LETTER TO THE EDITOR

Clinical experience of extracorporeal shockwave treatment on diaphyseal forearm non-union: effects on healing and bone density

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To the Editor,

Within 3-6 months after trauma the failure to respect physiological bone healing times is a possible eventuality and occurs in about 8% of cases of diaphyseal fractures (1). According to the literature, fracture healing is associated with an increase in bone mineral density (BMD), with values of at least 75% of the contralateral segment (2). Dual-energy X-ray absorptiometry (DXA) is an effective method for monitoring early local bone response, already at 3 weeks. In an animal model after Extracorporeal Shockwave Therapy (ESWT) on femur osteotomy, significant increases in callus size, bone mineral density and bone tissue formation have been found (3).

The initial interpretation of shock wave (SW) application and regenerative effects on bone tissue is a mechanical stimulation comparable to the micro-damage of a fracture (4). This mechanical stimulation on fracture is responsible for a subperiosteal hematoma, which should increase the volume of trabecular bone and cancellous bone in the first 2 weeks and, subsequently, a periosteal reaction with neo-cortical formation. According to recent literature, SWs are responsible for a mechanotransduction stimulation which may guarantee the transformation of the mechanical stimulation into biochemical signals. Osteogenesis is due to multiple endogenous pathways (5). SWs are able to improve the differentiation of stem cells into an osteogenetic line by inducing a RANKL/OPG ratio reduction with inhibition of osteoclastogenesis on osteoblasts, thus causing osteocyte death. In effect, the RANKL/OPG ratio reduction is able to modify sclerostin signalling so improving the efficacy of osteoblasts. In fact, these cells are able to produce more osteoid tissue and neo-cortex (6). Finally, SWs are responsible for angio- and lymphogenesis effects, and for inflammation modelling.

Due to the biological effects on bone tissue, ESWT is indicated for the treatment of delayed union (7). The success rate in terms of bone healing, documented by continuity of the cortical bone, ranges from 50 to 80% (7). A C-type grade of recommendation (level of evidence III) is identified. The aim of the present study is to quantify the quantitative modifications in bone fracture healing before and after ESWT.

Key words: fractures; delayed union; non-union; shock waves; densitometry

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

MATERIALS AND METHODS

This is an observational prospective study. For two years, 20 patients affected by delayed union or non-union of diaphyseal forearm fracture, who had undergone ESWT were enrolled. The study was approved by the local Ethics Committee and written consent was obtained from the patients. The following were used as inclusion criteria: patients affected by diaphyseal forearm fracture which showed delay or non-union linked to unsuccessful results of fracture treatment after the open reduction internal fixation with an extra-articular LCP plate (1/3 tubular plate and screws 2.5 mm, DePuy Johnson); SW treatment carried out by our Orthopedic Unit; requirement of X-ray and clinical evaluation for patient management. Exclusion criteria were: unstable fractures (not properly stabilized with plate); patients aged <18 years; neurological deficits with functional impairment of the area; the presence of endocrine-metabolic pathologies (hyperparathyroidism, chronic renal failure, etc.); incomplete follow-up.

The diagnosis of delayed union was confirmed by the absence of bone callus formation on X-ray images four months after the fracture. Non-union (or pseudoarthrosis) was diagnosed in patients, with no signs of bone union at 6 months following the fracture or most recent surgery. For each patient, the epidemiological data (age, gender) anthropometric data (weight, height, BMI), smoking habit (yes/no), anatomical site of delayed or non-union (radium or ulna), any previous treatment at least 4 weeks after the fracture (non-steroidal anti-inflammatory drugs, cortisone, vitamin D integration) were recorded. The detected fracture data were: trauma time and range of bone healing in order to define delayed union (from 3 to 6 months) or non-union (> 6 months), type of trauma (high or low impact), closed or open fracture, diastases (gap expressed as mm). Previous pulsed electromagnetic field (PEMF), information relating to the treatment of SW [Energy Density Flux (EDF), number of cycles] were recorded.

Each patient was followed-up for a period of 6 months after ESWT in order to evaluate the effect of SWs on bone healing. This represents the primary endpoint of the study. The assessment times were: at the time of recruitment (T0), 2 months after treatment (T1) then at 4 months (T2) and 6 months (T3). Possible adverse effects were monitored: hematomas, ecchymosis, hyperalgesia, rupture of metal devices. X-ray images were analyzed at all the time-points for each patient enrolled. A bony union was defined as the union where the callus is bridging the fracture site in more than three-fourths of the bone circumference on both anteroposterior and lateral views of the X-ray. The delayed consolidation of fracture was defined as the presence of less than three closed corticals. Furthermore, according to Weber-Cech classification, atrophic non-union was defined as the radiographical absence of callus across the fracture gap. Hypertrophic non-union was diagnosed as obvious callus formation without sclerosis at the end of the bone healing physiological process. Oligotrophic non-union, however, was diagnosed when there was the combination of atrophic and hypertrophic conditions and so incomplete callus formation. A fracture was considered healed if the closure of at least 3 out of 4 cortices was found on X-ray. The results of radiographic assessments were based on the consensus of two independent orthopedic surgeons blinded to patient profiles. In the case of a discrepancy, a third surgeon was called for a further assessment. A district DXA exam was conducted at T0 and T3. For unhealed fractures, the DXA exam was scheduled before starting another therapy.

ESWT

All patients were treated with ESWT at our Orthopedic Unit. ESWT was applied using a shock wave device (Minilith SL1, Storz Medical, Tägerwilen, Swiss) equipped with in-line ultrasound-guidance Aloka SSD 900 (Aloka Co., Ltd. Tokyo, Japan) set on the delivery of 4000 impulses at an energy flux density (EDF) between 0.08 and 0.17 mJ/mm^2. The probe focused the treatment on the area of fracture. The impulse frequency was 240/min. Visualization of non-union was carried out under ultrasound guide. The patients were followed-up for six months until fracture healing. In the case of failure of ESWT at the first cycle another ESWT was delivered. A maximum of 3 cycles of treatment was given, at 2-month intervals and then surgery was adopted.

Bone mineral density measurement by DXA scans

Bone mineral density (BMD) of calluses was determined using DXA in a high-resolution mode (Hologic Horizon, 35 Crosby Drive Bedford, MA, 01730 USA). The region of interest (ROI) was centered on the fracture gap. Point types were marked out to exclude artifacts from the fixation plate. The entire contralateral bone without fracture was used as an internal control. DXA equipment was calibrated using a lumbar spine phantom and following the Hologic guidelines. All scanning and analyses were performed by the same operator to ensure consistency. The precision error (per cent coefficient of variation with repositioning) of DXA measurement is 1% for BMD. The BMD value was expressed in gr/cm^2 (Fig. 1).

Statistic analysis

The compiled forms were put into a database using Office Excel and analysed using Stata MP16 software. Continuous variables were expressed in mean ± standard deviation and range, the categorical variables as proportions, with the indication of the 95% confidence interval (95% CI). The normality of continuous variables was assessed using the Skewness and Kurtosis test and for those not normally distributed, where possible, a normalization model was set. Continuous variables were compared across multiple times using the Friedman test, between two times using the student *t*-test for paired data (parametric) or the Wilcoxon sign rank test (non−parametric). Univariate and multivariate logistic regression was used to evaluate the association between the healing finding (yes/no) and the demographic variables, the characteristics of the fracture and the treatment; the Odds Ratio (OR) were calculated, with an indication of 95% CI. A value p value <0.05 was considered significant for all tests.

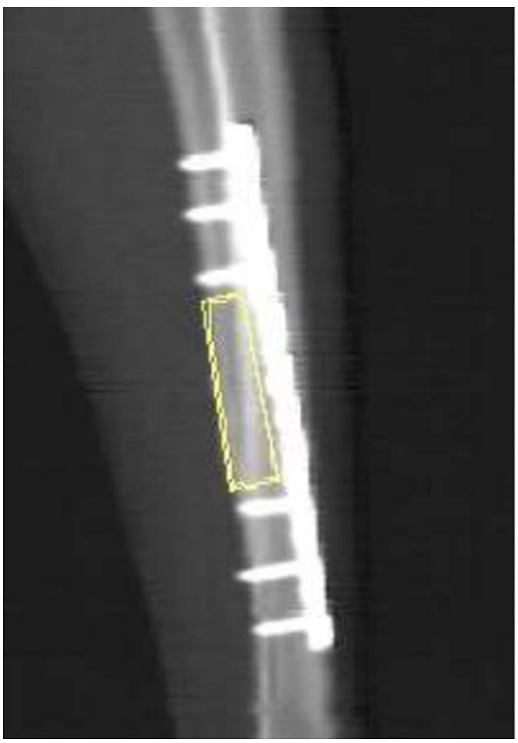

Fig. 1. *DXA image studied the fracture gap and excluded the fixation plate.*

Table I. *Baseline characteristics of sample.*

Variable	Value
Males; n (%)	14 (70.0)
Age; average± SD (range) (years)	44.9±14.5 (18-67)
Weight (Kg)	76.1±18.1 (50-122)
Height (cm)	174.1±10.9 (150-189)
BMI (kg/m^2)	24.9±4.0 (17.2-34.2)
Smokers; n (%)	8 (42.1)
Use of NSAIDs; n (%)	6 (30.0)
Use of corticosteroids; n (%)	1 (5.0)

RESULTS

The study group was made up of 20 subjects, 6 women (30%) and 14 men (70%). The mean age of the group was 44.9±14.5 years (range: 18-67), BMI 24.9±4.0 kg/cm2 (range: 17.2-34.2). The characteristics of the patients are described in Table I.

In 55% of the cases, radium was involved, in 45% ulna; 65% of the fractures were on the right, 35% on the left. The range from the traumatic event to the start of the SW was 7.5±4.2 months (range 4-20). 85% of the fractures were caused by high impact trauma, 75% were a closed fracture, and the mean value of diastasis was 2.5±1.7 mm (range: 0-7). 70% of the fractures were hypertrophic, 30% atrophic. 55% of the patients had to undergo CEMPs for an average of 24.1±31.6 days (range: 0-90). 45% of the patients took vitamin D supplementation. The number of SW cycles was 1.2±0.5 (range: 1-3), with an average EDF of 0.14±0.03 mJ/mm2 (range: 0.08-0.17 mJ/mm2). During the SW treatment sessions and at the follow-ups, no patient reported adverse reaction linked to the treatment. The study population was divided into two subgroups according to the treatment outcome. Group A (n = 4) included the cases with no complete bone union. Group B (n = 16) included the subjects with complete bone union. At T1 sixteen patients presented three closed corticals, and the data remained constant at T2 and T3. The values of the number of closed corticals and ROI, by detection time, are shown in Table II (Fig. 2). In 16/20

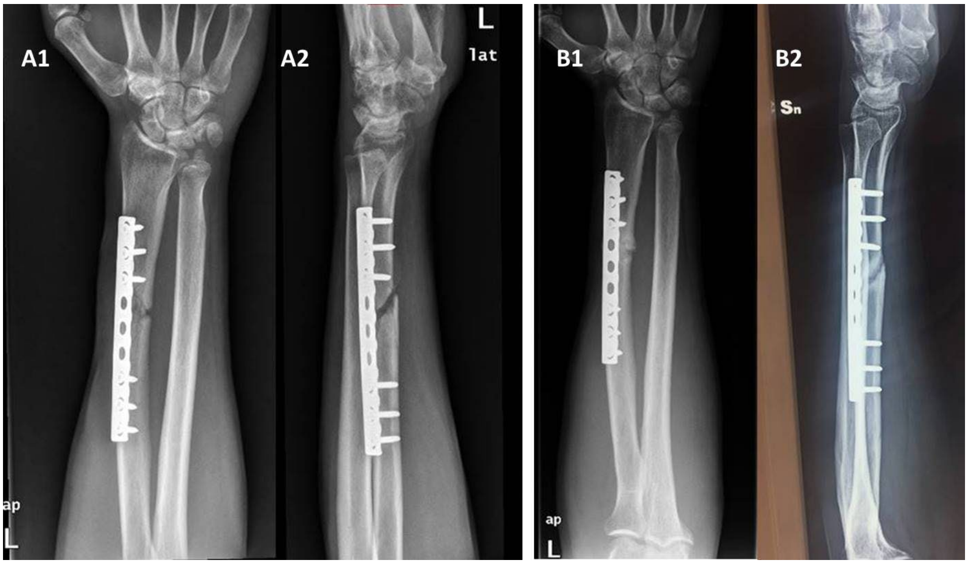

Fig. 2. *The X-ray images of a 54-year-old male showing the non-union of the left radial fracture. Before ESWT (T0) there were two open cortices in the two projections (A1 and A2). After 6 months (T3) three cortices were closed (B1 and B2).*

Table II. *Mean± SD and range of variables number of closed cortex and ROI, by detection time.*

Variable	T0	T1	T2	T3	p-value
n. of closed cortex	1.5±0.8 (0-1)	2.7±0.8 (0-3)	2.7±0.8 (0-3)	2.7±0.8 (0-3)	0.004
Fracture site ROI BMD (g/cm2)	0.47±0.15 (0.23-0.80)	-	-	0.48±0.15 (0.25-0.85)	0.162
BMD of the ROI of the contralateral seat ROI BMD (g/cm2)	0.20±0.08 (0.08-0.37)	-	-	0.20±0.08 (0.08-0.37)	0.006

(80%; 95% CI = 56.3-94.3%) treated patients there was evidence of functional recovery and bone healing.

A statistically significant difference emerged with the comparison of the pre-treatment (3.9±2.8; range: 0-8) and post-treatment (2.7±2.5; range: 0-7; p = 0.010) VAS value. Univariate and multivariate analysis did not show statistically significant associations between the healing finding (yes/no) and the determinants in analysis (p> 0.05).

DISCUSSION

In this study, by monitoring healing through the observation of the progressive closure of the callus, bridging the fracture site, it was verified that 80% of the consolidation defects of diaphyseal forearm fractures healed after SW treatment within 6 months. It was found that the density at the fracture site was greater than in the healthy contralateral segment and there were no significant changes after ESWT. While there is no experience to date on fresh fractures, it could be reasonable to use SWs on “iatrogenic fractures”, i.e. osteotomies, because these are considered likely sites of non-union, eventually even in young high-demanding patients who undergo hip replacement for sequelae of hip dysplasia (8, 9). According to the literature, there are no differences between the various types of focused generators (electromagnetic, piezoelectric, electrohydraulic) (10). Osteoporosis is not a contraindication to SW treatment, and the association with antiresorptive drugs could improve the healing effects (11). It has been found that the densitometric response was the same in cases that healed after ESWT and in cases that did not heal. These results are consistent with a previous clinical study that monitored the effects of SWs in treatment of pseudo arthrosis with bone scintigraphy: after 2 weeks, there was a significant increase in bone metabolism, both in patients with complete recovery and in those with treatment failure (12).

The present study has some limitations. Firstly, the absence of randomization, as there was no control group. Secondly, the small number of patients could potentially confound the clinical results. Thirdly, the treatment success was determined at 6 months after ESWT, a longer term follow-up may have been useful. Fourthly, only the X-ray method was used to identify fracture healing, while neither a CT scan nor a scintigraphy was performed. However, these evaluation methods are commonly accepted and considered appropriate according to clinical practice and literature.

In conclusion, ESWT is an effective method for delayed fracture healing and pseudarthrosis. In the literature, SW application in recent fractures improves densitometric values. However, the present study did not demonstrate an improvement of densitometric values. Therefore, the restorative effects may be more linked to the interaction with the collagen ultrastructure, the transmembrane molecular flows and the endocytoplasmic pathways that regulate nuclear functions than with effects on the structural and mechanical strength characteristics of the bone. Further investigations are needed to assess this hypothesis.

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