

A novel bimodal approach for treating atrophic bone non-unions with extracorporeal shockwaves and autologous mesenchymal stem cell transplant

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ABSTRACT

We propose a novel approach for the treatment of atrophic bone non-unions via parallel applications of extracorporeal shock wave therapy (ESWT) and an autologous mesenchymal stem cell transplant. The hypothesis resides on the potentiality of shock waves (SWs) to act as a tool for manipulating the patient's mesenchymal stem cells (MSCs). In addition to the conventional physical stimulus achieved by delivering SWs at the site of non-union to stimulate the well-known trophic effects on bone tissue, a series of concomitant ESWT would be administered in tandem at a bone marrow donor site, such as the iliac crest, to precondition resident bone marrow stromal cells (BMSCs) *in vivo*, priming resident MSCs by enlarging and conditioning their population prior to bone marrow aspiration. The resulting sample could then be treated to further augment cell concentration and injected, under fluoroscopic control, into the non-union site through a percutaneous approach.

Introduction

One of the most challenging problems in the orthopedic field is the management of bone non-unions. The incidence of this condition is highly variable depending on site, type of fracture, and whether it is closed or open. The annual incidence of bone fractures in the U.S.A. is approximately 6 million [1] whereas the rate of permanent failure of bone healing is estimated to be 5–10% [2], although other authors report an incidence up to 50% [3]. However, the incidence is believed to be increasing, because of the improved survival rates of patients with multiple injuries [4]. Patients with nonunion can expect more long-term pain, physical disability, mental health problems, higher medical treatment costs, and a slower return to normal work productivity [5]. The economic burden of not healed fractures is relevant because of the cost of the frequently multiple treatments required and the disability associated with the condition. Kanakaris and Giannoudis made a cost identification attempt on a “best-case” scenario in the United Kingdom [6]. They estimated the direct and indirect medical costs at £15,566–17,200 for humeral, tibial, and femoral non-unions. Heckman et al. calculated the cost of treating tibial non-unions in U.S.A. to range from \$23,246 to \$58,525, depending on the method of treatment provided [7].

Regardless of the surgical treatment adopted, the success rate remains relatively satisfactory with approximately 80% of patients with good to excellent final restoration of mechanical axis alignment and proper length [8]. However, these results include all types of non-unions, and it is realistic to assume that the outcome might be significantly less favorable in the case of atrophic non-unions. Moreover, in the event of further surgery, the rate of success is usually lower. As a consequence, bone regeneration strategies have been added for boosting non-union healing. The current gold standard remains biological autologous bone grafting which, beyond its indisputable effectiveness, has a limited supply, unpredictable reparative potential, requires an additional surgical procedure and is associated with morbidities related to the harvesting procedure [9]. The use of allografts has also been successful, although they are known to undergo resorption and their demand has grown much faster than number of donors. These shortcomings have encouraged the development of artificial scaffolds with the osteoinductive and osteoconductive properties of the natural bone graft and with the capacity of housing osteogenic cells and growth factors. However, these strategies are expensive, technically challenging, and require careful management. Moreover, their value is still uncertain because of the lack of adequate clinical studies necessary to establish their usefulness.

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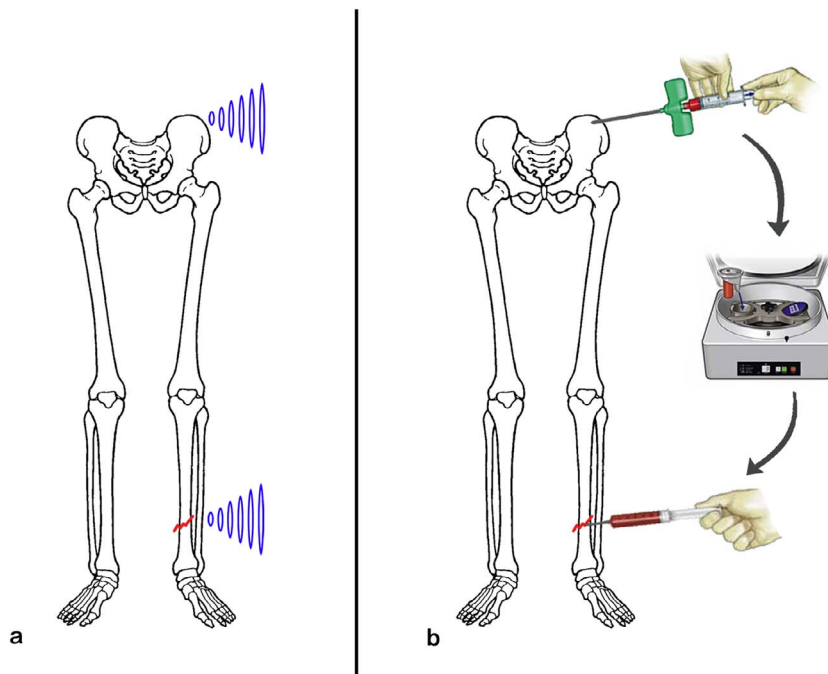


Fig. 1. a) A patient with tibial non-union undergoes 3 sessions of ESWT at the site of non-union and 3 sessions at bone marrow donor site. b) Immediately following the 3rd ESWT session, bone marrow is aspirated from the iliac crest, MSCs are concentrated via density gradient centrifugation, and the resulting BMAC is injected at the site of non-union under fluoroscopic control. *International Orthopaedics (SICOT) 2014;38:2585.*

Stem cell therapies are gaining momentum in translational research. For example, the use of MSCs via percutaneous bone marrow aspirate concentrate (BMAC) transplants is a potential tool for achieving the goal of augmenting patient biology to promote bone healing [10]. BMAC injections have been shown to be effective in the treatment of non-unions. It has also been demonstrated that the concentration of progenitors was positively correlated to a larger volume of mineralized callus and that greater numbers number colony-forming units lead to faster healing times [11].

Aside from stem cell therapies, ESWT is another conservative technique that has been successfully employed for treating bone non-unions [12–14]. The most relevant findings of many experimental studies indicate that SWs promote MSC growth and differentiation toward osteo-progenitors through Transforming Growth Factor β 1 (TGF- β 1) and VEGF induction [15,16]. Moreover, recently other mechanisms have been proposed among which Sun and colleagues showed that ESWT induces ATP release and promotes MSC osteogenic differentiation via P2x7 receptors [17]. SWs may also increase the expression of other relevant factors, such as SDF-1 [18–21], although there is not a consensus about the ability of ESWT to regulate SDF-1 expression [22]. Also relevant, SDF-1 it was discovered that SDF-1 is pivotal in the homing and repopulation of MSCs in bone marrow [23].

ESWT in long bone fracture non-unions has been shown to have a success rate ranging from 54% to 98%, depending on the anatomic location of the non-union as well as the elapsed time after the injury and before treatment [24–26]. In light of these results, it has been stated that ESWT is as effective as surgery in achieving healing of long-bone hypertrophic non-unions.[27] However, the results of ESWT in atrophic non-unions are definitively less successful [13,28,29]. Based on this body of evidence, there is an irrefutable need to develop innovative therapies to enhance the bone healing course.

Rationale

The rationale relies on three assumptions:

1. Atrophic non-unions are associated with a deficiency of MSCs at the fracture site [29]. This justifies the transplantation of new cells at the site of injury that can act with two mechanisms [30]:
 - a) direct pathway; transplanted cells integrate into the ischemic site

and then differentiate in cells specific to the host/homing tissue; b) indirect or paracrine pathway; transplanted cells secrete trophic agents and proangiogenic factors that attract resident MSCs to the site of injury and promote angiogenesis, indispensable for tissue reconstruction [31].

2. The number of MSCs in the bone marrow is limited (0.01% of bone marrow cell population) and the results following non-expanded MSC transplantation are unpredictable [32]. As a consequence, current use of MSC therapy often relies on laboratory cultivation and expansion of autologous bone marrow derived MSCs followed by reimplantation at the site of injury. However, cell culture has several drawbacks: the preparation of MSCs is time consuming and it may introduce potential risks; furthermore, therapeutic potency declines with time and with repeated passages in culture [33].
3. SWs are effective in promoting neovascularization and bone healing [19–21] Furthermore, SWs enhance trabecular bone volume and thickness of the treated bone [34] and are able to stimulate biological processes in MSCs, including increased proliferation, survival, and migration [35–37] and to promote osteogenic differentiation of MSCs and of adipose-derived stem cells [38,39]. ESWT may thus represent a potential tool for manipulating MSC behavior for clinical applications.

The hypothesis

Our idea is to the promote healing of atrophic bone non-unions with a combined strategy based on two, concurrent applications of ESWT. One implementation of ESWT would be employed for the well-established biophysical stimulation of the injury site, with the aim of inducing up-regulation and expression of several angiogenic and osteogenic growth factors. A common treatment protocol made of 3 high-energy focal SWs might be suitable. Contemporaneously, another course of ESWT should be delivered at a bone marrow donor site (e.g. the iliac crest) of the patient with the aim of stimulating the bone marrow resident cell population to induce MSC replication and, possibly, their differentiation toward the osteoblastic line. On the same day of the last series of coupled ESWT and after completing the treatments, a bone marrow sample would be harvested from the donor site, centrifuged to increase MSC concentration and then injected under fluoroscopic guidance into the site of pseudoarthrosis (Fig. 1).

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