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How Does Pulsed Low-Intensity Ultrasound Enhance Fracture Healing?

Pulsed low-energy ultrasound, a non-invasive therapeutic treatment modality, may improve callus formation and enhance fracture healing by initiating enhanced angioneogenesis.

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The use of pulsed low-energy ultrasound for the enhancement of fracture healing is a non-invasive therapeutic modality gaining popularity. It was first described by Heckman et al[1] in 1994 and Kristiansen et al[2] in 1997. Since then, the efficacy of this method has been supported by results published by a number of investigators[3-8] while others detected no benefit from its use.[5,9] Recent basic research projects have focused on the molecular-biologic algorithm of the bone-growth enhancement induced by pulsed low-energy ultrasound.[4,10-13]

All studies were conducted on experimental fracture models and on in vitro tissue cultures. They showed that daily use of pulsed low-energy ultrasound for 20 minutes per treatment until bone healing was completed stimulated the secretion and local concentration of biological active substances like IL-8, basic FGF, and VEGF,[10,14] and enhanced osteogenesis[4,9-12,14,15] and proteoglycan synthesis.[13] It was shown to increase mechanical strength of the healing callus in diabetic rats without affecting cell proliferation.[16] By what cellular mechanism can mechanical stimuli enhance bone healing?[3-5,9,17,18] The molecular biology of this reconstructive ladder has so far not been defined. For a fractured bone to heal, the biologic algorithm requires an optimal arterial blood supply and a preserved muscle envelope[19-21] as a basic condition. The following describes an unusual sequence of events in an adult patient that may shed light on the algorithm of events induced by pulsed low-energy ultrasound in bone formation and thus fracture healing.

Case Report

A 54-year-old man presented with persistent calf pain. On clinical examination, the color of the skin in the distal half of the left calf was dusky, and peripheral pulses could be palpated around the medial side of the ankle and on the dorsum of the foot (at the tibialis posterior and dorsalis pedis). Computerized angiography demonstrated a significant stenosis in the trunk of the celiac artery, and a significant stenosis at the origin of the left common iliac artery. No pathology was found in the femoral arteries (common, superficial and deep). A Doppler dynamic blood-flow study showed a 25% reduction in the left lower limb. It was concluded that the persistent pain in the left lower calf, aggravated by effort, was of ischemic origin.

Figure 1: Bone ends proximal to the femoral condyles, in end-to-end contact, aligned with an intramedullary rod. No callus or bone forming detectable proximal to the femoral condyles.

Past medical history revealed a comminuted fracture of the left patella caused by a low-energy injury sustained in 1979.

The leg was initially casted, but within a few weeks had developed a burning sensation behind the knee radiating along the calf. He underwent several conservative treatments that did not alleviate the pain.

In 1989, arthrodesis of the left knee was performed using Charnley's technique, using the patella as a bone graft. A good bony union was achieved, but the pain persisted.

In 2002, he underwent total knee replacement (TKR), with the bone cut in the femur just proximal to the remnants of the femoral condyles. The calf pain persisted and a deep surgical wound infection developed. Surgical debridement left a large soft-tissue defect, that was covered by a rotation flap of the medial head of the gastrocnemius muscle. Three months later, the prosthesis had to be removed and the bone ends brought into contact and stabilized with an intramedullary rod extending from the greater trochanter to the level of the ankle joint (Figure 1). The patient was ambulating on two Canadian crutches, but the original pain persisted. No signs of bone growth or bony union could be detected in the following nine months in the bone gap left by removal of the prosthesis. Therefore, an Ilizarov four ring frame was constructed around the knee. For six months, no radiological signs of osteoneogenesis around the bone gap in the femur developed, and the calf pain worsened.

Based on successful and rewarding clinical results in the treatment of difficult fracture nonunions and tendon-to-bone anchorage achieved with the use of pulsed low-energy ultrasound by our team[8] and by Tsunoda[22] and Deehan and Cawston,[23] our recommendation for this patient was a treatment protocol of local use of Exogen (Smith & Nephew, Memphis, Tenn) for 20 minutes daily for a maximum of 180 treatments. In addition, he was started on a home program of alternating distraction (0.25 mm, 8 hourly, for three consecutive days), 48 hours of rest followed by a similar period of distraction, and then 48 hours of rest in the Ilizarov frame. After 8 weeks on this program and 56 Exogen treatments, callus formation appeared at the bone gap. Radiological union with a proliferative callus was established after two further weeks of treatment (Figure 2).

Thus, the Ilizarov frame was removed after three months. For additional precaution, the patient was put into a knee cage with a locked knee hinge in extension. He reported a marked reduction in the pain intensity in the calf and behind the left knee.

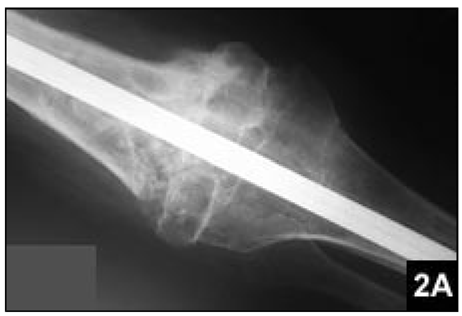

Figure 2: AP (A) and lateral (B) radiographs of the same supracondylar area of the femur as in Figure 1, with developing callus after pulsed low-energy ultrasound treatments.

Discussion

The use of pulsed low-intensity ultrasound as a non-invasive, bone-growth enhancing modality in fracture treatment has been reported extensively since 1994.[1-18,22,23] A multitude of findings have been reported by study groups investigating the molecular biology aspects of the pathway of its influence on connective tissues.[4,9-15] Gebauer et al[1 suggested that low-intensity pulsed ultrasound increased the callus strength in healing fractures but did not affect cellular proliferation. Wang et al[14] reported ultrasound treatment to induce nitric oxide-mediated hypoxia-inducible factor-1 alpha activation as well as vascular endothelial growth factor-A expression in human osteoblasts. Reher et al[10] published observations on it affecting tissue production of IL-8, basic FGF, and VEGF.

Successful osteoneogenesis in the biological algorithm requires an undisturbed arterial blood supply to the affected tissues.[19-21] Our patient provided an unusual opportunity to follow the sequence of this biological algorithm under relative ischemi as documented by computerized angiographic findings.

Osteoneogenesis was suddenly enhanced following continuous, daily exposure to pulsed low-intensity ultrasound supplemented by cyclic compression and distraction. Others have also reported bone-growth enhancement in healing of long bone fractures stabilized in thin-wire-ring fixation frames by the addition of pulsed low-energy ultrasound to the treatment protocol.[4-8,10,14,15,22] Therefore, the sequence of clinical events in the reported patient, together with the published findings that pulsed low-energy ultrasound stimulates VEGF secretion,[10,14] strongly support the possibility that pulsed low-energy ultrasound improves callus formation by initiating enhanced angioneogenesis[19,20] in the developing callus.

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