Postsurgical Enhancement of Fracture Repair: Biophysical Alternatives to Bone Grafting*

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ABSTRACT: Surgical intervention of fracture repair is usually achieved without complication. Although bone grafting is the most common method of enhancing fracture repair, several biophysical alternatives may accelerate the natural healing process and can be used to treat complications, such as delayed or nonunion fractures. This article describes low-intensity pulsed ultrasonography, electrical stimulation, and axial dynamization.

Veterinary orthopedic surgery is continually developing. There is growing interest in alternative therapies for improving and accelerating fracture healing. This article discusses the availability and possible clinical use of biophysical alternatives to bone grafting, including low-intensity pulsed ultrasonography (LIPU), electrical stimulation, and axial dynamization.

THERAPEUTIC ULTRASONOGRAPHY

Ultrasonography has various applications in surgery, diagnostics, and therapy. The frequency range commonly used in ultrasonography varies from 0.8 to 15.0 MHz. Surgical and physical therapy intensities range from 1 to 50 W/cm², with the aim of inducing significant tissue heating. To avoid tissue heating in diagnostic ultrasonography, much lower intensity (1 to 50 mW/cm²) is employed. Recent investigations have suggested that LIPU in the diagnostic range can stim-

*A companion article entitled “Postsurgical Enhancement of Fracture Repair: Biologic Alternatives to Bone Grafting” appeared in the March 2001 (Vol. 23, No. 3) issue of Compendium.
the treated fractures was greater than that of the controls, but the difference was only significant in patients treated with the 1.5-MHz signal (P < .02).

In 1994, an LIPU device received FDA approval for use in human patients on a prescription basis to treat fresh tibial diaphyseal and distal radial metaphyseal fractures. A log of cases recorded over the subsequent 3-year period showed an overall healing rate of 91.8% (3432 of 3737). This study included fresh, delayed-union, and nonunion fractures. In nonunion fractures (those not healed at 270 days or longer after fracture), the healing rate varied from 70% for humeral fractures to 90% for radial fractures.

These results support other findings in the literature that have described a 38% acceleration in healing rate for LIPU-treated fractures, with treated cases reportedly healing in 61 days compared with 98 days in those not subjected to LIPU.

Possible Mechanisms of Healing

The specific mechanism by which LIPU stimulates healing is unknown, but a number of possible mechanisms have been proposed. These include suggestions that the ultrasound pressure waves may mediate biological activity due to mechanical deformation of the cell membrane or by an indirect response to an electrical current caused by cell deformation. The absorption of ultrasonographic energy is directly related to the density of the tissue through which it is passing. Absorption results in heat production; reflection of the incident beam can cause acoustic pressure variations within the tissues.

Additional suggestions include oscillation of small air bubbles (stable cavitation) that may be involved in speeding the fracture repair process; this may be facilitated by accumulation of air at a fracture site after traumatic fracture. The process by which the molecular and biochemical effects arise is the subject of much investigation. An increase in exchange rates of potassium ions in rat thymocytes has been shown to occur under the influence of LIPU.

In another study, the effect of LIPU was examined in rats with surgically created bilateral femoral shaft fractures stabilized with intramedullary Kirschner wires. Treated limbs were exposed to 15 minutes of ultrasonography, providing an average intensity of 30 mW/cm², with the contralateral limb acting as a control. At 21 days after surgery, the average maximum torque was 22% greater than that of the control legs. The stiffness of the treated fractures was greater than that of the controls, but the difference was only significant in patients treated with the 1.5-MHz signal (P < .02).

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Others have reported acceleration of tibial fracture healing by approximately 40%.

In both the previously described studies, no surgical intervention was necessary and a cast was the sole means of external support. Data from some of these studies cannot be applied directly to veterinary patients as some of the fractures (e.g., humeral) were of non–weight-bearing limbs.

Aggrecan gene expression in cultured chondrocytes has been shown to be upregulated. The importance of...
Pulsed electromagnetic fields have been shown to result in an increase in transforming growth factor–β (TGF-β) mRNA, and it has been proposed that this could be related to the induction of cartilage differentiation. Alternate mechanisms have been suggested, such as upregulation of mRNA for bone morphogenetic protein (BMP)–2 and BMP-4.

Current uses of electrical stimulation can be categorized into three types: constant direct-current stimulation using percutaneously placed electrodes (invasive), time-varying inductive coupling produced by a magnetic field (noninvasive), and capacitative coupling (noninvasive).

**Indications for Use**

The use of electric stimulation in fracture healing has been confined largely to symptomatic, unstable, and radiographically confirmed nonunion fractures. It has been suggested that biologically inactive and avascular nonunion fractures required a bone graft to start the healing process as this type of fracture is largely unresponsive to electrical stimulation alone. A previous report has suggested that nonunion fractures with pseudarthrosis or a fracture gap greater than half the diameter of the bone are unlikely to respond to electrical stimulation. Thus it is still important to ensure that adequate stabilization of the fracture site is implemented. Because several reports have suggested that this technique is of little benefit in treating fresh fractures and treatment often lasts for hours at a time, electrical stimulation is unlikely to become widely used in routine veterinary orthopedics. However, the value of this method of treatment in human orthopedics is demonstrated by the fact that in 1997, pulsed electromagnetic field therapy generated $180 million of revenue.

**Constant Direct-Current Stimulation**

Constant direct-current stimulation requires the placement of stainless-steel cathodes into tissue. The cathodes are used to electrically induce osteogenesis. This system permits a constant current between 1 and 20 µA to be delivered to the fracture site. Using this technique, one study reported a success rate of 62.5% for nonunion fracture repair in 24 human patients. A later study by the same lead author described an overall healing rate of 78% (258 patients) for nonunion fractures treated with 20 µA of constant direct current. The authors concluded that a rate of union comparable to that of bone grafting could be achieved with a lower associated risk.

**Time-Varying Inductive Coupling**

The inductive coupling method was developed by Bassett and colleagues. This technique uses pulsed electromagnetic fields to produce a current of 20 mV, which equates to 10 µA/cm² in the tissues. This tech-
These findings contradicted the expectancy that there was a statistically significant decrease in the probability of healing if a previously used treatment was repeated. This was repeated.

In another human study, authors described an overall success rate of 64% (149 patients) for patients treated with the inductive coupling method, where the mean time after injury was 2.5 years. The authors stated that radiographic interpretation at 3 months could be predictive of the potential success of the treatment in 85% of cases.

A controlled double-blind randomized study on fracture healing in humans described the efficacy of a pulsed electromagnetic field on tibial nonunion fractures (16 to 32 weeks after injury). Fifty-one patients who had previously received cast fixation were included in the study. An electromagnetic field was applied for 12 hours per day for 12 weeks. Blind radiographic assessment demonstrated union in 9 of 20 patients (45%) who received the treatment, whereas only 3 of 22 patients (14%) showed signs of union in the placebo group. The authors concluded that electromagnetic stimulation accelerates the progress to union. This technique usually requires an average of 10 hours of treatment per day with no break longer than 10 minutes. The fracture must also be well immobilized with little weight bearing.

**Capacitative Coupling**

The noninvasive capacitative coupling method developed in 1985 involves the use of disc electrodes attached to the skin, with use of a conductive gel in order to deliver a uniform electric field to the fracture site. Investigators performed a prospective double-blind study using this technique in 23 patients with a nonunion fracture of a long bone. The nonunion fracture responded in 6 of 10 patients receiving electrical stimulation administered for 24 hours daily and none of the 11 who received a placebo treatment.

A retrospective study to compare the effectiveness of bone graft versus capacitative coupling devices for treatment of tibial nonunion fractures compared healing rate and risk factors and made predictions of success and probability based on the outcome of 271 human patients with nonunion fractures. A major finding was that there was a statistically significant decrease in the probability of healing if a previously used treatment was repeated.

**AXIAL DYNAMIZATION**

The concept of axial dynamization has been described for the treatment of long bone fractures. Axial dynamization has been defined as fixation that allows unrestricted axial loading of a fracture by physiologic weight bearing and muscle contraction while bending and rotational loading are controlled. The proposed mechanisms by which dynamization affects the process of healing include stimulation of periosteal callus proliferation in the early phase and acceleration of remodeling and hypertrophy of the bone cells later in the healing phase of repair. There is further evidence that interfragmentary motion stimulates callus formation, consolidation, and osteogenesis. Investigations have shown that axial dynamization can decrease load sharing by an external skeletal fixator and increase load transmission through an intact bone column. This reduces pin–bone interface stresses and decreases the frequency of pin loosening and pin-tract infection in dog tibiae.

**Studies**

Dynamization has been studied most extensively in long bone fractures, particularly of the tibia and femur. One author described his initial experiences with a dynamic axial fixator in 288 human patients with fresh fractures and another 50 with ununited fractures. The success rate (described as less than 5° angular deviation or rotation, less than 1 cm shortening, full range of motion, and no requirement for external support to assist full weight bearing) was 94% in both groups, with average healing times of 3.4 to 6.5 months and 4.7 to 6.5 months for the fresh and ununited fractures, respectively. The dynamic axial fixator has a telescopic facility within the body of the bar that allows conversion from rigid to dynamic fixation by removal of a single screw. These fractures were initially fixed in a rigid configuration, and only then was radiographic evidence of periosteal callus formation (usually around 3 weeks). The screw blocking axial movement was then removed and dynamic loading begun. The motion is uniaxial, with the design of the equipment preventing bending or torque.

Studies have been performed on the effect of the Orthofix dynamic axial fixator (Orthofix SRL, Verona, Italy) in order to quantify the type and size of motion that occurred with this type of external skeletal fixation. The findings showed that there was a greater cyclic motion at 2 to 4 weeks (average, 0.75 mm) when the fixator was in a rigid configuration than when it was released into its dynamic form. It was proposed that unlocking the fixator allows permanent closure of the fracture gap and prevents the rigid external skeletal fixator from acting like a spring. This in turn reduces the weight load on the external skeletal fixator and allows for more direct load transfer through the fracture gap. These findings contradicted the expecta-
tions of some authors who expected increased motion at the fracture site after dynamization. Large cyclic movements may act as a stimulus to callus growth in the early phases of fracture repair, but increased stability and compression may be more appropriate in the later stages.

The effect of imposed axial dynamic micromovement has been studied. Forty-five human patients with severe tibial diaphyseal fractures were treated using a unilateral external skeletal fixator. Twenty-three patients had a firmly rigid spinal column, and 22 had a column in which longitudinal micromovement could be generated by a spring system attached to the rod. The module was adjusted to permit 1 mm additional axial movement than would have been possible with the natural stiffness of the column. The fixed frames had a maximum fracture movement between 7 to 13 weeks, which then decreased as fracture stability increased. The rigid frames had 50% greater longitudinal axial motion compared with when the module was activated. A further component of this study was micromovement initiated by a pneumatic system giving 1 mm axial movement at 0.5 Hz for 20 minutes per day. The patients in whom micromovement was initiated had a mean healing time of 23 weeks compared with 29 weeks for the rigid constructs. The authors proposed that the addition of a pneumatic system might be beneficial in the early non–weight-bearing postoperative phase as there is no motion at the fracture site during this period.

A prospective randomized trial of human patients investigated three different methods of external skeletal fixation. Group 1 was treated with a fixator that was unlocked at 4 to 6 weeks by removal of a locking nut to allow axial motion. Group 2 was similarly unlocked at 4 to 6 weeks when there was radiographic evidence of callus, but a silicon spring was included to allow 2 mm of axial motion; group 3 had the same mechanism, but it was unlocked at the start of weight bearing. The results of the study showed that 2 mm of axial cyclic micromotion on weight bearing produced (1) a mean delay in healing of 3 weeks when results were compared with the fixator, with an accompanying spring being unlocked at 4 to 6 weeks, and (2) a delay of 6 weeks compared with the rigid fixator that was unlocked, allowing axial compression at 4 to 6 weeks. The conclusion of this study was that axial dynamization in group 1 tended to close the fracture gap and allow faster healing than in groups 2 or 3. The authors further suggested that 2 mm of cyclic motion might be too great as previous studies had shown that 0.7 mm of motion at an early stage in the repair decreased time to union. This extra motion may obliterate the periosteal collateral circulation present in the early phase of the fracture repair. This finding was consistent with previous suggestions on the topic.

Few studies actually describe the optimal type and degree of motion and when it should be applied to the fracture. From the reports discussed in this series, it would seem that induced micromovement during the non–weight-bearing phase followed by rigid fixation for 4 to 6 weeks and then destabilization of the construct to permit axial compression of the fracture gap may provide optimal conditions for rapid repair. In veterinary patients, this destabilization may be best achieved by simply reducing the number of pins or by staged disassembly of the construct. This technique has previously been described. Rigid external fixation of transverse canine tibial osteotomies was initially destabilized and compared with the same osteotomies that were continuously stabilized with rigid external fixation on the contralateral limb. Destabilization by conversion from a type III to type I configuration after 4 to 6 weeks resulted in increased periosteal callus formation but decreased mechanical strength with a high degree of fibrous and cartilaginous tissues. Destabilization at 6 weeks did not result in increased periosteal callus formation or bending strength, but histologic sections of the fracture site demonstrated a combination of woven and lamellar bone, with the appearance of more active remodeling of primary bone healing. Destabilization at 12 weeks did not produce any noticeable effects when studied at 15 weeks. The overall impression from this study was that increased weight bearing and fracture loading at the appropriate time might enhance the remodeling and hypertrophy of the primary bone healing.

**SUMMARY**

Several biophysical methods are available to supplement fracture repair and stimulate healing. LIPU and axial dynamization appear to be the techniques most suited to applications in veterinary medicine. The FDA has already approved LIPU for use in human orthopedics, and research and clinical use have demonstrated that its use is beneficial in both fresh-fracture and delayed-healing situations. This technique would be particularly suited to veterinary patients because it could be used by the owner on a daily basis or alternatively on an outpatient basis. Because of cost and availability, the most likely way of using axial dynamization in veterinary patients would be progressive destabilization of an external skeletal fixator rather than use of a dynamic-type construct used in human patients.
REFERENCES

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The most commonly used frequency of LIPU is in the range of 10 to 20 KHz.

LIPU intensity recommended in the described studies is in the range of 1 to 50 mW/cm^2.

The types of electrical stimulation that have been used to aid fracture healing include all but which of the following?

1. High-voltage point therapy
2. Inductive coupling
3. Capacitative coupling
4. Constant direct-current stimulation

Active fracture site micromotion is most beneficial at what stage of healing?

1. At the conclusion of healing, to stimulate remodeling
2. During late callus formation when stability has already been achieved
3. Early in the process, before weight bearing has begun
4. Active micromovement has been shown to be contraindicated.

Which of the following is not a documented theory explaining the mechanism by which LIPU works?

1. Ultrasonic pressure waves cause cell membrane deformation, thereby directly stimulating biologic activity.
2. Cell deformation creates an electric current, which stimulates biologic activity.
3. Ultrasonic waves generate heat, which increases blood supply to the callus.
4. Ultrasonography may cause oscillation of small air bubbles, which in turn may stimulate biologic effect.

Which of the following fracture-healing aids is currently most applicable to veterinary medicine?

1. LIPU therapy
2. Constant direct-current stimulation
3. External fixation providing active micromotion

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d. No method has been shown to have efficacy, and therefore none should be used.

7. Which of the following has not been suggested as a mechanism by which electrical stimulation may act?
   a. increased insulin-like growth factor II
   b. increased synthesis of extracellular matrix molecules
   c. increased mRNA for BMP-2 and BMP-4
   d. increased blood flow to the fracture site

8. Which of the following combinations is a noninvasive method of electrical stimulation?
   a. inductive coupling and constant direct current
   b. inductive coupling and capacitative coupling
   c. capacitative coupling and constant direct current
   d. constant direct-current and high-voltage point therapy

9. Electrical stimulation has been shown to have its greatest effect when used to treat
   a. fresh closed fractures.
   b. fresh open fractures.
   c. nonunion or delayed-union fractures.
   d. cases where osteomyelitis is present.

10. The method of dynamization most applicable to veterinary orthopedic surgery is
    a. progressive destabilization by cutting or removing pins.
    b. the addition of a module to provide axial motion.
    c. the addition of extra pins to the external skeletal fixator.
    d. use of a specially designed dynamic fixator.