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The Impact of Low-Intensity Pulsed Ultrasound (LIPUS) on Risk Factors for Fracture Nonunion

Gregory J. Della Rocca,[1] Christopher R. Brodie,[2] Andrew J. Harrison[2]

[1]University of Missouri Orthopaedics, Columbia, Missouri, [2]Bioventus LLC, Durham, North Carolina

Correspondence to: Andrew J. Harrison, Email: andrew.harrison@bioventusglobal.com

ABSTRACT: Approximately 5% of bone fractures fail to completely heal, and can thus progress to nonunion. We evaluated the evidence relevant to four risk factors known to be associated with impairment of fracture healing (smoking, diabetes, advanced age and osteoporosis), and the effects of low-intensity pulsed ultrasound (LIPUS) on fracture healing for patients with these risk factors. Clinical evidence for risk-factor mitigation and nonunion healing is consistent with a large body of research on the LIPUS mechanism of action, demonstrating that LIPUS can enhance key biological processes involved in bone repair including angiogenesis, progenitor cell recruitment and differentiation, callus mineralization and remodeling.

Keywords: Fracture, LIPUS, ultrasound, nonunion, smoking, diabetes, age, osteoporosis

In 1994, the United States Food and Drug Administration approved low-intensity pulsed ultrasound (LIPUS) to accelerate healing of fresh fractures of the mid-shaft tibia or distal radius (EXOGEN, Bioventus LLC, Durham, NC). Currently, EXOGEN is the only drug or device approved by the FDA for acceleration of fresh fracture healing. This therapy was also approved in 2000 for treatment of established fracture nonunions in all bones, exclusive of skull and vertebrae.

Approximately 5% of fractures progress to nonunion.[1] Patients with a fracture nonunion often have continued pain, are unable to work, and may require additional surgical intervention. LIPUS has been evaluated for the treatment of established nonunions in various bones.[2] Multiple definitions of fracture nonunion exist, with various time periods after fracture used to define a nonunion. Nevertheless, it is

evident from the orthopedic literature that all healing processes have stopped in a nonunion, and healing can only be initiated by another procedure, since no spontaneous healing is expected.[3] This definition accepts the fact that bones heal at different rates and relies on the experience of the treating physician to decide when to intervene.

RISK FACTORS FOR NONUNION

Fracture healing is a complex process which involves multiple cell types and coordinated biological actions. Healing requires reduction of the fracture gap, re-establishment of cortical continuity, stabilization of the fracture, with eventual normalization of blood perfusion.[4] For most patients, these criteria are sufficient to support healing. However, some patients do not heal even when the mechanical requirements for bone repair have been met. Orthopedic surgeons know from experience that certain patient-related risk factors can adversely affect fracture repair. A survey of 157 orthopedic surgeons was done to identify risk factors believed to influence healing.[5] In rank order, these factors were fracture location (13%), smoking status (11%), fracture gap (10%), diabetes (7.5%), osteoporosis (6%) and advanced age (5%). Smoking status, diabetes, osteoporosis, and age are patient-related factors, rather than injury-specific factors, that may impact fracture biology.[5] In this review, we evaluate the evidence related to four risk factors known to be associated with impairment of fracture healing: smoking diabetes advanced age and osteoporosis. We also report on the effects of LIPUS on fracture healing for patients with these risk factors.

Smoking

Smoking is one of the most widely recognized risk factors for impaired bone healing. In a survey of 335 orthopaedic surgeons, approximately 82% believed that a history of smoking would increase the risk of healing complications.[5] Smoking is associated with a variety of physiological changes that inhibit fracture healing.[6] Impaired perfusion of the extremities is common in smokers, perhaps due to chronic vasoconstriction from nicotine. Smokers are also 6-fold more likely to develop deep infections after surgery.[7] A study of tibial shaft fracture patients concluded that smokers are significantly more likely to develop delayed unions and nonunions ($p=0.0007$) and more than three times more likely to have impaired bone healing.[8]

LIPUS treatment was shown to accelerate healing of fresh fractures in two randomized placebo-controlled clinical trials. Acceleration of healing was noted in both smokers and nonsmokers, though the acceleration was greater among smokers. In conservatively-managed fractures of the tibial diaphysis[9] and distal radius,[10] patients treated with LIPUS healed 38% faster, on average, than controls. A further analysis of

these patients revealed that smokers improved healing rate even more, with 41% faster healing of tibia fractures and 51% faster healing of radius fractures.[11] In data from an FDA-mandated post-market registry of nonunion patients, smoking was commonly associated with patients developing a chronic nonunion of longer than one year duration.[3] Chronic nonunion patients allocated to treatment with LIPUS heal in approximately 86% of cases.[3]

Diabetes

The prevalence of diabetes continues to rise, with 29.1 million cases in the United States (9.3% of the total population), according to a 2014 report from the U.S. Centers for Disease Control and Prevention.[12] In the U.S., 25.9% of people over the age of 65 have diabetes. Individuals with diabetes are known to have compromised healing in both soft tissue and bone. The combination of impaired healing and peripheral neuropathy can be problematic; 60% of non-traumatic lower limb amputations involve diabetics.[12] The effect of diabetes on fracture healing was documented in a large, retrospective case-control study, comparing 563 fractures with complications (delayed union, nonunion or mal-union) to 2,252 matched controls; diabetes emerged as one of the key risk factors (along with NSAID use and motor vehicle crash), regardless of fracture location or type of complication.[13] In a cohort of 31 closed diabetic fractures of the lower extremities, time to fracture healing was 63% slower than normal, and 87% slower in cases with initial fracture displacement that required open reduction.[14] Given the complex pathophysiology of diabetes, many aspects of the disease may contribute to poor healing, including electrolyte and endocrine imbalances, compromised immune responses and infection, peripheral neuropathy, vascular insufficiency, and microvascular pathology.[15]

Despite the biological challenges faced by diabetic fracture patients, clinical evidence suggests that LIPUS may overcome these obstacles. In a large, FDA-reviewed registry of fracture nonunions treated with LIPUS, the healing rate for known diabetics was 82% (71/87). This value is not significantly different from the heal rate of 83% (1283/1546) for the entire registry.[16] Given the similarity, one may infer that LIPUS mitigated the impact of diabetes on healing of nonunions. Animal studies provide the most robust mechanistic explanation for how LIPUS might enhance fracture healing in diabetics. Compared with nondiabetic controls, diabetic rats healed more slowly and produced substantially lower levels of VEGF and fewer new blood vessels within the fracture callus.[17] Treatment of diabetic fractures with LIPUS significantly increased VEGF and the number of new blood vessels, restoring them to levels comparable to those of normal (nondiabetic) control rats.[17]

Age

Humans heal more slowly with advanced age, and aging is a risk factor for delayed fracture healing.[18]

Most fractures in the elderly are low-energy fractures as a result of falls, and are often associated with osteoporosis.[19]

LIPUS has a proportionately greater effect on fracture healing times in older patients.[9] Patients older than 30 years of age required an average of 187 days to heal tibial fractures, but this was reduced to 103 days when LIPUS therapy was utilized. The average time to fracture healing in patients over age 30 who were treated with LIPUS was 3 weeks faster on average than untreated patients under 30. In a cohort of 4,190 patients with fresh fracture (< 90 days) treated with LIPUS,[20] older patients (≥60 years) had a similar heal rate to the population as whole, suggesting that older age can be mitigated as a risk factor for impaired fracture healing by LIPUS.

Osteoporosis

Osteoporosis, a metabolic condition in which bone mineral density is lower than normal, is common in the elderly. Bones are therefore more likely to fracture after low-energy trauma. Osteoporosis is a challenge for fracture management because of the difficulty of achieving stable internal fixation in patients with poor bone stock.[21]

LIPUS was effective at healing chronic nonunions in patients with osteoporosis, based on data from a post-market registry of 1,546 nonunions.[16] Patients with osteoporosis healed at a rate of 78% (32/41), compared to the overall healing rate in the registry of 83%, which suggests that osteoporosis is not a risk factor for healing in the presence of LIPUS.[16] A possible explanation of this effect is that LIPUS may enhance the expression of genes important for osteogenesis, angiogenesis, or bone remodeling, which may be down-regulated in the pathological osteoporotic state.[22,23]

In a preclinical study investigating the use of LIPUS for fracture healing in osteoporotic rats, analysis of callus morphometry demonstrated a 26–30% increase in callus size, with significant differences noted between LIPUS-treated rats and non-LIPUS controls, with regard to callus width and callus area ($p<0.05$). Radiography also showed that bridging of the fracture gap occurred about 2 weeks earlier in the LIPUS group than the control group.[24] LIPUS triggered significant, phase-specific increases in expression of

osteogenesis-related genes for type I collagen, BMP-2, angiogenesis-related VEGF, and for the remodeling gene RANKL, all of which are postulated to potentiate efficient fracture healing.

DISCUSSION

LIPUS can accelerate fresh fracture healing and can induce healing in fracture nonunions, even in the setting of compromised healing of the patient. Fracture-specific characteristics may not be susceptible to intervention by the clinician, yet patient-specific risk factors can be modified to augment patient healing. The orthopedic surgeon can potentially use LIPUS to create an optimal mechanical and biological environment for healing following appropriate reduction and stabilization of the fracture.

Surgical treatment of established fracture nonunions can be associated with patient morbidity, and may not be effective for patients with key risk factors. For example, smoking, diabetes, advanced age, or osteoporosis can all contribute to nonunion and may not be mitigated by surgery. Even small increases in fracture healing potential may be beneficial, since the alternative (surgical intervention) is costly to the patient and the medical system, and may fail.[5] While future research could be beneficial in further quantifying the mitigating effect of LIPUS on nonunions in patients who present to the clinic with underlying, complicating patient factors, it is evident from existing reports that LIPUS can mitigate certain patient-related risk factors that impair fracture healing.

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