Extracorporeal shockwave therapy for atrophic and oligotrophic nonunion of tibia and femur in high energy trauma patients. Case series

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Case Report

Extracorporeal shockwave therapy for atrophic and oligotrophic nonunion of tibia and femur in high energy trauma patients. Case series

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ABSTRACT

Background: High energy diaphyseal fractures constitute a complicated matter for trauma units and urgent medical and surgical decisions to prompt stabilization of these patients, might leave some skeletal distortions that affect bone union. The objective is to evaluate the safety and efficacy of extracorporeal shockwave therapy (ESWT), as a treatment for patients with atrophic or pseudoatrophic nonunion.

Patients and Methods: Case series which included 50 patients with nonseptic and stable nonunion diaphyseal fracture of femur and tibia. They received a defined protocol of up to three high-energy ESWT (10.000 shocks per session). Each patient was evaluated with x-rays or CT between 4 and 6 weeks, to determine the necessity to continue the protocol and obtain data about initial periosteal-endosteal responses and its evolution. We analyzed, semi-quantitatively, the volume of the fracture zone from initial CT using a mathematical method to calculate the volume in cylinders, and confronting this data with Winquist Classification.

Results: 17/25 (68%) tibia and 13/25 (52%) femur nonunion were treated successfully. There were no complications during or after treatment.

Conclusions: ESWT induced bone healing in an average 60% of cases, which is consistent with current reported literature. CT studies gave some clues to patients' real condition of fracture anatomy before treatment, allowing a better decision in the orientation of ESWT application for each case. Volumetric Fracture Analysis for Winquist Classification shown that ESWT was able to induce significant bone regeneration in fractures with high volume. This kind of therapy was well accepted in reluctant patients to invasive methods.

1. Introduction

In our institution for work injuries, femur nonunion occurs in 16% considering 92,4% of high-energy fractures for this segment; for tibia, it occurs in 10% of cases, where 84% are from high-energy fractures. Nowadays accepted surgical methods to treat those difficult patients have a 50–80% of success in our hands, not free from surgical complications that prolongs time and cost of recovery and may induce psychological distress.

In many situations we need to evaluate the use of bone grafts to induce healing upon ischemic bones and/or to solve initial and significant bone fragments gaps. For these scenarios, the possibility of nonsurgical treatment like Extracorporeal Shockwave Therapy (ESWT) appears as an attractive therapeutic alternative due to its precise technical approach, noninvasiveness, being a procedure that can be repeated, presenting very low complication rates and reported bone healing percentages between 55% and 87% [1–3]. Our objective is to evaluate the safety and efficacy of ESWT, as a treatment for patients with atrophic or oligotrophic nonunion.

2. Patients and method

A case series with patients between 18 and 65 years old treated from January 2012 to December 2014 who received ESWT for management of posttraumatic aseptic nonunion of tibia or femur, significant proportion of these patients had received previous treatment for non-union including re-stabilization of bone fracture, bone autograft, bone allograft, hyperbaric oxygen therapy or a

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combination of these treatments. Were excluded patients with previous surgery in another center, pathologic fracture, septic nonunion, need for additional stabilization or loss of follow up. Were analyzed 65 patients who received ESWT, of which 15 were excluded (8 osteomyelitis, 5 surgery in another center, 2 incomplete follow up).

Success was defined as clinical signs of healing (no pain) and 70% or more of bone healing in CT or at least 3 cortices in X-ray within 10 months of the follow up period. Failure was defined as absence of any biological reactivity in the treated area at 5 months after first session of ESWT or non-achievement of success criteria.

ESWT was performed by a unique operator following a protocol of up to three sessions. Each session included fluoroscopic guidance and skin-marking for fracture topography, general sedation (iv) by Anesthesiologist, 10.000 pulses per session-Hz 3, energy flux density per pulse of 0,55mJ/mm2, using an electromagnetic Storz Duolith SD1 device with hand-piece without stand-off (Focal Area (F2) equivalent to 35 mms-65 mms and reaching up to 125 mms in depth according device specifications). ESWT was equally applied along the bone fracture rims and orientated towards exposed endosteal areas; neuro-vascular structures and areas with plates were carefully avoided. Number of ESWT sessions for each patient was based on clinical and radiological response evaluated at four to six weeks' intervals after ESWT with x-rays and/or Computed Tomography (CT).

Winquist Classification was used and complemented with Volume Fracture Analysis (VFA). Data was obtained from measurements in millimeters from first CT using formulae **(π x h x r^2)**, where **"h"** represented the longest proximal-distal distance of the fracture line and **"r^2"** corresponded to radius squared obtained from the longest transversal measurement between fragments.

The study was registered in http://www.researchregistry.com, and no ethical committee approved was required because is a observational study, the patients data remains confidential and the patients are not identifiable in the study. This research work has been reported in line with the PROCESS criteria [4].

3. Results

A total of 50 patients (femur n = 25, tibia n = 25) with diagnosis of atrophic nonunion after failure of previous treatments were included in this study, only 2 patients were excluded because loss of follow up (3,8%). 80% of the patients included were initially treated with endomedular nail device and 20% stabilized with plate. The mean age was 39,7 years, the majority of patients had and open fracture (53,7%). 47,4% required an external fixation and 38,9% went thought plastic surgery before the definitive treatment. 44% of patients had an associated fracture (long bones, pelvis or spine). These characteristics are describe in Table 1.

All patients went through surgical treatment within 48 hours after injury. Before starting ESWT, patients were in an outpatients setting, with partial weight-bearing, receiving physical therapy and psychological support if needed. The median period between definitive surgery and first session of ESWT was 9,6 months. Twelve cases of bone healing occurred after two sessions of ESWT (mostly metaphyseal fractures) and the rest received full protocol. 60% of the patients showed bone healing in an average of 5, 3 months. (Table 2). The Winquist Classification distribution was 6% for type 0, 20% for type I, 28% for type II, 28% for type III and 18% for type IV. It's correlation between the analysis of average fracture volume and success/failures for each instance is shown in Table 3, representing an estimated relationship between progressive grade of injury, volume of tissue injury and showing the final result. No complications (local edema, petechiae, skin bruises) were described among the subjects and no patient discontinued treatment prematurely. When asked about treatment, they described progressively less pain and more comfort, but those patients with painful muscle or fascial defects after trauma or plastic surgical procedures persisted with different levels of pain.

Table 1
Patient's characteristics.

	Femur	Tibia	Total
Age	36,1 yr.	43,9 yr.	39,7 yr.
Gender (male)	89,7%	88%	88,9%
External Fixation	48,3%	40%	47,4%
Open Fracture	34,5%	76%	53,7%
Plastic Surgery	41,4%	36,0%	38,9%
Smoking	45%	20%	30%
Fracture Associated	58,6%	24%	44%

4. Discussion

According to the literature [1–3] ESWT should be applied for stable and non-infected non-unions in fractures without malalignment and a gap of less than 5 mm. between bone fragments. Because many of our cases were secondary to a high energy mechanism, in some cases there was more than a 5 mm gap in their longitudinal or transverse axis. During this analysis, using CT, emerged the idea to work with "volume in fractures" and this data was obtained from a mathematical formula that provided the volume in cylinders, representing a semi-quantitatively ratio of volume to be re-vascularized. In this group of non-unions with VFA semi quantitatively measured between 8cm^3 to 171cm^3 (highest volume values represent significant gaps between unreduced fracture fragments), we proposed that the selected number of pulses are enough to induce vascular and cellular responses from endosteal to muscular areas. In this cohort, 47,4% required initially an external fixation to manage open fractures, requiring secondary plastic surgical procedures in a 38,9%, 44% had associated fractures, this added to the fact that 46% of the fractures ranked in group Winquist III and IV, reflects the high energy mechanism that provoked most of these lesions.

The programmed schedule for three ESWT sessions with CT control in 4–6 weeks after each procedure, allowed a controlled drop-out for healed patients (in this series 12 patients were able to demonstrate 70% of bone healing or more with two applications). The healing capacity of this therapy depends on its effective induction of neo-vascularization of a volume of chronic damaged tissue, a process that should occur in different areas inside this considered volume and must connect with the surrounding stable and functional blood-vessels in order to complete maturation. Different analysis of this condition indicate that oxygen tension plays an important role in healing time and its presence, delivery and consumption rates are variables altered in the central zones of the original injury volume, resulting in massive cell death and altered bone healing mechanism [5,6]' the recovery of original healing several months later, is possible when adequate and progressive revascularization ([1,3,5,7–9]) is provided. This induced repair is probably due to the appearance of progenitor cells and continue delivery of new de-differentiated cells to complete bone

Table 2
Clinical course.

	Femur	Tibia	p-value	Total
Days to Surgery (p50)	2	1		1
Months to ESWT (p50)	11,6	8,2	0,0017	9,6
Healing after ESWT	52%	68%	0,023	60%
Time to healing after ESWT	5,2 m	5,3m	0,53	5,3 m

Table 3
Fracture volume.

	Winquist 0	Winquist 1	Winquist 2	Winquist 3	Winquist 4
Number (%)	3/(6%)	10/(20%)	14/(28%)	14/(28%)	9/(18%)
^{healed} Tibia number $_{failure}$	$^{2}2_{0}$	$^{3}5_{2}$	$^{6}9_{3}$	$^{3}5_{2}$	$^{3}4_{1}$
^{healed} Femur number $_{failure}$	$^{0}1_{1}$	$^{5}5_{0}$	$^{2}5_{3}$	$^{4}9_{5}$	$^{2}5_{3}$
Average volume (cm^3)[a]	15,3	55,6	40,4	59,4	101,8

[a] Relationship average volume, W0–W2/W3–4 = 1: 2,1 cm^3.

and soft tissue remodeling [10]. These two important features, revascularization and presence of progenitor cells, have been observed and described for ESWT [11–14]**.** In this scenario it is also possible to take into account the biological process described as Endothelial Mesenchymal Transition (EndMT) [15–17], which describes the de-differentiation of endothelial cells, producing neovascularization, these cells also assume mesenchymal properties (mobility, invasiveness, phenotypic changes) and ultimately are able to transform themselves into osteoblast, chondroblast, adipoblast and myofibroblasts. EndMT is an embryological normal process involved in cardiac tissue development and today is considered a “recall mechanism” associated to normal neoangiogenesis and postnatal vasculogenesis, these two last processes induced by ESWT [18,19].

Tischer et al. [20] described a dose-dependent new bone formation induced by ESWT on intact rabbit's femurs, using 1500 pulses at 0,35–0,5-0,9–1,2mJ/mm^2 applied on a fixed ventral point in single session schedule. New bone formation was progressive in periostal-ventral position (single application point) according augmented energy flux densities (EFD), but endosteal-ventral, endosteal-dorsal and periostal-dorsal areas were almost non-reactive to EFD from 0,35 to 0,9mJ/mm^2; however, a significant response at FED 1,2mJ/mm^2 was observed in periostal-dorsal area, proposing that reflection and refraction mechanisms of shock wave have influence on bone activation. The diffraction mechanism appears to be inefficient in this study, besides the fact that it has been reported, in animal studies, that cortical bone obstructs more than 90% of the energy due to its acoustic impedance [21]. This situation suggests that shock waves should be oriented along the entire fracture bone rims and also into the exposed endosteal zones preferentially, in order to obtain a complementary induced response from endosteal areas that help recover unknown ischemic bone areas. Adequate periosteal responses was observed from two sessions in different patients beside this study, situation that it is in accordance with experimental data obtained by Kearney [22,23]**.** Our results are similar to those reported in literature [7,8,13,24] (Figs. 1 and 2), but with higher femur failure numbers (12/25, 48%). Kuo [7] reported 36,2% of failure in 22 femur atrophic fractures non-healed series.

Higher volumes fracture does not appear specifically associated with a significant index of failure. Carlier [5,9,10] consider this and others variables for critical size bone defects using an integrative in vivo-in silico approach, emphasizing about when to intervene to increase good results.

Santolini [25] in a recent review analyzed the risk factors for long bone fracture non-union, proposing an approach tending to obtain an early and precise picture of the patient's condition to achieve more accurate therapeutic decisions. In our series, to identify the cause of failures after shockwave treatment was a difficult task and we agree with Schaden [3] and Santolini [25] about the multifactorial aspects that influence these bad results. Comprehensive reviews for biological mechanisms induced by this technique have been recently published by d'Agostino [14], Ioppolo [8], Cheng [13] and prognostic factors in relation to shock wave

Fig. 1. Male, 54 y.o., high energy accident. Winquist IV, VFA: 71,6 cm^3, considering only non-healed areas at the moment to start with therapy. a) postoperative X-rays, day 2 after accident. b) due to non healing, he received firstly bone allo-autograft and secondly ORIF with second bone graft. Derived to shock wave treatment received 2 consecutive sessions; it was demonstrated initial healing at 3rd month (c–d), which evolved progressively to higher bone healing with 80% of consolidation at 6 months (e–f).

Fig. 2. Patient male, 48 y.o., high-energy open fracture (April 5, 2013); same day fracture stabilization with External Fixator (A, B). Closed intramedullary static nailing (April 11th, 2013) (C). He received autologous bone graft and 60 sessions in Hyperbaric Chamber during period till October 10th 2013. Classified as Winquist IV, semi-quantitatively calculation for volume fracture display 112 cm^3 , data obtained from (3,14 (pi) × 72,4 (h) × 492,84 (r^2)), (D, E) and display a classical view corresponding to atrophic non-union. Extracorporeal Shockwave therapy started November 15th 2013, receiving 3 treatments in a row according schedule; it was considered as advanced healing non-union by surgeon-in-chief at April 17th 2014. Last X-rays October 10th 2015 (F). In this case, significant osteogenesis has been induced from soft-tissue envelope, solving gaps between original fragments.

results for this condition have been reported by Elster et al. [1], Stojadinovic et al. [2], Schaden et al. [3], and Haffner et al. [26] describing useful considerations to take into account before deciding the use of this type of treatment, such as to recognize that patients lose their biological capacity to respond as time passes, defining 11 months as the period of time beyond which success decays [1–3,26]. We propose that patients with risk factors for bad outcome such as described by Santolini [25], should start ESWT earlier than sixth months after surgical treatment in order to have the best biological healing environment possible. Similar considerations have been proposed for cellular therapies [27] in this kind of patients, remarking the importance of treating rapidly the soft tissue damage that accompanies bone fractures, in order to minimize the devastating impact of fracture nonunions [28].

Limitations of this study include a relative short number of cases, the type od study, absence of a control group and empirically selected extracorporeal shock wave dosage and methodology in a specific cohort that received many other previous treatments like bone autograft, bone allografts or hyperbaric oxygen treatments, situations that reflect their critical condition and impaired biological responsiveness.

5. Conclusions

ESWT induced bone healing in an average 60% of cases, which is consistent with current reported literature. CT studies gave some clues to patients' real condition of fracture anatomy prior to treatment, allowing a better decision in the orientation of ESWT application for each case. Volumetric Fracture Analysis for Winquist Classification shown that ESWT was able to induce significant bone regeneration in some fractures with high volume. This kind of therapy was well accepted in reluctant patients to invasive methods.

Conflict of interest

No potential conflicts of interest were disclosed.

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Author contribution

All authors contributed equally in the research of data, concept of the manuscript and writing, approving the final manuscript.

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