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Supplementary material

Commentary and Perspective, data tables, additional images, video clips and/or translated abstracts are available for this article. This information can be accessed at <http://www.ejbjs.org/cgi/content/full/91/11/2589/DC1>

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A commentary by J. Lawrence Marsh, MD, is available at www.jbjs.org/commentary and as supplemental material to the online version of this article.

Extracorporeal Shock-Wave Therapy Compared with Surgery for Hypertrophic Long-Bone Nonunions

By Angelo Cacchio, MD, Lucio Giordano, MD, Olivo Colafarina, MD, Jan D. Rompe, MD, Emanuela Tavernese, MD, Francesco Ioppolo, MD, Stefano Flamini, MD, Giorgio Spacca, MD, and Valter Santilli, MD

Investigation performed at the Department of Physical Medicine and Rehabilitation and the Division of Orthopaedic Surgery, Department of Surgery, "San Salvatore" Hospital of L'Aquila; the Physical Medicine and Rehabilitation Center, Nomentana Hospital, Rome; and the Department of Physical Medicine and Rehabilitation, School of Medicine, "La Sapienza" University, Rome, Italy

Background: The authors of several studies have recommended extracorporeal shock-wave therapy as an alternative to surgical treatment for long-bone nonunions. This study was performed to compare the results of extracorporeal shock-wave therapy produced by two different devices with those of surgical treatment in the management of long-bone nonunions.

Methods: One hundred and twenty-six patients with a long-bone nonunion were randomly assigned to receive either extracorporeal shock-wave therapy (Groups 1 and 2) or surgical treatment (Group 3). The patients in the shock-wave groups received four treatments with 4000 impulses of shock waves with an energy flux density of 0.40 mJ/mm² (Group 1) or 0.70 mJ/mm² (Group 2). The patients in the three groups had similar demographic characteristics, durations of nonunion, and durations of follow-up. Radiographic results (the primary outcome) and clinical results (the secondary outcomes) were determined before and three, six, twelve, and twenty-four months after treatment.

Results: The radiographic findings did not differ among the three groups of patients. At six months, 70% of the nonunions in Group 1, 71% of the nonunions in Group 2, and 73% of the nonunions in Group 3 had healed. Three and six months after treatment, the clinical outcomes in the two shock-wave groups were significantly better than those in the surgical group ($p < 0.001$). However, at both twelve and twenty-four months after treatment, there were no differences among the three groups, with the exception of the DASH score, which differed significantly between Groups 1 and 3 ($p = 0.038$) and between Groups 2 and 3 ($p = 0.021$) at twelve months.

Conclusions: Extracorporeal shock-wave therapy is as effective as surgery in stimulating union of long-bone hypertrophic nonunions and yields better short-term clinical outcomes.

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

Extracorporeal shock-wave therapy has been investigated as a nonsurgical means of achieving fracture-healing. This therapy was first described by German authors¹⁻³. Although the advantages of extracorporeal shock-wave therapy, such as its noninvasiveness and a low complication rate, in the treatment of nonunions have been reported in various experimental⁴⁻⁷ and clinical studies^{3,8-10}, there is not yet conclusive

proof that extracorporeal shock-wave therapy is as effective as, or better than, other forms of treatment¹¹. To our knowledge, no prospective clinical studies have been performed to assess the effectiveness of extracorporeal shock-wave therapy, to compare it with surgery, or to ascertain whether there are any differences in the effectiveness of different extracorporeal shock-wave generators in the treatment of long-bone nonunions.

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We hypothesized that extracorporeal shock-wave therapy is as effective as, or more effective than, surgical treatment of long-bone nonunions.

The purposes of this double-blind, controlled study were (1) to assess the effectiveness of extracorporeal shock-wave therapy in the treatment of long-bone nonunions, (2) to compare extracorporeal shock-wave therapy with surgical treatment of long-bone nonunions, and (3) to ascertain any differences in effectiveness between two different extracorporeal shock-wave generators in the treatment of long-bone nonunions.

Materials and Methods

Between October 2001 and September 2004, we conducted a prospective, randomized, multicenter trial using a three-sample parallel-group design (Fig. 1). The study protocol was approved by the local ethical committees at all of the participating centers. Two shock-wave-therapy centers (the Department of Physical Medicine and Rehabilitation, "San Salvatore" Hospital, L'Aquila, Italy, and the Physical Medicine and Rehabilitation Center, Nomentana Hospital, Rome, Italy) and one orthopaedic surgery center (Division of Orthopaedic Surgery, Department of Surgery, "San Salvatore" Hospital, L'Aquila) were involved in the study. Both types of the shock-wave device were used at both of the shock-wave-therapy centers during the study period. Randomization of the patients and monitoring of the data were performed in a university hospital (Department of Physical Medicine and Rehabilitation, School of Medicine, "La Sapienza" University, Rome) not involved in the treatment procedures, according to the CPMP/ICH (Committee for Proprietary Medicinal Products/International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guideline for Good Clinical Practice¹² and Guideline for Statistical Principles for Clinical Trials¹³. Patients were seen at one of the three participating centers and then, on the basis of the randomization, referred to one of the three institutions for treatment.

In this study, nonunion was defined as a fracture that did not show any progress toward healing on radiographs made at one-month intervals for at least six months following treatment. Before randomization, all patients were evaluated clinically by two independent clinicians and the radiographs were reviewed by two independent radiologists who were unaware of the purposes of this study and made the final decision that there was no progress toward union.

Inclusion criteria were a long-bone nonunion and skeletal maturity. Both hypertrophic and atrophic nonunions were considered for this study. Hypertrophic nonunions show prolific callus formation, bone vascularity is present, and the bone has a good healing potential. Atrophic nonunions are characterized by an absence of callus and the presence of atrophic bone ends, which may be tapered and osteopenic or sclerotic; bone vascularity is deficient, and the bone has poor healing potential.

Exclusion criteria were bone tumors, pathologic fractures, infected nonunions, breakage of fixation devices, an implanted

pacemaker, blood coagulation disorders, use of anticoagulant drugs, and pregnancy. The presence of bone fixation devices was not a reason for exclusion.

The patients were informed of the possible advantages and disadvantages of surgery and extracorporeal shock-wave therapy for the treatment of nonunions. Signed informed consent was then obtained from all of the patients before they were assigned to a group. The treatment group was assigned at a central location, with use of a separate random-assignment list for each center; the lists were computer-generated with the use of random permuted blocks of nine patients for each list.

One hundred and twenty-six patients satisfied the inclusion criteria and were randomized into fifteen blocks, with assignment either to one of the two extracorporeal shock-wave therapy groups (Group 1 and Group 2) or to the surgical group (Group 3).

All patients had undergone prior surgery, and twenty patients had had more than one operation (Table I). One hundred and eleven patients were noted to have signs of instability such as pain, loosening of implants, or mobility of the fracture site under fluoroscopy.

All patients voluntarily participated in the study.

Shock-Wave Therapy

Four extracorporeal shock-wave therapy sessions were performed at one-week intervals, with 4000 impulses applied to the center of the fracture gap at each session with one of two types of extracorporeal shock-wave generator (as described below) that satisfied the requirements for their use in the treatment of musculoskeletal disorders. Both of the shock-wave generators used in this study are licensed by the European Union and were used exclusively within the bounds of their intended applications. Extracorporeal shock-wave therapy measurement was carried out according to International Electrotechnical Commission (IEC) procedures¹⁴.

The head of the extracorporeal shock-wave generator was positioned in the plane of the fracture (Fig. 2), which was determined on the basis of previous radiographic images and an outline or inline ultrasound positioning system. Once the position and depth of the fracture site were located, the treatment area was prepared with a coupling gel (Aquasonic 100; Parker Laboratories, Fairfield, New Jersey) to minimize the loss of shock-wave energy at the interface between the head of the device and the skin. Each center was monitored to ensure appropriate execution of the intervention. All of the physicians were experienced in the use of extracorporeal shock-wave therapy to treat various musculoskeletal disorders.

The treatment was administered with the use of regional anesthesia in all patients. The patients received a peripheral lower-limb (sciatic-femoral nerve) or upper-limb (axillary brachial plexus) block with 1% mepivacaine with the aid of an insulated atraumatic needle and a nerve stimulator. Almost all of the patients recovered from the regional anesthesia within two to three hours. No complications related to the regional anesthesia were observed. No therapeutic cointervention was administered in any group.

The limb was immobilized in a plaster cast (a long leg cast for the tibial and femoral fractures and a plaster cast for the ulnar and radial fractures) or a brace for six weeks to three months after the therapy.

The patients were instructed to use nonsteroidal anti-inflammatory medication (ibuprofen, 600 mg) once a day for the first three days after each extracorporeal shock-wave treatment. Moreover, we recommended that an ice pack be placed over the treated area for fifteen to twenty minutes every hour during the first three days after each extracorporeal shock-wave treatment. Patients who had treatment of the lower limb returned to their pretreatment weight-bearing status three days after the shock-wave treatment.

Group 1 consisted of forty-two patients (Table I), all of whom had had surgery as the treatment of the initial fracture:

twenty-four had had intramedullary nail fixation; eleven, plate fixation; and seven, combined nail and plate fixation. In this group, an electromagnetic extracorporeal shock-wave generator (Dornier Epos Ultra lithotripter; Dornier Medizintechnik, Wessling, Germany) equipped with an outline 7.5-MHz linear array ultrasound positioning system was used to provide four extracorporeal shock-wave therapy sessions at one-week intervals, with 4000 impulses applied to the center of the fracture gap at each session with an energy flux density of 0.40 mJ/mm².

Group 2 consisted of forty-two patients (Table I), all of whom had also had surgical treatment of the initial fracture: twenty had had intramedullary nail fixation; nine, plate fixation; and thirteen, combined nail and plate fixation. In Group 2, an electromagnetic extracorporeal shock-wave generator (Modulith SLK; Storz Medical, Tägerwil, Switzerland)

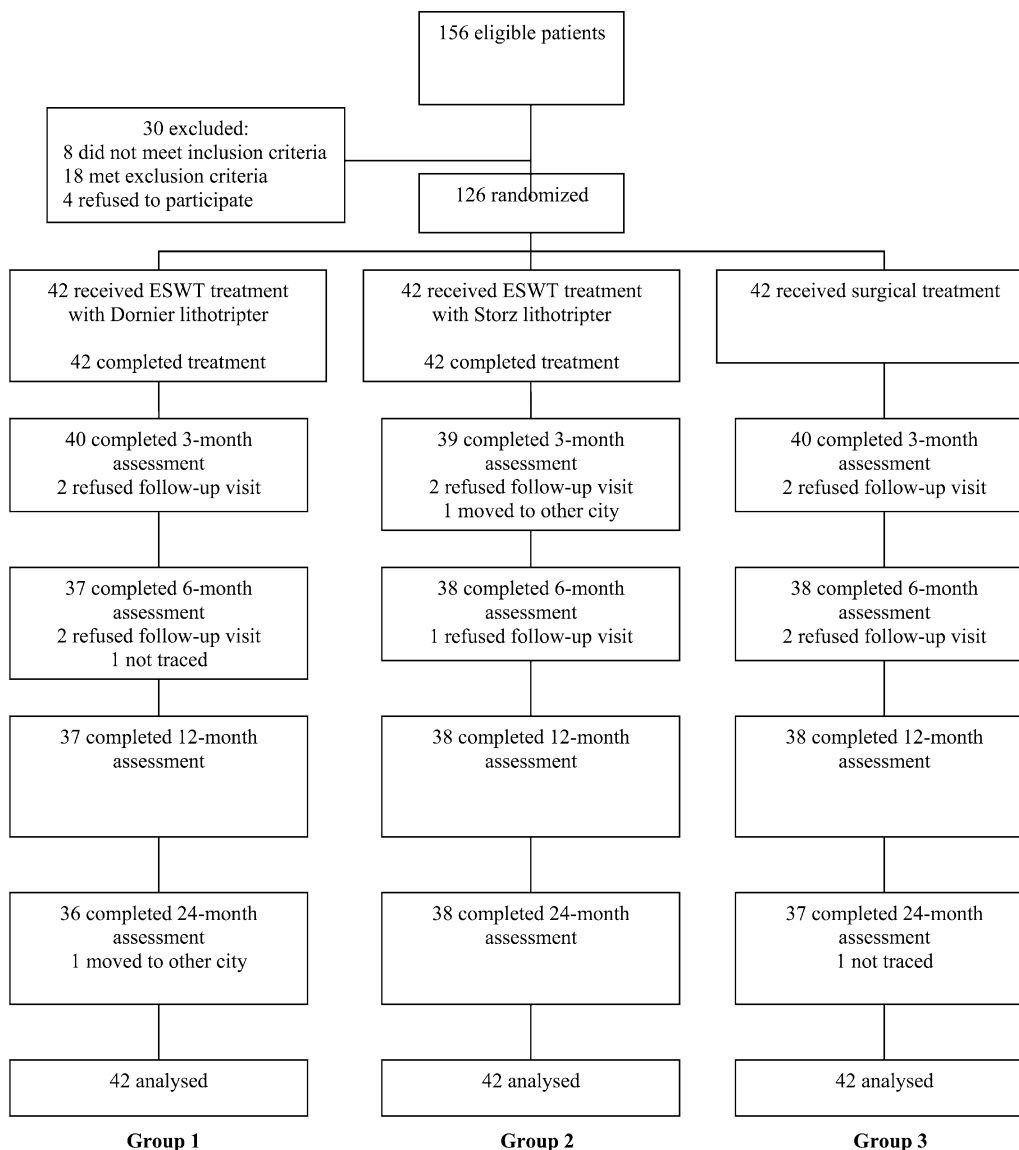


Fig. 1

Flow diagram of study. ESWT = extracorporeal shock-wave therapy.

TABLE I Baseline Characteristics of Randomized Patients

| | Group 1 | Group 2 | Group 3 | Overall |
|---|---------------|---------------|---------------|---------------|
| Patients (no.) | 42 | 42 | 42 | 126 |
| Male/female* | 32/10 (76/24) | 31/11 (74/26) | 30/12 (71/29) | 93/33 (74/26) |
| Age† (yr) | 42.8 ± 6.3 | 43.1 ± 5.4 | 42.5 ± 6.2 | 42.7 ± 5.9 |
| Previous surgical procedures† (no.) | 1.4 ± 1.1 | 1.5 ± 1.2 | 1.4 ± 0.9 | 1.5 ± 0.8 |
| Patients with >1 surgical procedure (no.) | 7 | 7 | 6 | 20 |
| Duration of nonunion†† (mo) | 11.5 ± 4.9 | 10.8 ± 5.4 | 10.2 ± 6.1 | 10.7 ± 5.5 |
| Site of nonunion* | | | | |
| Femur | 11 (26) | 11 (26) | 12 (29) | 34 (27) |
| Tibia | 22 (52) | 22 (52) | 23 (55) | 67 (53) |
| Ulna | 5 (12) | 6 (14) | 4 (10) | 15 (12) |
| Radius | 4 (10) | 3 (7) | 3 (7) | 10 (8) |
| Type of nonunion* | | | | |
| Hypertrophic | 30 (71) | 31 (74) | 31 (74) | 92 (73) |
| Atrophic | 12 (29) | 11 (26) | 11 (26) | 34 (27) |
| Pain score†§ (cm) | 4.3 ± 2.2 | 4.4 ± 2.0 | 4.2 ± 2.4 | 4.2 ± 2.2 |
| DASH score†# (points) | 44.8 ± 11.5 | 43.5 ± 18.3 | 45 ± 14.7 | 44.4 ± 14.8 |
| LEFS score†** (points) | 28.5 ± 8.9 | 29.3 ± 7.7 | 30.2 ± 10.6 | 29.3 ± 9.1 |

*The values are given as the number of patients, with the percentage in parentheses. †The values are given as the mean and standard deviation. ††The mean time from the original fracture to enrollment in this study. §The pain score was measured on a visual analogue scale ranging from 0 to 10 cm, with 0 indicating no pain and 10 indicating "worst pain I ever had." #The DASH (Disabilities of the Arm, Shoulder and Hand questionnaire) score ranges from 0 (no disability) to 100 (most severe disability) and was used only for patients with an upper-limb nonunion. **The LEFS (Lower Extremity Functional Scale questionnaire) score ranges from 0 (most severe disability) to 80 (no disability) and was used only for patients with a lower-limb nonunion.

equipped with an inline ultrasound positioning system was used to provide four extracorporeal shock-wave therapy sessions at one-week intervals, with 4000 impulses applied to the center of the fracture gap at each session with an energy flux density of 0.70 mJ/mm².

Surgical Treatment

Group 3 consisted of forty-two patients (Table I), treated by two senior surgeons. All forty-two patients had had surgical treatment of the initial fracture, consisting of intramedullary nail fixation in twenty-one of them, plate fixation in ten, and combined nail and plate fixation in eleven.

All of the surgical revisions of the nonunions were performed with the patient on a fracture table and under general anesthesia. Fixation with a locked intramedullary nail was performed in twenty-three patients, fixation with a locked intramedullary nail combined with autogenous bone graft was done in twelve patients, and an external fixator was used for seven patients. The choice depended on the fracture pattern and the soft-tissue conditions as dictated by a standard protocol for the treatment of long-bone nonunions. This protocol consists of removing the previous implant if there is one, de-cortication of the fracture site, refreshing the fracture site (removal of interposed soft tissue), recanalizing the medullary

canal, reducing and fixing the fracture, and, if necessary, applying a cancellous bone graft harvested from the ipsilateral anterior iliac crest. Autogenous bone graft is indicated in cases of large bone defects.

All patients received intravenously, once a day for the first three days after the surgical procedure, a drug cocktail with an anti-H₂ receptor (50 mg/5 mL of ranitidine hydrochloride), a nonsteroidal anti-inflammatory drug (30 mg/1 mL of ketorolac), an analgesic drug (50 mg/1 mL of tramadol hydrochloride), and an antiemetic drug (10 mg/2 mL of metoclopramide hydrochloride) in 500 mL of physiological solution. Moreover, all of the patients received antibiotic prophylaxis with ciprofloxacin (200 mg/100 mL) and teicoplanin (200 mg/3 mL) twice a day for the first ten days after the surgical procedure.

Outcome Measures

Assessments of anteroposterior and lateral radiographs and clinical examination were performed at five time points—before treatment and at three, six, twelve, and twenty-four months after treatment—by two independent radiologists and two clinicians who were blinded to the nature of the intervention. Every discrepant decision was discussed, and a result was arrived at by consensus.

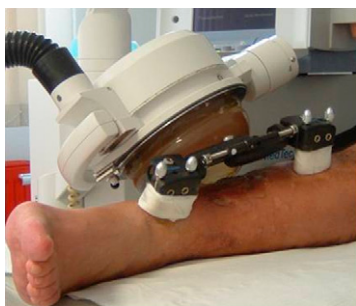


Fig. 2
Positioning of the extracorporeal
shock-wave therapy generator.

Primary End Point

The primary end point of this study was healing of the nonunion as determined with a radiographic assessment at six months. A nonunion was judged to be healed when callus bridged the nonunion site on all four cortices (two seen on the anteroposterior radiograph and two seen on the lateral radiograph).

Secondary End Points

The secondary end points were the patient's functional status as assessed with one of two functional status questionnaires and pain as assessed with a self-rated pain intensity scale. The functional status questionnaires were the 100-point Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire¹⁵ (available in several languages at <http://www.dash.iwh.on.ca>) for the patients with an upper-limb nonunion and the 80-point Lower Extremity Functional Scale (LEFS) questionnaire¹⁶ for the patients with a lower-limb nonunion. The self-rated pain intensity scale was a 10-cm horizontal visual analogue scale with 0 cm labeled "no pain" and 10 cm labeled "worst pain I have ever had." The subjects were asked to mark the scale in answer to the question: "Referring to the worst pain you have experienced in your life, what is the relative level of your limb pain?" Moreover, at the six-month follow-up evaluation, the overall estimate of the efficacy of the treatment was rated by the patients as very good/good, satisfactory, or poor.

At six months, the opportunity to have surgical treatment was offered to the patients in the two extracorporeal shock-wave therapy groups; however, none chose this option.

Statistical Analysis

The primary aim of this study was to compare the outcome after shock-wave therapy with that after surgical treatment.

The primary efficacy end point was prospectively defined as the radiographic healing of the nonunion from baseline to the six-month evaluation. All outcome analyses were performed according to the intention-to-treat principle. The intention-to-treat analysis was carried out according to a "worst-case scenario" analysis: subjects who did not complete the treatment or did not undergo the post-treatment or final follow-up assessments were assigned a poor outcome, with the final follow-up evaluation considered to be the last observation performed.

To test the primary end point, a two-sided chi-square test was carried out to compare the success rate at six months in the extracorporeal shock-wave therapy groups with that in the surgery group; the level of significance was 5%.

To test the secondary end points, a two-way analysis of variance, with the group as the between-subjects factor and time as the within-subjects factor, was used to assess whether there were significant differences in the DASH, LEFS, and visual analogue scale scores among the three groups and between the preoperative and scheduled follow-up time points within each group. A Tukey post hoc comparison was used to assess significant differences between mean values when a significant main effect and interaction were found. The model for all of the analyses included the main effects of treatment, time, and the treatment \times time interaction. Significance levels for multiple comparisons were adjusted with the Bonferroni procedure. The level of significance was set at $p < 0.05$.

It was determined that, in order to detect a difference of 30% in the success rates with a power of 80%, the necessary sample size was thirty-five subjects in each group. Success rates were assumed to be 65% and 95% in the extracorporeal shock-wave therapy groups and surgery group, respectively.

Source of Funding

No funding or other assistance was obtained from either of the manufacturers of the shock-wave generators or any other source.

Results

A total of 126 patients with a diagnosis of nonunion (ninety-two hypertrophic and thirty-four atrophic) caused by failure of fracture treatment were enrolled in the study (Fig. 1). No bilateral or multiple nonunions were treated.

The baseline characteristics, which did not differ significantly between groups, are shown in Table I. The patients were followed for a mean of 21.7 months (range, two to

TABLE II Healing of the Nonunions in the Shock-Wave and Surgical Groups at the Four Time Periods*

| | 3 Mo | 6 Mo | 12 Mo | 24 Mo |
|------------|---------|---------|---------|---------|
| Group 1 | 40 | 37 | 37 | 36 |
| Healed | 22 (55) | 26 (70) | 31 (84) | 34 (94) |
| Not healed | 18 (45) | 11 (30) | 6 (16) | 2 (6) |
| Group 2 | 39 | 38 | 38 | 38 |
| Healed | 21 (54) | 27 (71) | 31 (82) | 35 (92) |
| Not healed | 18 (46) | 11 (29) | 7 (18) | 3 (8) |
| Group 3 | 40 | 38 | 38 | 37 |
| Healed | 21 (52) | 28 (74) | 33 (87) | 35 (95) |
| Not healed | 19 (48) | 10 (26) | 5 (13) | 2 (5) |

*The values are given as the number of patients, with the percentage in parentheses.

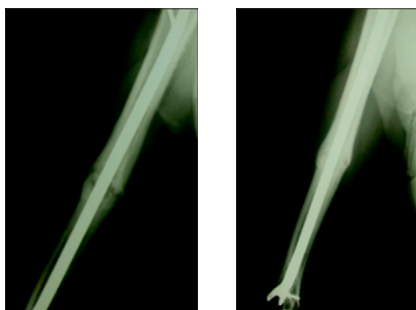


Fig. 3-A

Fig. 3-B

Figs. 3-A and 3-B Serial radiographs of a left humeral nonunion in a twenty-five-year-old woman. **Fig. 3-A** Before shock-wave treatment. **Fig. 3-B** Three months after treatment, the fracture had healed and the patient had no pain and a fully functional upper limb.

twenty-four months). Fifteen patients were lost to follow-up: seven were lost at three months; six, at six months; and two, at twenty-four months (Fig. 1). Eleven of these patients refused to undergo the follow-up examinations, while two could not be traced and two had moved to another city. Therefore, a follow-up examination was performed on 119 patients at three months, 113 at six and twelve months, and 111 at twenty-four months. Eleven of the fifteen patients who dropped out of the study had an atrophic nonunion and four had a hypertrophic type. Of the twenty-three atrophic nonunions that remained, thirteen (seven in the surgical group [Group 3], four in extracorporeal shock-wave therapy Group 1, and two in extracorporeal shock-wave therapy Group 2) healed while ten (four in Group 3 and three each in Group 1 and 2) did not.

The high number of drop-outs among the patients with an atrophic nonunion necessitated a separate statistical analysis of this group, but the number of patients with atrophic nonunion (twenty-three) was too small for this to be carried out.

Primary End Point

Treatment was successful with regard to the primary end point (radiographic evidence of healing at six months) (Table II;

Figs. 3-A through 4-C) in twenty-six (70%) of the thirty-seven patients in Group 1, twenty-seven (71%) of the thirty-eight in Group 2, and twenty-eight (74%) of the thirty-eight in Group 3. There was no significant difference in the rate of successful treatment among the three groups (chi square = 0.08, $p = 0.95$).

At twelve and twenty-four months (Table II), the healing rates were substantially increased in all three treatment groups, without significant differences among the groups.

Every radiographic assessment of cortical bridging was repeated, after a one-week interval, by one of the radiologists, who was blinded to the previously determined result. We then evaluated the interobserver and intraobserver correlation using intraclass correlation coefficients ($ICC_{[2,k]}$ and $ICC_{[2,1]}$, respectively), which range from 0 to 1 with 1 indicating perfect reliability¹⁷. Both the interobserver correlation ($ICC_{[2,k]} = 0.88$) and the intraobserver correlation ($ICC_{[2,1]} = 0.85$) were high.

Secondary End Points

Data for the secondary end points (scores on the DASH and LEFS questionnaires and visual analogue pain scale) are shown in Table III. A two-way analysis of variance of these scores demonstrated a significant effect of treatment ($F = 23.8$, $p < 0.001$) and a significant treatment-time interaction ($F = 16.5$, $p < 0.001$). These significant variations in treatment effects over time were greater in Groups 1 and 2 than in Group 3 up to six months, but then these advantages diminished.

At three and six months, the pain, DASH, and LEFS scores were significantly better in Groups 1 and 2 than in Group 3 (Table III). At twelve and twenty-four months, the differences between these groups were no longer significant, with the exception of the DASH score at twelve months, which differed significantly between Groups 1 and 2 ($p = 0.038$) and between Groups 2 and 3 ($p = 0.021$).

At six months, 71% of the patients in Group 1, 73% of those in Group 2, and 72% of those in Group 3 rated the efficacy of treatment as very good/good; 11% in Group 1, 15% in Group 2, and 16% in Group 3 rated the result as satisfactory; and 18% in Group 1, 12% in Group 2, and 12% in Group 3 rated the result as poor.



Fig. 4-A

Fig. 4-B

Fig. 4-C

Figs. 4-A, 4-B, and 4-C Serial radiographs of a right tibial nonunion in a thirty-eight-year-old woman. **Fig. 4-A** Before shock-wave treatment. **Fig. 4-B** Three months after treatment. **Fig. 4-C** Six months after treatment, the fracture had healed and the patient had no pain and a fully functional lower limb.

TABLE III Pain, DASH, and LEFS Scores in the Shock-Wave and Surgical Groups Before and After Treatment

| | Baseline | 3 Mo | 6 Mo | 12 Mo | 24 Mo |
|---|-------------|-------------|-------------|-------------|-------------|
| Group 1 | | | | | |
| Patients (no.) | 42 | 40 | 37 | 37 | 36 |
| Pain score*† (cm) | 4.3 ± 2.2 | 1.8 ± 1.2 | 1.1 ± 0.9 | 0.8 ± 1.0 | 0.5 ± 0.4 |
| Difference vs. baseline (<i>p</i> value) | | <0.001 | <0.001 | <0.001 | <0.001 |
| Difference vs. Group 2 (<i>p</i> value) | 0.823 | 0.680 | 0.600 | 0.639 | 0.265 |
| Difference vs. Group 3 (<i>p</i> value) | 0.835 | <0.001 | <0.001 | 0.261 | 0.267 |
| DASH score*‡ (points) | 44.8 ± 11.5 | 33.3 ± 9.8 | 22.4 ± 10.1 | 17.1 ± 8.9 | 13.8 ± 9.3 |
| Difference vs. baseline (<i>p</i> value) | | 0.001 | <0.001 | <0.001 | <0.001 |
| Difference vs. Group 2 (<i>p</i> value) | 0.575 | 0.825 | 0.830 | 0.713 | 0.817 |
| Difference vs. Group 3 (<i>p</i> value) | 0.943 | <0.001 | <0.001 | 0.038 | 0.132 |
| LEFS score*§ (points) | 28.5 ± 8.9 | 46.3 ± 9.8 | 52.8 ± 10.0 | 68.9 ± 8.5 | 73.8 ± 9.2 |
| Difference vs. baseline (<i>p</i> value) | | <0.001 | <0.001 | <0.001 | <0.001 |
| Difference vs. Group 2 (<i>p</i> value) | 0.646 | 0.764 | 0.766 | 0.546 | 0.861 |
| Difference vs. Group 3 (<i>p</i> value) | 0.406 | <0.001 | <0.001 | 0.112 | 0.177 |
| Group 2 | | | | | |
| Patients (no.) | 42 | 39 | 38 | 38 | 38 |
| Pain score*† (cm) | 4.4 ± 2.0 | 1.9 ± 1.0 | 1.2 ± 0.8 | 0.7 ± 0.8 | 0.6 ± 0.3 |
| Difference vs. baseline (<i>p</i> value) | | <0.001 | <0.001 | <0.001 | <0.001 |
| Difference vs. Group 3 (<i>p</i> value) | 0.839 | <0.001 | <0.001 | 0.107 | 0.556 |
| DASH score*‡ (points) | 43.5 ± 10.3 | 32.8 ± 11.0 | 21.9 ± 10.8 | 16.3 ± 9.6 | 14.2 ± 10.2 |
| Difference vs. baseline (<i>p</i> value) | | 0.005 | <0.001 | <0.001 | <0.001 |
| Difference vs. Group 3 (<i>p</i> value) | 0.582 | <0.001 | <0.001 | 0.021 | 0.182 |
| LEFS score*§ (points) | 29.3 ± 7.7 | 45.7 ± 8.4 | 53.4 ± 9.2 | 70.3 ± 11.1 | 74.2 ± 8.8 |
| Difference vs. baseline (<i>p</i> value) | | <0.001 | <0.001 | <0.001 | <0.001 |
| Difference vs. Group 3 (<i>p</i> value) | 0.651 | <0.001 | <0.001 | 0.056 | 0.116 |
| Group 3 | | | | | |
| Patients (no.) | 42 | 40 | 38 | 38 | 37 |
| Pain score*† (cm) | 4.2 ± 2.4 | 3.8 ± 2.5 | 3.6 ± 2.0 | 1.1 ± 1.2 | 0.7 ± 0.9 |
| Difference vs. baseline (<i>p</i> value) | | 0.446 | 0.214 | <0.001 | <0.001 |
| DASH score*‡ (points) | 45 ± 14.7 | 42.4 ± 12.1 | 34.8 ± 11.6 | 21.9 ± 9.9 | 18.2 ± 12.7 |
| Difference vs. baseline (<i>p</i> value) | | 0.369 | <0.001 | <0.001 | <0.001 |
| LEFS score*§ (points) | 30.2 ± 10.6 | 32.4 ± 11.3 | 44.2 ± 10.6 | 65.5 ± 9.0 | 70.7 ± 8.1 |
| Difference vs. baseline (<i>p</i> value) | | 0.349 | <0.001 | <0.001 | <0.001 |

*The values are given as the mean and standard deviation. †The pain score was measured on a visual analogue scale ranging from 0 to 10 cm, with 0 indicating no pain and 10 indicating "worst pain I ever had." ‡The DASH (Disabilities of the Arm, Shoulder and Hand questionnaire) score ranges from 0 (no disability) to 100 (most severe disability) and was used only for patients with an upper-limb nonunion. §The LEFS (Lower Extremity Functional Scale questionnaire) score ranges from 0 (most severe disability) to 80 (no disability) and was used only for patients with a lower-limb nonunion.

All patients returned to work, but 19% of those with an upper-limb nonunion and 30% of those with a lower-limb nonunion had to reduce their work activity.

Adverse Effects

No neuromuscular, systemic, or device-related adverse effects were observed in the extracorporeal shock-wave therapy groups. Local complications included hematomas, which lasted from four to six days and were observed in twenty-three patients (27%); this problem resolved spontaneously after the

use of ice packs for a few days. No other adverse effects were noted.

The rate of adverse effects in the surgical group was 7% (three of forty-two). Two cases of wound infection were observed, both in the lower limb. The infections healed after surgical débridement and antibiotic therapy. There were no deep infections in this series. A radial nerve neurapraxia was noted in a patient in the surgical group with a nonunion of the distal third of the humerus. The neurapraxia is likely to have been due to inappropriate cast positioning. The patient re-

covered completely after four months without any treatment and with no functional impairment.

Discussion

On the basis of numerous trials showing effects that varied greatly but were all positive, extracorporeal shock-wave therapy has been used for the treatment of nonunions^{8-10,18}. A systematic review of the literature on the use of this therapy for nonunions¹¹ identified ten high-quality clinical trials with a total of 631 patients. Success rates ranged from 41% to 91%. Schaden et al.⁹ reported a success rate of 74% with a single shock-wave treatment in an uncontrolled study. Similarly, Rompe et al.¹⁰ reported successful treatment in 72% of their patients in an observational cohort study.

Similar results were reported by Xu et al.¹⁸, who observed a success rate of 76% in total and 91% for hypertrophic nonunions, and by Wang et al.⁸, who found a success rate of 40% at three months, 61% at six months, and 80% at twelve months for hypertrophic nonunions but only 27% for atrophic nonunions. Beutler et al.¹⁹ reported a success rate of 53% for hypertrophic nonunions but only 25% for atrophic nonunions. Taken together these data indicate that shock-wave treatment is more successful for hypertrophic nonunions than for atrophic nonunions. A direct comparison of the various study results with one another is difficult because of the use of different devices with different mechanisms of shock-wave generation and application of different energy flux densities. However, the results for the hypertrophic nonunions in the current study were comparable with or better than those reported in the other series^{8-10,18}.

In our study, the drop-out rate was greater for the patients with atrophic nonunion (eleven of thirty-four; 32%) than it was for those with hypertrophic nonunion (four of ninety-two; 4%). Therefore, there were too few atrophic nonunions to allow us to draw any conclusions regarding the results of their treatment. We suggest that a future study focusing only on atrophic nonunions should be performed.

We did not find any significant differences in the success rate determined by the radiographic evaluation between the extracorporeal shock-wave therapy groups (70% and 71% in Group 1 and Group 2, respectively) and the group treated with surgery (73%).

Although the clinical results in the shock-wave groups were significantly better than those in the surgical group at three and six months, there were no significant differences at twelve or twenty-four months, with the exception of the DASH score at twelve months.

The early (three and six-month) clinical differences may be ascribable to the direct and indirect actions that shock waves have on pain mechanisms, as reduced pain could lead to improved limb function. Although the mechanism by which shock-wave treatment results in a clinical improvement remains unknown, it has been postulated that shock waves induce hyperstimulation analgesia by raising the patient's pain threshold and promote bone-healing by creating microfractures that induce a healing reaction and increased vascularity, as occurs during the natural bone-healing process^{3,8-10,20}.

Studies have demonstrated that shock-wave treatment stimulates neovascularization in association with an increased expression of angiogenic growth markers, including endothelial nitric oxide synthase (eNOS), vessel endothelial growth factor (VEGF), and proliferating cell nuclear antigen (PCNA) in tendon and bone as well as at tendon-bone interfaces^{21,22}.


Some recent *in vitro* studies^{23,24} have shown that the ability of extracorporeal shock-wave therapy to enhance osteoblast metabolic activity, particularly the proliferation of MG63 osteoblast-like cells, is greater when an energy level of 0.15 mJ/mm², as opposed to a higher energy level, is used. Although we used higher energy levels (0.40 and 0.70 mJ/mm²), we observed a high rate of successful healing of long-bone nonunions without adverse effects. Our results are in agreement with those reported in other clinical studies^{3,8-10}.

Our study design has some inherent limitations. The principal limitation was the lack of an untreated control group, which we did not include because of the restrictions defined by our ethics committee. In addition, blinding was not complete as the radiologist would have been able to sometimes recognize that a patient belonged to the surgical group simply by detecting a change in the implanted fixation device or a change in the appearance of the nonunion gap due to surgery. It should also be noted that the use of ketorolac in the surgically treated patients could have impeded the healing process.

The generalizability of our findings is limited by the facts that the patient sample was conveniently selected (with exclusion of patients with osteomyelitis or with breakage of fixation devices), the extracorporeal shock-wave therapy parameters were empirically selected, and we did not use validated outcome measures for the assessment of nonunions (as no such measures are available).

The results of this randomized controlled trial strongly suggest that extracorporeal shock-wave therapy is a simple and safe alternative to surgical treatment of hypertrophic long-bone nonunions. The results need to be confirmed, and different treatment protocols as well as treatment parameters should be investigated; these include the number of shock waves used, the energy levels applied, and the frequency of application.

Appendix

 The Lower Extremity Functional Scale is available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD/DVD (call our subscription department, at 781-449-9780, to order the CD or DVD). ■

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