	11 (10.6)	-
Partially healed	94 (65.7)	11 (73.3)	70 (67.3)	13 (54.2)
Not healed	37 (25.9)	3 (20)	23 (22.1)	11 (45.8)
6 months post treatment	**All patients**	**Hypertrophic**	**Oligotrophic**	**Atrophic**
Cases, no. (%)	131	14 (10.7)	93 (71)	24 (18.3)
Age, mean (SD)	41.6 (15.6)	42.5 (16.8)	41.9 (16.4)	40 (16.7)
Duration of nonunion, mean (SD)	14.7 (13.4)	20.9 (23.4)	12.3 (9.6)	20.2 (15.8)
Results, no. (%)				
Healed	30 (22.9)	8 (57.1)	21 (22.6)	1 (4.2)
Partially healed	78 (59.5)	5 (35.7)	59 (63.4)	14 (58.3)
Not healed	23 (17.6)	1 (7.2)	13 (14)	9 (37.5)
9 months post treatment	**All patients**	**Hypertrophic**	**Oligotrophic**	**Atrophic**
Cases, no. (%)	101	6 (5.9)	72 (71.3)	23 (22.8)
Age, mean (SD)	42 (15.9)	46.5 (20.7)	41.9 (17)	41.2 (10.6)
Duration of nonunion, mean (SD)	15 (12.1)	15.3 (5.9)	13.2 (10.6)	20.8 (15.9)
Results, no. (%)				
Healed	23 (22.8)	1 (16.7)	18 (25)	4 (17.4)
Partially healed	56 (55.4)	4 (66.6)	42 (58.3)	10 (43.5)
Not healed	22 (21.8)	1 (16.7)	12 (16.7)	9 (39.1)
12 months post treatment	**All patients**	**Hypertrophic**	**Oligotrophic**	**Atrophic**
Cases, no. (%)	78	5 (6.4)	54 (69.2)	19 (24.4)
Age, mean (SD)	42.5 (16.6)	50.4 (20.5)	42.2 (17.9)	41.6 (10.9)
Duration of nonunion, mean (SD)	15.3 (12.9)	15.6 (6.5)	13.2 (11.2)	21.4 (16.9)
Results, no. (%)				
Healed	15 (19.2)	-	13 (24.1)	2 (10.5)
Partially healed	41 (52.6)	4 (80)	29 (53.7)	8 (42.1)
Not healed	22 (28.2)	1 (20)	12 (22.2)	9 (47.4)

achieved in the lower extremity nonunions (75 cases) at any follow-up period (P>.05).

Discussion

Basic scientific studies have shown that application of shock waves produces a biological effect on treated bone. Using animal models, ESWT has been shown to induce healing of fracture defects, usually by creating microfractures and bleeding in the treated bone.[5,7-17] It has been hypothesized that the treated tissues release local growth factors such as bone morphogenetic proteins, which ultimately recruit stem cells and mesenchymal progenitor cells and initiate the healing cascade.[18,19,22,23] However, the precise biological mechanism of action remains only partially understood.

Shock wave application clearly has an osteogenic effect on treated bones. Maier and colleagues[20] used a rabbit model to demonstrate that application of shock waves with an energy flux density of 0.5 mJ/mm^2 resulted in new periosteal bone formation in treated femurs.

In another series of trials, selective destruction of osteocytes, microfractures of trabeculae, and minor bleeding in the medullary space were observed in rabbits treated with ESWT.[22] Approximately 3 weeks after treatment, histological and biochemical analysis revealed thickening of the cortex, increase in the number of bony trabeculae, and a significant increase in the number and activity of treated osteoblasts.[10]

Johannes and colleagues[8] used a canine nonunion model to study the effects of high energy ESWT on cortical bone. All of the treated subjects reached radiographically observable bony union 12 weeks after the shock wave treatment, whereas untreated control subjects had radiographically persistent nonunions at termination of the study.

Uncontrolled clinical trials using ESWT as a method to treat fracture nonunions have been promising. Schaden and colleagues[36] reported on 115 patients with nonunions or delayed unions of various fractures treated with high energy ESWT and immobilization. Follow-up ranged from 3 months to 4 years. Overall, 87 patients (75.7%) were reported to have healed fractures.

Rompe and colleagues[33] reported their experience using high-energy shock wave therapy to treat 43 patients with either a tibial or femoral diaphyseal nonunion. They noted bony consolidation in 31 of 43 cases

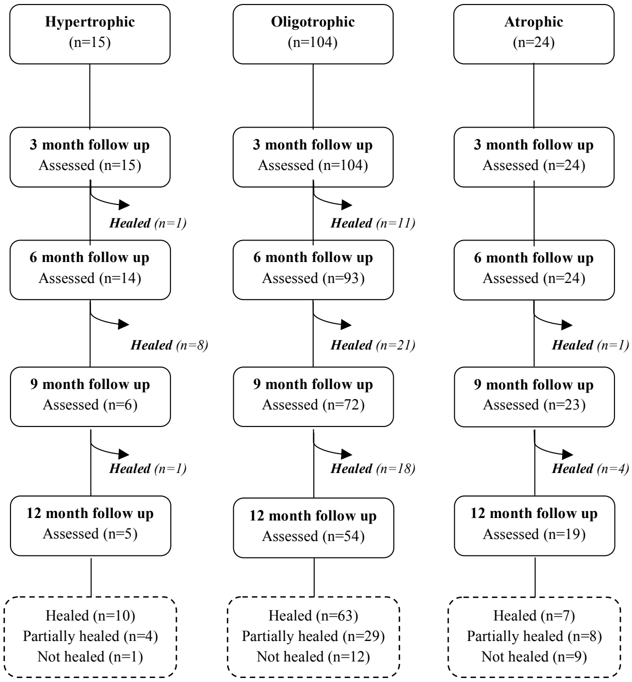

Figure 3. Flow chart of the trial until the last follow-up at twelve months from baseline.

(72%) after an average of 4 months posttreatment. Wang and colleagues[35] used high-energy ESWT as a treatment for 72 nonunions of long bone fractures. Twelve-month follow-up was available for 55 patients and for the entire cohort, they noted an overall healing rate of 80% (44 of 55 patients).

The present study evaluated the effects of ESWT on a consecutive series of patients with a nonunion who had not responded to nonoperative or operative management. The outcome for the entire population was evaluated. Subgroup analysis based on the type of nonunion was performed. Overall, 8.4% (12/143) of the nonunions were healed 3 months after treatment; 29.4% (42/143) of the nonunions were healed 6 months after treatment; 45.5% (65/143) of the nonunions were healed 9 months after treatment and 55.9% (80/143) of the nonunions were healed 12 months after treatment (Figures 1 and 2). ESWT was well-tolerated and yielded no complications. The overall healing rate for trophic nonunions (hypertrophic and oligotrophic) was 61.3% (73/119), compared with 29.2% (7/24) for atrophic nonunions ($P<.05$).

Our overall success rate of 84.6% (completely healed and partially healed) is similar to the 75-91% success rates reported in prior studies.[27-39] The heterogeneity of the patient groups, type and duration of the nonunions, differences in shock wave generating devices and length of follow-up, make it difficult, however, to formulate valid comparisons between trials. Treatment protocols and device-specific parameters vary among orthopedic centers and the definition of what constitutes a "nonunion" is not standardized. For these reasons, as is true with all studies involving ESWT, the results of this trial are parameter-specific.

There were 27 nonunions that did not heal with ESWT. As with any procedure, there is the possibility that a technical error contributed to this treatment outcome. In some of these cases it is possible that we did not succeed in properly localizing the targeting device on the fracture gap, that is, the shock waves may have "missed" the area of intended treatment. We reviewed all pretreatment radiographs of these 27 patients to identify any other potential explanations as to why ESWT was unsuccessful. Eleven of these 27 cases occurred in atrophic nonunions, which may in part be the result of a biological predisposition for deficiency in bone healing. Six of the 27 persistent nonunions occurred in fractures that were treated surgically with intramedullary devices. Upon review of these radiographs by the senior orthopedic surgeons, the intramedullary devices were deemed undersized and perhaps provided inadequate fracture fixation. In 4 patients who were treated nonoperatively, we noted a very large (>2 cm) fracture gap on the pretreatment radiographs. We could not identify any potential reasons why 6 of the persistent nonunions did not heal.

This study is a prospective cohort study and, as such, has some inherent limitations that require consideration. There was no control group. A study design with a placebo control group was considered unethical by our Institutional Review Board. Although similar in size to other clinical trials involving ESWT and nonunions, this study was relatively small and we did not limit the study to one bone. Nonunions of various bones are routinely treated at our center with ESWT and we wanted this study to reflect the heterogeneity of our clinical experience with this technique.

Mean follow-up was 8.9 months. For the vast majority of the patients, a positive treatment effect, that is, fracture healing, was already evident just 3 months after treatment.

Finally, magnetic resonance imaging and computed tomography scans were not performed for each patient with a persistent nonunion. However, the symptoms used to define a nonunion, moderate-to-severe pain located over the fracture site, pain with physical activities and radiographic evidence of an incompletely healed fracture are generally accepted and considered to be appropriate diagnostic descriptors of this condition.

Acknowledging these limitations, this series contributes valuable information. The results from this study suggest that ESWT can be a safe and effective treatment for stable fracture nonunions. Like other studies, our data shows that trophic nonunions respond better to ESWT than atrophic nonunions. Additional randomized, prospective clinical trials are needed to substantiate these conclusions.

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