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Impact of Analgesia on Bone Fracture Healing

BONE fractures are painful and, in general, temporarily disabling injuries that occur after trauma or as an end result of various pathologic conditions, such as osteoporosis or bone invading cancer (pathologic fracture). It is common practice for acute pain services to be heavily involved in the treatment of orthopedic patients, and although it is usually understood that fractures are very painful, few studies have directly attempted to measure or define the nature of the pain after a fracture. In addition, controversy exists regarding the effects of analgesics, including opioids and nonsteroidal antiinflammatory drugs, on skeletal tissue healing. In this issue of ANESTHESIOLOGY, reports from Freeman *et al.*[1] and Minville *et al.*[2] show that commonly used fracture healing models also can be used to assess pain quantitatively and therefore to assess analgesic efficacy. Because bone is a highly innervated tissue, these models also can be applied to define the mechanism of pain transmission after fracture. Furthermore, and of even greater clinical importance, these fracture pain models lend themselves to studying the effects of pharmacologic interventions on bone healing.

Bone fractures are treated by restoring the anatomy of the broken bone (reduction) and immobilizing the bone pieces (fixation) while regeneration proceeds. Commonly, fracture fixation is done by casting the broken bone. This also can be achieved surgically by use of intramedullary rods or external fixators that use percutaneous pins or rods to hold the bone fragments in correct anatomical alignment. In these cases, the fracture site is not significantly disturbed and the fractures heal by bone regeneration. Initially, the fracture causes localized tissue hypoxia and hematoma formation and is soon followed by a robust inflammatory response. Next, mesenchymal cells migrate and proliferate at the fracture site to form a callus. Concomitantly, osteoblasts in the periosteum near the fracture site begin to proliferate. At the interface with the periosteal osteoblasts, the mesenchymal cells differentiate into chondrocytes and elaborate a cartilage matrix. Eventually, the chondrocytes undergo hypertrophy and mineralize the cartilage matrix, which then acts as a substratum for osteoblast bone formation. This process is reiterated from the periphery of the fracture site toward the center until the fracture is bridged with newly formed bone and is dependent on angiogenesis. Subsequently, the bony callus is remodeled to restore the mechanical properties of the bone. This is the normal endochondral ossification pathway of fracture healing and is often referred to as secondary fracture healing. In contrast, primary fracture healing occurs only after surgical fixation of the fracture in which the fracture callus is removed, and the bone ends are closely abutted and rigidly fixed in place, usually with a plate. In this case, the fractures heal slowly *via* normal bone remodeling mechanisms while the metal plate stabilizes the fracture and provides for any weight-bearing functions.

Pharmacologic treatments that can affect the molecular and cellular processes of bone regeneration can have a significant impact on healing. For example, fracture healing is severely impaired in rats treated with TNP-470, an antiangiogenic compound.[3] More important in terms of pain management, nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors, such as celecoxib, impair fracture healing in animal models.[4,5] Eight weeks after fracture, twice the normal bridging time in rats, femur fracture healing had failed in approximately one third of female rats treated with celecoxib (4 mg/kg daily) for 5 days after fracture. However, celecoxib therapy before fracture or celecoxib therapy initiated 2 weeks after fracture had no significant effect on healing in rats. Limited retrospective data also indicate that these effects may translate to humans.[6] Among acetabular fracture patients treated with indomethacin or localized radiation to prevent heterotopic ossification, 29% of those patients treated with indomethacin experienced a non-

This Editorial View accompanies the following two articles: Minville V, Laffosse J-M, Fourcade O, Girolami J-P, Tack I: Mouse model of fracture pain. ANESTHESIOLOGY 2008; 108:467–72; Freeman KT, Koewler NJ, Jimenez-Andrade JM, Buus RJ, Herrera MB, Martin CD, Ghilardi JR, Kuskowski MA, Mantyh PW: A fracture pain model in the rat: Adaptation of a closed femur fracture model to study skeletal pain. ANESTHESIOLOGY 2008; 108:473–83.

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union in another long bone fracture as compared with 7% of the patients treated with localized radiation.

Similarly, opioids are most frequently used to treat severe pain caused by metastatic bone cancer (*e.g.*, breast and prostate cancer) but do have a variety of nonskeletal (and potentially skeletal) side effects that could inhibit bone healing. Opioid side effects such as sedation, clouding of mental status, or cognitive impairment can reduce mobility, resulting in loss of bone and muscle mass. This is particular disturbing in the elderly population, where hip fractures have a 20% mortality rate within the first year and bed rest needs to be as short as possible to minimize inactivity-induced bone and muscle loss as well as pulmonary complications.

Opioids also may have direct, detrimental effect on bone healing. Recently, it was shown that analgesic therapy provided by morphine accelerated sarcoma-induced bone destruction and doubled the incidence of spontaneous fracture in mice.[7] It is not known whether the findings in this model of osteolytic sarcoma will generalize to other cancers or opioids. For example, tramadol did not significantly inhibit human osteoblast activity *in vitro*.[8] Undoubtedly, these data suggest a need for increased research in this field. Identifying new analgesic therapies that will enable early physical therapy and that do not impair healing or cognitive function may provide real lifesaving benefits for many patients.

Despite this obvious need, the pain response after fracture has not been studied previously in detail in any animal model. Minville *et al.*[2] and Freeman *et al.*[1] demonstrate that common fracture models used in mice and rats to study fracture healing can be applied to studying the mechanisms of pain transmission and the extent to which analgesic therapies can ameliorate pain. Using a closed tibia fracture model in mice, Minville *et al.* assessed subjective pain and measured mechanical and thermal nociception in the affected limbs using von Frey hairs and a modified hot-plate test, respectively. As expected, pain scores were highest in the days immediately after fracture and began to decline approximately 5 days after fracture, which likely corresponds to resolution of inflammation after the fracture. Morphine or ketoprofen treatment significantly reduced pain. Similarly, using a closed femur fracture model in rats, Freeman *et al.* were able to show that behavioral indications of pain after fracture (guarding behavior and flinching) closely followed the voluntary amount of weight displaced by the rat on the fractured limb. As might be expected, these indicators of pain were highest in the first days after fracture and began to recede after approximately 7 days. Morphine treatment dose-dependently decreased measures of pain. However, the investigators noted that the highest morphine dose tested (10 mg/kg) led to lethargy in the rats, which impeded the researchers' ability to measure improvements in weight bearing with this dose.

The animal models described in this issue of ANESTHESIOLOGY by Freeman *et al.*[1] and Minville *et al.*[2] seem to be posed ideally to advance the science in this field further and foster collaborations among orthopedic surgeons and anesthesiologists. An advantage of the rat fracture model seems to be that the fracture production is easily accomplished in the larger rats and, overall, more knowledge has been gained in various pain models in rats, but the mouse fracture model affords the possibility of using genetically modified animals. Although neither study ultimately assessed the effects of morphine or ketoprofen on fracture healing outcomes (yet), these studies demonstrate that established fracture models can be used to measure the effects of different therapies on pain and bone healing, thereby providing us with a tool for further improvement of the surgical outcome of our orthopedic patients.

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