Researchers offer simple, inexpensive way to improve healing after massive bone loss

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Bones are resilient and heal well after most fractures. But in cases of traumatic injury, in which big pieces of bone are missing, healing is much more difficult, if not impossible. These so-called "large segmental defects" are a major clinical problem, and orthopaedic surgeons struggle to treat them, especially among the military in places like Afghanistan.

Now research led by investigators at Beth Israel Deaconess Medical Center (BIDMC) offers surgeons a new approach. Described on-line in today's issue of the Journal of Bone and Joint Surgery, the results confirm that the bone healing process of large segmental defects is exquisitely sensitive to its mechanical environment and suggests that "reverse dynamization," a straightforward and inexpensive process, could help speed healing of these traumatic injuries.

"Bones are greatly influenced by their mechanical environment, which is why casts, rods, plates and screws are typically used to heal fractures – with a great deal of success," explains senior author Christopher Evans PhD, Director of the Center for Advanced Orthopaedic Studies at BIDMC. "But until now, no one has examined the relevance of the mechanical environment to the healing of large segmental bone defects."

According to the American Association of Orthopaedic Surgeons (AAOS), these injuries are one of the most demanding surgical challenges faced by orthopaedic trauma surgeons. Often as large as 20 centimeters in length, large segmental defects can be complicated by regional soft-tissue loss, reduced vascularity, regional scarring and infection. The AAOS notes that an increased number of missions being conducted on foot in Afghanistan has led to an increase in this type of combat blast injury.

Changing levels of stiffness during bone healing is known as "dynamization." During standard dynamization, bone is first held rigidly in place by a mechanical intervention, or fixation device. Once healing has begun, the stiff rigidity is loosened to allow movement. "An 'external fixator' is placed on the outside of the skin and usually has a 'cross-bar' that determines the level of rigidity and can be adjusted to allow more or less motion," explains Evans, who is also the Maurice Edmond Mueller Professor of Orthopaedic Surgery at Harvard Medical School. Evans and his colleagues thought that how firmly or loosely injured bone is held together by mechanical interventions –casts, rods, plates and screws – could impact these large segmental bone defects, just as it does for more minor fractures—but with one big difference. The scientists changed stiffness levels in the opposite order—hence, "reverse dynamization."

"Our laboratory has a lot of experience with a rat model of segmental defect healing, and we noticed that during the healing process, the defect first fills with cartilage, and then the cartilage turns to bone," says Evans. Technically known as "endochondral ossification" this process is well documented to occur in fracture healing. 'We knew from other previous work that the early formation of cartilage is helped when mechanical fixation is loose. We also knew that a subsequent increase in fixator stiffness would provide the rigidity needed for the ingrowth of blood vessels and other aspects of healing." Evans and his coauthors hypothesized that a period of loose "fixation" followed by a period of stiffened "fixation" would accelerate healing of large segmental defects. "If bones are allowed to move slightly, cartilage will form in the defect," he adds. "If the area is then held rigidly in place, the new cartilage will then turn to bone."

The team constructed external fixators capable of providing varying degrees of stiffness during the healing process. By implanting a growth factor called bone morphogenetic protein-2 on a collagen sponge, the scientists initiated healing of segmental defects in the femurs of 60 rats. Groups of the animals were then allowed to heal with either low-, medium-, or high-stiffness fixators. Healing also took place under conditions of reverse dynamization, in which the stiffness levels were changed from low to high after a period of two weeks. After eight weeks, the researchers assessed healing using various measures including radiographs, microscopic analyses, and mechanical tests.

The investigators found that when they looked only at unchanging stiffness, the low-stiffness fixator produced the best healing; however, by comparison, the reverse dynamization provided considerable improvement, leading to a marked acceleration in the healing process by all tests. Also, notes Evans, the bone mineral content and bone area of the defects healed by reverse dynamization were closer to normal, and the healed bone had greater mechanical strength.

"Our study confirms the exquisite sensitivity of bone healing to its mechanical environment," he notes. The next step, says Evans, will be to see if this therapy works in large animals, while also gathering more information about the biological mechanisms that are at play. But, he adds, moving these findings into a clinical setting should be relatively straightforward. "The nice thing about this approach is that it's simple and could be rapidly translated to human use if our proposed large-animal studies are successful. The regulatory hurdles should be minor." Furthermore, he adds, reverse dynamization might also be applicable to other situations for which bone healing is problematic. "Sometimes in smokers or individuals with diabetes, fractures heal poorly," he notes, adding that the same can be true when an infection is present.

Reverse dynamization is also an attractive option in terms of cost.

"Often, strategies devised in the lab to solve clinical problems are far too complex and expensive to be translated into meaningful clinical use," notes study coauthor Mark Vrahas, MD, Chief of the Harvard Orthopaedic Trauma Service. "But if the promise of this strategy holds out, it will be inexpensive enough to be used even in developing countries, where the burden of severe injuries are particularly high."

Provided by Beth Israel Deaconess Medical Center

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