Nonsteroidal Anti-Inflammatory Drug-Induced Fracture Nonunion: An Inhibition of Angiogenesis?

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Nonsteroidal Anti-Inflammatory Drug-Induced Fracture Nonunion: An Inhibition of Angiogenesis?

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Background: Approximately 5% to 10% of fractures may result in delayed union or nonunion. The results of research done over the past three decades have shown that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has an inhibitory effect on fracture repair, but the exact mechanism of action remains to be elucidated. Cancer research has identified that NSAIDs impede cell proliferation by inhibiting angiogenesis. It is proposed that a similar mechanism occurs in the induction of NSAID-induced nonunions. This hypothesis was investigated in a randomized placebo-controlled trial of the NSAID rofecoxib with use of a murine femoral fracture model.

Methods: Two hundred and forty mice were randomized to receive either the nonsteroidal anti-inflammatory drug rofecoxib (5 mg/kg orally) in a 0.5% methylcellulose solution (the NSAID group) or the 0.5% methylcellulose solution only (the control group). Two hundred and thirty-five of the 240 mice underwent surgery to induce an open transverse mid-diaphyseal femoral fracture, which was then treated with use of a custom-made external fixator. Five additional animals underwent sham surgery with no fracture induced. Outcomes measures included radiographic assessment, histologic analysis, biomechanical testing, and use of laser Doppler flowmetry to assess blood flow across the fracture gap.

Results: Radiography revealed similar healing patterns in both groups; however, at the later stages (day 32), the NSAID group had poorer healing. Histological analysis demonstrated that the control animals healed quicker (at days 24 and 32) and had more callus and less fibrous tissue (at days 8 and 32) than the NSAID animals did. Biomechanical testing found that the control animals were stronger at day 32. Both groups exhibited a similar pattern of blood flow; however, the NSAID group exhibited a lower median flow from day 4 onward (significant at days 4, 16, and 24). Positive correlations were demonstrated between both histological and radiographic assessments of healing and increasing blood flow. NSAID-treated animals exhibited lower blood flow and poorer healing by all parameters. Regression analysis, however, demonstrated that the negative effect of NSAIDs on fracture repair is independent of its inhibitory action on blood flow.

Conclusions: Following the development of a novel method of analyzing functional vascularity across a fracture gap, we have demonstrated that the cyclooxygenase-2 (COX-2) inhibitor rofecoxib has a significant negative effect on blood flow across the fracture gap as well as an inhibiting effect on fracture repair.

Clinical Relevance: COX-2 inhibitors are marketed as having low side-effect profiles. We propose that these drugs should be used with caution in all patients following osseous trauma and, in particular, after injuries that may already predispose a fracture to a delayed union due to osseous, vascular, or patient-related factors.

Five to 10% of all fractures may result in delayed union or nonunion[1]. Reports of the association between nonsteroidal anti-inflammatory drugs (NSAIDs) and impaired fracture-healing have been published in the literature since the 1970s[2]. Since then, many laboratory studies[3-7] have confirmed this association and, more recently, several clinical studies[8-10] have demonstrated a strong correlation between NSAIDs and fracture nonunion, particularly in association with long-bone and high-energy injuries.

An audit was conducted of all general practitioners in Northern Ireland to determine their analgesic prescribing pattern following osseous trauma[11]. The results of the audit indicated that NSAIDs were the second most commonly prescribed drug across all injuries studied and that more than 50% of respondents prescribed this class of medication for injuries that were already prone to nonunion, such as compound diaphyseal tibial fractures[11].

NSAIDs exert an effect on fracture-healing by inhibiting

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cyclooxygenase and thereby inhibiting the formation of prostaglandins. Prostaglandin E_2 (PGE_2) is abundantly produced by osteoblasts and is known to have both anabolic and catabolic effects[12-14]. Over a period of time, however, the effect is primarily weighted in favor of bone formation. Therefore, an inhibition of cyclooxygenase[15] will lead to less PGE_2 and, therefore, less bone production[16,17].

The use of traditional NSAID medications has been reported to be the cause of more than 100,000 hospital admissions and 16,500 deaths in the United States per year[18]. Following the identification of the inducible cyclooxygenase-2 (COX-2) enzyme in the late 1980s, increasingly specific COX-2 medications were developed, as these medications were expected to have decreased side-effect profiles. In addition, much investigation has been directed toward possible new therapeutic uses of COX-2 medications, including for the treatment of primary and secondary tumors[19,20] or for neurological disorders, such as schizophrenia[21] and Alzheimer's disease[22]. The mechanism behind the effect of NSAIDs on tumors is relevant to the current investigators because this class of drugs has been shown to act by inhibiting angiogenesis by a COX-2 pathway[23,24]. As far back as the 18th century, it has been recognized that blood flow is essential for normal osseous formation and subsequent fracture-healing[25]. We propose that the mechanism of action of NSAIDs in the inhibition of fracture repair is by an inhibition of blood flow to the fracture gap. This hypothesis was investigated with use of an externally fixated murine femoral fracture model of repair.

Materials and Methods

Animal Model of Fracture Repair

All animal experiments were carried out in accordance with the United Kingdom Animals (Scientific Procedures) Act (1986) at the Queen's University Belfast Biomedical Research facility. Four-month-old male Carworth Farms Lane-Petter mice (Laboratory Services, Queen's University of Belfast, Belfast, Northern Ireland, United Kingdom) underwent a standard open femoral osteotomy as previously described[26]. General anesthesia was induced with use of a gaseous mixture of 3% isoflurane in a 50:50 mixture of N_2O_2:O_2 at 2 L/min in a sealed chamber. Once anesthetized, the animals were transferred to the operating table, with the same mixture of gases delivered by way of a Hunt mask. The animals were given a bolus dose of 1 mL of 0.9% sodium chloride containing 0.1 μg of buprenorphine to maintain fluid homeostasis and for postoperative analgesia. Through an anterolateral approach, the left femoral shaft was exposed and clamped in a specially designed jig. Four holes, each angled at 7° to the perpendicular, were drilled through both cortices with use of a 0.55-mm drill bit. Fixator pins (0.51 mm) were inserted into the holes, and a metal fixator crossbar was loosely placed over the pins and held at 10 mm from the bone surface while a low-energy transverse osteotomy was made between the two central drill holes. The geometry of the drilling jig and crossbar ensured that the distance between the central two pinholes in the crossbar was 0.7-mm less than the distance between the two pinholes in the femur; thus, sliding the crossbar down the pins and toward the bone produced compression of the fracture gap at a standard bone-to-bar distance of 4 mm. The tops of the pins were then cut and secured with use of a small drop of quick-drying glue, and the wound was closed. To enable the assessment of sequential radiographic and vascular changes across the fracture gap, the external fixator bar was modified from a four-hole to a seven-hole construct. Two perpendicular holes were created to allow connection with an x-ray jig, and a central conduit was made to enable passage of an optical fiber.

In total, 235 animals (103 control animals and 132 NSAID-treated animals) underwent surgery to induce a fracture. To further validate the model for sequential assessment of radiographic changes and blood flow at the fracture site, five additional animals underwent sham surgery. These animals had a routine surgical approach with the application of an external fixator and a laser Doppler probe; however, no actual fracture was induced. It was hypothesized that as there was no fracture to heal, these animals would have no changes in either radiographic or Doppler readings. A radiographic assessment of healing was carried out for all 240 animals, histologic analysis was obtained for fifty-four, biomechanical testing was performed on fifty-two, and laser Doppler blood-flow measurements were acquired for sixty.

Delivery of Treatment

The human dose of rofecoxib is 12.5 to 25 mg per day for osteoarthritis and 25 to 50 mg per day for acute pain. We used an equivalent murine dose to the human dosing regimen of 25 mg per day. The murine equivalent dosage (5.1 mg/kg per day) was calculated with use of the approved dose calculator of the United States Food and Drug Administration[27]. Once daily, with use of an oropharyngeal feeding tube, the animals received a 0.2 mL oral solution that contained either 0.25 mg of rofecoxib in a 0.5% methylcellulose solution (the NSAID group) or 0.5% methylcellulose solution only (the control and sham surgical groups).

Outcome Measures

Radiographic Assessment

Following surgery, each of the animals had a digital radiograph made of the fractured limb (at days 4, 8, 16, 24, and 32). With the animals under light general anesthesia, the x-ray jig was placed through the external fixator bar, thereby controlling for rotation in all planes, and the animal was placed on its side in the x-ray chamber. Digital radiographs were quantitatively analyzed with use of a freely available software program (UTHSCSA ImageTool; Department of Dental Diagnostic Science, University of Texas Health Science Center at San Antonio, San Antonio, Texas [http:ddsdx.uthscsa.edu]). The pixel density of the fracture gap was compared with two adjacent areas of uninjured bone. As callus was laid down at the fracture gap during repair, the pixel density of the fracture gap increased with respect to that of the uninjured adjacent bone. Results were expressed as "relative bone-mineral content." In-

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traobserver analysis with use of this method was associated with a low error rate with a single-measure intraclass correlation coefficient of 0.9769 (p < 0.0001).

For all animals, the density of the fracture gap was assessed until the animals were killed or until it was noted that the fracture had >50% displacement or that the fixator had displaced or broken. If this occurred, the animals were killed and removed from further study.

Histologic Analysis

After each animal was killed (fifty-four animals total, days 8, 16, 24, and 32), the hind limb was disarticulated and amputated below the knee. Specimens were coded and then fixed in 4% paraformaldehyde for twenty-four hours before undergoing decalcification in 7% formic acid. Following decalcification, the external fixators were carefully removed, taking care not to damage the fracture morphology. The specimens were then embedded in paraffin blocks, from which 7 μm sections were cut, mounted on slides, and stained with hematoxylin and eosin. Slides were analyzed under a light microscope with use of qualitative as well as semiquantitative scoring systems. Each slide received a score that was based on the type of tissue that was observed at the fracture gap: a score of 1 indicated the presence of mostly fibrous tissue; 2, mostly cartilage; 3, both cartilage and bone; 4, little cartilage remaining and mostly bone; and 5, remodeled bone. Specimens were also analyzed with use of an image analysis software program (Scion Image; Scion Corporation, Frederick, Maryland) to calculate areas of bone, new callus, cartilage, or fibrous tissue. All results were calibrated to the femoral diameter in order to standardize for variances in animal size. Slides were examined on two occasions at two months apart with the examiner blinded to time of harvest and to whether or not the animal had received drug treatment. Examination revealed a high intraobserver correlation (intra-class correlation coefficient 0.8461; p < 0.000). To further validate the model, radiographic and histologic results were correlated, and they demonstrated positive relationships at both day 24 (r = 0.849, p = 0.016) and 32 (r = 0.626, p = 0.013).

Biomechanical Testing

After each animal was killed (fifty-two animals total, days 24 and 32), the hind limbs were disarticulated and amputated below the knee. Sharp dissection was used to dissect off all soft tissues, taking care not to disturb the callus. The specimens were stored in moist gauze for transport to the testing facility. All femora were analyzed with use of three-point bending (NEXYGEN MT data-analysis software; Lloyd Instruments, United Kingdom) within six hours after harvesting. The femur was placed on custom-made struts, 9 mm apart, with a 100-N superior load cell delivered through a superior strut directed to the mid-diaphyseal region at a rate of 3 mm/min. Data were collected concerning peak load to failure, and stiffness was calculated from load-displacement curves. Data were also collected from the contralateral intact limb of each animal, and the results were expressed as a percentage of this limb to control for variations in animal size.

Laser Doppler Flowmetry

To measure blood flow at the fracture gap in real time, the principles of laser Doppler flowmetry were utilized in sixty animals. We used a laser Doppler flowmeter (Oxylab ML192 Dual Flow meter; Oxford Optronics, Oxford, United Kingdom), which comprised a light source and receiver, optical cables, and data-analysis software. This unit utilized a 1-MW Class-1 laser with a 780-nm wavelength and a sampling rate of 10 to 22 Hz. A 0.5-mm chronically implantable optical fiber was passed through the central conduit of the external fixator and secured adjacent to the fracture gap. The tip of this cable became surrounded by the callus during repair. The remaining cable was secured inside a snap-fit cylindrical container that surrounded the external fixator, and was removed only at testing intervals (days 4, 8, 16, 24, and 32). To minimize any extraneous influences of atmospheric conditions and movement artifact during testing, the animals were placed on a heating mat (37° C) and kept under light general anesthesia, the overhead lights were switched off, and after a three-minute settling period, the lowest value of flow was measured over a one-minute testing period. Following testing, the optical cable was disconnected from the light source and replaced in the protective cylindrical container.

Statistical Analysis

All data were transferred to statistical spreadsheets and analyzed with use of a commercially available statistical program (Statistical Package for the Social Sciences [SPSS] software, version 11; SPSS, Chicago, Illinois). Whenever possible, data were analyzed with use of parametric measures (independent-samples t test). However, because of the small size of some groups and the nonconformity of some results to the normal distribution, it was also necessary to use a nonparametric mode of analysis (Mann-Whitney U test). Differences due to treatment and healing time were considered significant at p < 0.05 for all tests. Correlations were analyzed with use of the Spearman rank-correlation test, and backwards linear regression was then performed. Data were expressed on box and scatter plots where appropriate.

Results

Etiological Variables

Animal age (and standard deviation) ranged from ten to twenty weeks (mean 14.1 ± 2.98 weeks). It was noted that the NSAID animals were, on the average, two weeks older than the control animals (p = 0.014). Animal weight ranged from 35.6 to 56.0 g (mean 45.28 g ± 4.28), and there was an average nonsignificant weight change of –0.42 g during the investigation.

Radiographic Assessment

Radiographic assessment revealed that the sham group had a small drop-off in bone-mineral content at the fracture gap during the period of the experiment, but the magnitude of this change was small when compared with the change in the two treatment groups (change in bone mineral content at the fracture gap from day 0 to day 32: sham group, 0.35%; control

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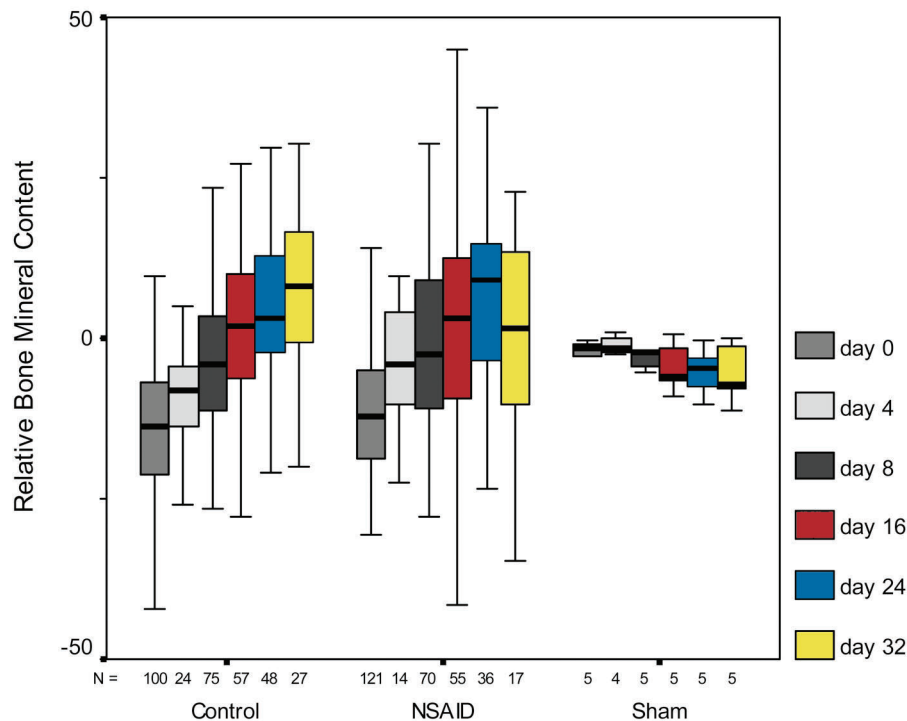NONUNION: AN INHIBITION OF ANGIOGENESIS?

Fig. 1
Graph shows the relative bone-mineral content for the control and NSAID groups.

group, 29.8%; NSAID group, 24.5%). There were no statistical differences between the two groups (control and NSAID) immediately after surgery, and both groups demonstrated a stepwise increase in bone density during the experiment with a gradual widening in the range of results as time progressed. There was a trend toward significant differences between the control and the NSAID groups at day 32, with the control group exhibiting greater bone-mineral content at the fracture gap (p = 0.051, Fig. 1).

Histologic Analysis
Results of the qualitative histologic analysis are illustrated in Figure 2 and demonstrate a progressive increase in scores in both groups. Control animals scored significantly better than the NSAID animals from day 8 to day 24 and through day 32 (p = 0.016 and 0.003, respectively) and between day 16 and day 32 (p = 0.013). There were no significant differences for the NSAID-treated animals across these time intervals. There was a significant difference between the treatment groups at day 32 (p = 0.004), with the control animals having more advanced stages of repair. Semiquantitative analysis suggested that control animals tended to exhibit more callus at day 8 (p = 0.050) and at day 32 (p = 0.070). NSAID-treated animals had a significantly greater area of cartilage at day 8 (p = 0.014) and more fibrous tissue at day 32 (p = 0.024).

Biomechanical Testing
Control animals achieved a greater median value for both peak load to failure and stiffness across time compared with

NSAID-treated animals. These differences, however, were not significant. A significantly larger proportion of animals from the NSAID group failed to survive until the predesignated harvesting date (58% of the NSAID group compared with 28% of the control group; p = 0.001). This was primarily due to fixator failure and fracture displacement. If all animals that were entered into this limb of the study were examined on an "intention-to-treat" basis and assigned a value of 1% if removed from the study due to fixation and/or fracture displacement, then the control animals did exhibit a significantly greater biomechanical integrity for peak load and stiffness at day 32 (p = 0.028 for both).

Laser Doppler Flowmetry
Results for control, NSAID, and sham blood flows are illustrated in Figure 3. The sham group had a small but significant rise in flow from day 0 at both days 8 and 24 (each p = 0.043). Both the control and the NSAID groups exhibited a greater magnitude of change. There were no significant differences between the two groups at day 0. Thereafter, flows in both groups rose, peaking at days 8 to 16 before falling back to resting levels at day 32. Control animals exhibited a greater median flow at all time intervals, which was significant at days 4 (p = 0.050), 16 (p = 0.032), and 24 (p = 0.007).

Correlations and Regressions
There were significant relationships between higher blood flow and improved fracture repair at various time intervals; higher flows at day 4 were associated with improved healing

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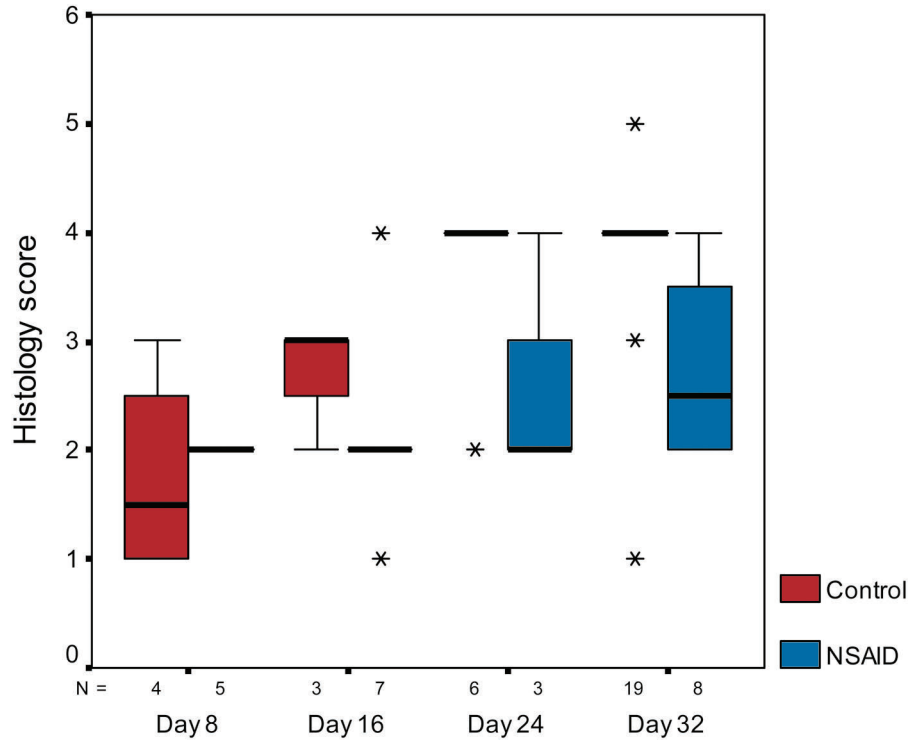NONUNION: AN INHIBITION OF ANGIOGENESIS?

Fig. 2

Graph shows the qualitative histologic scores over time. The results for the control group are significantly different from the results for the NSAID group at day 32 (p = 0.004).
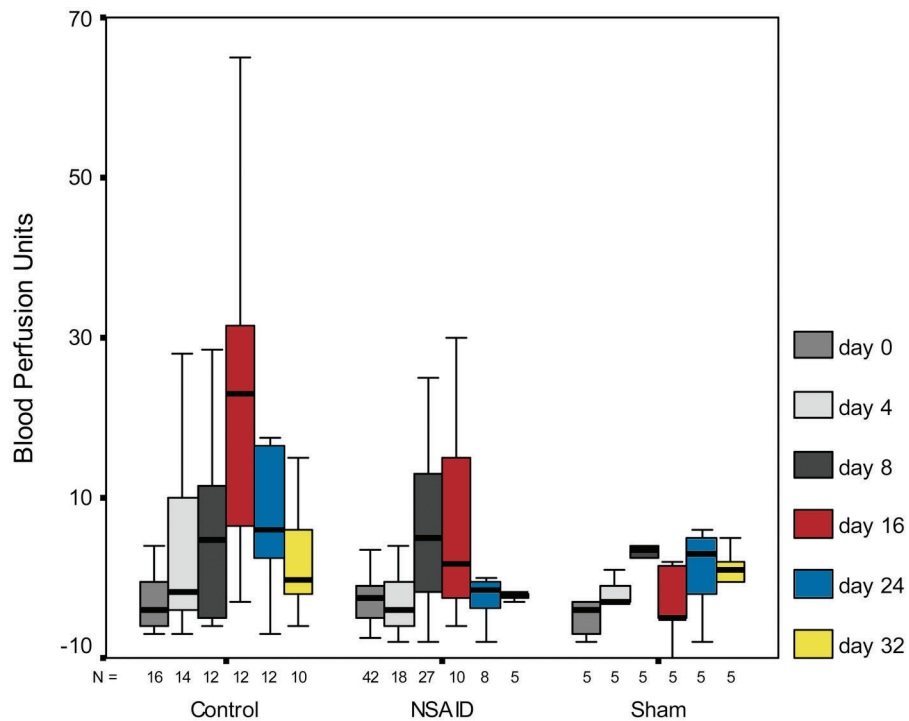

Fig. 3

Graph shows the blood flow (blood perfusion units) for each treatment group. The results for the control group are significantly greater than those for the NSAID group at day 4 (p = 0.050), day 16 (p = 0.032), and day 24 (p = 0.007).

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radiographically at day 24 (p = 0.020, r = 0.657), and higher flows at day 16 were associated with improved healing radiographically also at day 16 (p = 0.045, r = 0.645). A greater change in blood flow from day 0 was also associated with better repair histologically at day 32 (p = 0.002, r = 0.724).

To investigate if the relationships between alterations in flow and fracture repair were causal, linear regression models were then completed. These results suggested that, although alterations in blood flow had a significant association with fracture repair, this effect was independent of the effect from NSAID treatment.

Discussion

The animal model used in this study was both reliable and valid as an assessment of fracture-healing. The results from the intraobserver correlation analysis for both radiographic and histologic analysis illustrated that the mechanisms of deriving data and the subsequent analysis of those data were highly repeatable. Outcome measures also correlated across the variables as reflected by positive correlations between radiographic and histologic outcomes both at days 24 and 32. The validity of the radiographic and blood-flow outcomes that were used in demonstrating real changes across the fracture gap was reflected by the differences that would be expected, and these were noted when comparing the differences between control and sham fracture animals. The small drop in bone-mineral content noted in the sham group was likely due to some degree of osteopenia secondary to decreased weight-bearing and to a stress-shielding effect of the external fixator. The small changes noted in blood-flow measurements were likely to be secondary to increased flow due to soft-tissue repair or callus formation at the tips of the external fixator pins.

Results from the fracture outcome analysis confirm what would be expected in a fracture-repair model in an animal of this size. A stepwise progression in healing was identified histologically: a maximum area of cartilage formation was seen at day 8, progression to bone formation was seen at day 24, and a decline in healing was seen at day 32, secondary to remodeling. Radiographic analysis showed a gradual increase in density throughout the investigation. These time scales of healing corresponded to those of other authors who used similar models of repair: Connolly et al. reported maximum bone formation and osseous union histologically at day 24 in the same model as in this study[26], whereas Zhang et al., using as a model a murine femoral fracture treated with an intramedullary nail, noted abundant callus formation at day 14 histologically and evidence of union radiographically at day 21[7].

When the histologic characteristics of the animals treated with rofecoxib were examined, NSAIDs had no effect on cortical bone resorption. They did not produce as much new bone as their control counterparts did, but they exhibited a greater area of cartilage. We had expected to see a rise in cartilage formation in the control animals during endochondral ossification, but it is possible that the earliest time interval (day 8) was too late to identify such a change. Analysis illustrated that the rofecoxib-treated animals attained poorer ra-

diographic as well as biomechanical profiles of repair and had a greater propensity toward failure of fracture fixation. This is consistent with a similar response to NSAIDs as reported in the literature. Connolly illustrated that meloxicam inhibited fracture repair; treated animals had less bone and more cartilage both at days 16 and 24 and had less biomechanical integrity at day 16[28]. Zhang et al., in a COX knockout model, demonstrated significantly less bone formation alongside decreased mesenchymal cell differentiation at day 16[7]. Simon et al. demonstrated that while NSAID treatment did not prevent the formation of callus as seen on radiographs, few animals achieved radiographic union and treated animals attained very poor biomechanical integrity with less callus apparent on histologic analysis[6]. In a similar manner to the present study, Simon et al. experienced a high pin-slippage rate across all NSAID treated animals, which was particularly evident in the animals that had been treated with rofecoxib.

There are several methods of assessing changes in bone vasculature that have been described in the literature. The most frequently used assessments are based on vessel counting of histologic samples, with use of either traditional staining techniques or immunolocalization of the vessels. These methods are based on anatomy and do not make any reference to the functional compatibility of the vessels, and each measure requires killing the animals for assessment. In addition, these methods do not account for vessel size, as a larger arteriole establishes a similar "count" as a smaller, newly formed and friable capillary, although capacity for the volume of nutrient and cellular delivery is vastly different. In our study, we employed a functional outcome measure of flow that would enable sequential assessment in the in vivo environment.

Following fracture, the animals in the present study exhibited a rise in blood flow until day 16, at which time the blood flow returned to resting levels at day 32. Both control and NSAID animals followed a similar pattern, and no differences were identified between the two groups on the day of surgery, before any rofecoxib had been prescribed. Thereafter, the magnitude of change exhibited by the control animals was significantly higher (days 4, 16, and 24), and that group displayed a higher median blood flow at all time points. These differences between the groups were noted despite the fact that approximately 50% more NSAID animals than control animals were entered into the trial for the Doppler study. This was secondary to greater numbers of NSAID-treated animals being removed from investigation after they had development of fracture displacement or a failure of the fracture fixation. It may be that, while some NSAID-treated animals were able to achieve healing of the fracture, the added insult of carrying the laser Doppler and Doppler protection container was too great a burden and therefore compromised the healing process in others. The flow results in this study correspond well to those reported in the literature with regard to angiogenesis and fracture-healing. Pufe et al. and Uchida et al. suggested that the maximal release of the cytokines involved in signaling angiogenic growth occurs at approximately day 5 following injury in murine models of repair[29,30]. In human studies, maxi-

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mum flow to a tibial corticotomy (identified with use of Doppler ultrasound) has been identified as occurring between fourteen and twenty-eight days following injury[31]. The increase in flow in our study, peaking at day 16, would correspond to the principle first predicted in an early work by Trueta and Morgan that angiogenesis directly precedes osteogenesis[32]. This was subsequently illustrated by Winet with use of intravital microscopy in bone-chamber models[33].

The molecular basis behind this effect is likely to be by an action on vascular endothelial growth factor (VEGF). NSAIDs inhibit circulating levels of tumor necrosis factor alpha (TNF-α)[28], a cytokine that has been noted to be activated early in the inflammatory cascade and that is both a trigger for the release of pro-angiogenic cytokines from polymorphonuclear cells[34] and also a pre-activator of cells to a "VEGF-responsive" status[35]. VEGF has been illustrated to be of importance in enhancing both leukocyte adhesion and rolling, thus enabling recruitment by chemotaxis and diapedesis of inflammatory cells from the circulation to a site of injury[36]. These polymorphonuclear cells are known to secrete the cytokines required in the early stages of repair, with the degranulation process of these cells being induced by TNF-α[37], an effect illustrated to be negated by the addition of the COX-2 specific inhibitors meloxicam and piroxicam[38].

The results found in this study suggest that while NSAIDs do exert an inhibitory action on vascularity, the effect on fracture-healing is independent of this reduction in blood flow. Although TNF-α has importance as an upstream regulator of vasculogenic proliferation, it has also been shown to influence osteogenic development as well. Inhibition of the above mechanisms involved in cell adhesion by NSAIDs may decrease the attraction and transport, and thus the accumulation, of circulating mesenchymal stem cells to the site of injury[39]. Gerstenfeld et al.[40,41] demonstrated that TNF knockout mice have a slower recruitment of osteoblasts and an almost complete lack of intramembranous ossification. It has also been noted that inhibiting the release of early inflammatory cytokines can result in enlargement of the soft callus and a delay in chondrocyte hypertrophy. Specifically, TNF-α is important in the regulation of the chondrocytic population, and a decrease in circulating levels of this cytokine may lead to desensitization of cells with a resultant loss of an apoptotic response by the hypertrophic chondrocytes[42]. This finding of an increased mass of soft callous and cartilage with slower progression to bone formation has been noted in the present study at day 8 and also by Connolly et al.[26], who postulated that this alter-

ation in the tissue volume and content was secondary to an inhibition of mesenchymal cell differentiation or an inhibition of chondrocytic apoptosis. Zhang et al.[7] proposed a similar conclusion following work that utilized a COX knockout murine tibial fracture model and demonstrated a delay in mesenchymal differentiation in COX-2 knockout but not COX-1 knockout animals, with a resultant increase in fibrous nonunion.

Although the newer COX-2 inhibitors are marketed as having a lower side-effect profile than traditional NSAIDs, particularly with regard to gastrointestinal effects, this study has illustrated that they continue to exert an inhibitory action on fracture repair. We therefore propose that it might be appropriate to withhold NSAIDs when treating patients following osseous injury. Withholding NSAID treatment has particular importance in the treatment of fractures that are associated with a delay in healing and that often are accompanied by a reduction in blood flow to the fracture site. This caution should include fractures to bones that, by their very nature, have a tenuous blood supply (scaphoid, talus, subcapital neck of femur, and diaphysis), fractures and/or injuries that compromise the vascular supply itself (fractures associated with vascular damage, and crush and high-energy injuries), and fractures in patients with concomitant conditions that may already predispose to delayed osseous repair (smoking, diabetes, anemia, and malnutrition). ∎

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