

Does the Use of Cyclooxygenase Inhibitors Delay Fracture Healing?

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Abstract

Cyclooxygenase (COX) inhibitors have long been used by medical practitioners to treat pain and inflammation associated with common medical problems including fractures. There are two types of COX inhibitors: COX-1 and COX-2. COX-2 inhibitors have an advantage over COX-1 inhibitors in that they are more selective in inhibiting the COX enzyme and do not carry the same side effect profile that the COX-1 inhibitors do.

It has been hypothesized that the use of COX inhibitors does have a deleterious effect on fracture healing. The present survey analyzes whether or not the use of cyclooxygenase inhibitors has a negative effect on fracture healing. A computerized literature search was done regarding the effects that NSAIDs have on fracture healing. Trials chosen for this survey involved the effect of COX inhibitors on the long bones of rats. Several trials done have shown that the use of COX-1 inhibitors does in fact delay fracture healing. However, other studies found that COX-2 inhibitors, due to their selectivity, do not delay fracture healing. The studies selected showed that use of COX-2 inhibitors do not have as much of a detrimental effect as the COX-1 inhibitors.

INTRODUCTION

Cyclooxygenase (COX) inhibitors, which belong to the drug class of nonsteroidal anti-inflammatory drugs (NSAIDs), have long been used by medical practitioners to treat pain and inflammation associated with common medical problems including fractures. However, recent studies have shown that the use of NSAIDs in fractures can actually lead to delayed or even non union healing (1).

Of the 5.6 million fractures that occur in the United States each year, 5-10% go on to be either delayed or non-union fractures. A great majority of health care practitioners prescribe NSAIDs to help alleviate the pain. Although, the majority of studies done on rats have shown that NSAIDs do increase the risk of delayed healing, there is only limited data regarding the effects of NSAIDs on fracture healing in humans (2). Of the studies that have been done in humans, most have been retrospective, and results of these studies have shown that NSAIDs have inhibitory effects on fracture healing (3). Despite this, many medical practitioners continue to prescribe NSAIDs for analgesia following a trauma such as a fracture (2).

The purpose of this paper is to examine several studies on the effects that NSAIDs have on fracture healing,

particularly the effects on fracture of long bones and show whether or not their use does in fact have a deleterious effect on the healing process of fractures.

METHODS

A computerized literature search was done regarding the effects that NSAIDs have on fracture healing. The best study to answer a therapy question is a randomized double-blinded study, placebo control trial. The studies that were found were randomized single and double blinded, however, they were all done animals. The studies chosen for this particular review fall under the criteria of level I evidence. Studies chosen for this review were found using both EBSCO Host and Pubmed search engines through the King's College Love Library computer databases. When searching the data bases, keywords nonsteroidal anti-inflammatory drugs, NSAIDS, fracture, and fracture healing were used in different combinations to find articles related to this particular topic. Other criteria used to narrow article selection included studies only written in English and studies that had been published within the past five years.

BACKGROUND

A fracture is defined as a complete or incomplete disruption in the continuity of a bone resulting from the application of

force, either direct or indirect, or from the application from repeated stress. A fracture usually comes as a result of a traumatic injury, resulting in the bone tissue and cartilage being disrupted or broken.

Fractures are classified into different categories such as simple, compound, displaced, and non-displaced. Simple fractures, also called closed fractures, involve a break in the bone without rupturing through the skin. Compound fractures, also called open fractures, involve a break of the bone as well as the bone breaking through the skin. Displaced fractures are those in which the bone is broken in two or more pieces and the ends of the bone are separated from one another. In non-displaced fractures, the bone cracks, with both ends of the bone still being in alignment.

The symptoms associated with fractures include pain, swelling, ecchymosis, crepitus, deformity, and abnormal motion. The pain resulting from a fracture is usually immediate with resulting swelling and inflammation for several hours. On physical exam, the practitioner will palpate the area for tenderness to better pinpoint the exact area of injury. Practitioners will note any signs of ecchymosis, decreased or abnormal motion, deformity, and crepitus. To evaluate whether or not a major blood vessel was ruptured, the closed pulse to the injury will be palpated in order to assess proper blood flow to the area of injury.

The diagnosis of a fracture is made with the aid of plain x-rays. When looking at an x-ray the appearance of the fracture is described by the type of fracture line, the angle of the fracture, displacement, and whether it is open or closed. If an x-ray does not show a fracture that is strongly suspected by physical exam, a CT or MRI can be done. Patients who are suspected of sustaining a fracture must be examined for ischemia, compartment syndrome and nerve injury. In order to assess for ischemia and blood flow, ultrasound and use of a Doppler will aid in assessing blood flow to the area of injury.

There are several complications that can result from a fracture, although these complications are rare after proper treatment. One such complication that can result from a fracture is compartment syndrome, which results in nerve damage. Compound or open fractures can predispose a patient to bone infection. Fractures of long bones may cause the release of fat that may embolize through the veins to lungs and cause respiratory complications.

Treatment for long bone fractures usually requires using the

mnemonic device of R.I.C.E., rest, ice, compression, and elevation. Using this mnemonic is by far the least invasive form of treatment for a fracture. The patient should be advised to stay off or not use the fracture. The patient should apply ice to the area of injury in order to decrease the amount of swelling. Compression to the area of fracture when appropriate with dressings such as a brace or a cast to decrease compression and allow for adequate healing to occur. Elevation involves elevating the fracture in order to allow for venous return and prevents clot formation and venous stasis. Along with the R.I.C.E. mnemonic patients should also be educated on the use of analgesia for pain.

The next most invasive form of treatment for a fracture involves splinting and casting for an extended period of time to allow for correct remodeling and alignment of the bone. When casting a fracture, the proximal and distal joints are immobilized to allow for correct remodeling. Compound fractures require sterile wound dressing, tetanus prophylaxis, and broad spectrum antibiotics to prevent infection.

By far the most invasive form of treatment for a fracture involves surgery. Surgical treatment is required for a fracture if the patient is suspected of having any of the following: damage to a major vessel, and open fracture, or if closed reduction of the fracture is unsuccessful.

Fracture healing is divided into three phases: reactive, reparative, and remodeling. The rate of fracture healing is influenced by the location and type of fracture, treatment methods, and overall health of the patient.

The reactive phase, which typically lasts 2 weeks, is the most important phase in fracture healing. It is during this phase that inflammation occurs and subsequent formation of a hematoma occurs. Throughout this phase the body releases proteins called cytokines and an enzyme, cyclooxygenase (COX), which cause the area of fracture to begin an inflammatory mechanism to attract other cells within the body to begin the healing response (4). The COX enzyme allows for the production of prostaglandins through the conversion of another enzyme arachidonic acid. The COX enzyme has two types: COX-1 and COX-2. COX-1 is present in most tissues of the body and generates prostaglandins that allow for maintenance of organ function. COX-2 on the other hand, is induced during the inflammatory response, and produces prostaglandins which help to mediate pain and inflammation within the body. The COX-2 enzyme allows for the production of prostaglandins through the conversion of another enzyme arachidonic acid.

The healing response involves cellular signaling mechanisms to work via chemotaxis and an inflammatory process to attract the cells to initiate the healing response within the body. It is during this phase that it is believed that NSAIDs have a detrimental effect on fracture healing due to their anti-inflammatory effects.

The second phase of fracture healing, the reparative phase which lasts 1 to 2 months involves callus formation and lamellar bone deposition. During callus formation, cell proliferation and differentiation begin and produce osteoblasts, which are cells that deposit osseous material on the outside of the fractured bone providing a sheath of new bone over a fibrocartilaginous callous. During lamellar bone deposition, the callus is now replaced by lamellar bone.

The third phase of fracture healing, which usually lasts about 1 to 4 years, involves remodeling of the bone. During this phase the lamellar bone is now replaced with compact bone, and the lamellar bone gets reabsorbed, by mature bone cells called osteoclasts, forming new bone.

A vital part of treatment for a fracture involves analgesia. NSAIDs are the drugs most widely used for their analgesic effects particularly for pain of post operative procedures, posttraumatic pain, and fever. Other uses for NSAIDs include alleviation of headaches, pain associated with arthritis, sports injuries, and menstrual cramps. Side effects of NSAIDs include nausea, vomiting, diarrhea, constipation, decreased appetite, and dizziness. GI side effects like stomach pains and the development of ulcers and GI bleeding are more commonly the result of using COX-1 inhibitors.

COX inhibitors are NSAIDs that are divided into two classes COX-1 and COX-2 inhibitors. COX-1 inhibitors include ketorolac (Toradol), aspirin, ibuprofen (Motrin, Advil), and naproxen (Naprosyn, Aleve). The COX-2 inhibitors selectively inhibit the COX-2 enzyme. COX-2 inhibitors cause less GI side effects. Another advantage of COX-2 inhibitors is that because of their selectivity, these drugs do not affect blood coagulation. This is extremely important when dealing with post operative pain. COX-2 inhibitors will not impair platelet mediated blood clotting. COX-2 inhibitors include celecoxib (Celebrex), rofecoxib (Vioxx), and valdecoxib (Bextra), however, the only true COX-2 inhibitor on the market now is Celebrex (5).

COX inhibitors work by inhibiting the activity of the COX enzyme, which leads to a reduction in the production of

prostaglandins, which cause a decrease in pain, inflammation, and fever (3). COX-1 is expressed in normal bone and at the site of a bone fracture while COX-2 is upregulated particularly during the initial stages of bone repair. It is the reduction of prostaglandins, which raises the question to whether or not the use of COX inhibitors in fact delays fracture healing.

DISCUSSION

The first study entitled "Effect of COX-2 inhibitors and non-steroidal anti-inflammatory drugs on a mouse fracture model" published in *INJURY* was a randomized, blinded, prospective study which was performed to evaluate the biomechanical, biomolecular, biochemical, and histological effects of anti-inflammatory medications on fracture healing in rats (2).

The study used 296 male mice and examined the effects that certain anti-inflammatory medications had on healing of a tibial fracture. At the beginning of the study, the mice were given anesthesia with an intraperitoneal injection of 2.5% Avertin, and a 0.2mm intramedullary pin was placed in the right tibia and a closed diaphyseal fracture was created. Once fracture was created, radiographs were taken to confirm pin placement and quality of fracture. All researches were blinded to treatment until after biochemical testing had been completed.

Researchers randomly assigned mice to one of seven groups which included: an NSAID group, four COX-2 inhibitor groups, a positive control and a placebo group. Mice in the NSAID were treated with 2 mg/kg/day of ketorolac. The four COX-2 inhibitor groups consisted of the first group given celecoxib at a low therapeutic dose of 10 mg/kg/day. The second group was given celecoxib at a high therapeutic dose of 50 mg/kg/day. The third group was given rofecoxib at a low therapeutic dose of 1 mg/kg/day. The fourth group was given rofecoxib at a high therapeutic dose of 5 mg/kg/day. The last two groups consisted of a negative control, which was the placebo group and a positive control, in which the group was given ibuprofen 30 mg/kg/day.

For each group, there were three time points, 4, 8, and 12 weeks, in which each group was tested biomechanically. Twelve mice were harvested from each group at each time point. Mice who suffered premature death were not included in testing data. These mice were autopsied and a veterinary pathologist consulted when the cause of death was unclear.

Delivery of the drug was standardized for all groups and consisted of delivering the medication in peanut butter chow pellets that were consumed daily. All mice in the study were caged individually to ensure complete consumption of the pellets. Pellets were provided immediately after surgery for all groups. Along with the pellets a narcotic analgesic, Butorphanol, given at 0.05 mg/cc, was dissolved in the drinking water of the mice for 3 days post operatively. At the time of harvest, samples were wrapped in saline-soaked gauzed, then double bagged, and placed in a freezer at a temperature of -20 ° C. Before biomechanical testing was performed, the samples were thawed overnight in a refrigerator, at a temperature of 8 ° C.

Biomechanical testing consisted of a three point bending test where both the right fractured tibia and normal left tibia were tested. When doing biochemical testing, outcomes measured included maximum load, energy absorbed to maximum load, and stiffness based on a least squares regression between load limits of 25% and 75% of the maximum load.

All data from the samples were normalized by researchers by dividing fractured side outcome by normal side outcome, and was reported as a percent. Both the raw and the normalized data were analyzed using a one-way analysis of variance (ANOVA) at each time point and two-way ANOVA once the study was completed.

Results showed that there were differences in fracture healing, particularly at 4 and 8 weeks. Results of biomechanical testing showed ketorolac had an effect on fracture healing at 4 weeks, but showed no differences at later time points. The displacement from initial load to maximal load was different between the placebo and ketorolac group. The ketorolac group showed increased displacement before maximum load had been achieved. Biomechanical testing of the fracture callus created by the celecoxib group showed higher maximum load and stiffness as compared to the rofecoxib group at 8 weeks. No differences in biomechanical testing were appreciated at 12 weeks.

Histologic studies showed subjective differences in the ketorolac group as compared to other groups. The studies of this group showed decreased cartilage formation and differences in collagen expression.

Results of the entire study, once all data was collected and normalized, showed that ketorolac at 4 weeks was the only

drug to have an effect on the biomechanical testing of a healing fracture. Although, the data from this particular study showed strong evidence that NSAIDs do affect fracture healing, no significant effects were able to be obtained in this model which used juvenile mice.

This study attempted to show that NSAIDs do have a detrimental effect on fracture healing. Although, much of the data suggested it, no significant effects were seen fully back up the claim

On the positive side, the study used a randomized, blinded study which would make this particular study level 1 of evidence. The study also used a large sample size, which adds to the significance of the results of the study. The study was also able to treat each mouse in the study as equal and was able to eliminate bias from the study and eliminated outliers by not including mice that had passed away before the completion of the study.

Some of the negatives of the study were noted by its authors. Bos et al noted that because of their use of very young rats, aged 8-10 weeks, this could have explained the lack of inhibition of healing. This lack of inhibition of healing could probably be attributed to younger mice being more resilient to injury and healing better and faster than mice that are older. It was also noted by the authors that other studies, which had found NSAIDs to delay fracture healing, used older mice to show a significant lack of fracture healing with the use of these drugs. Another negative aspect of this study was that it gave no mention of whether or not rats were placed in groups at random. In fact no mention of how groups were selected at all was given. There was no mention of why researchers decided to use male rats as opposed to using female rats.

The second study entitled "Cyclooxygenase-2 inhibitor delays fracture healing in rats" published in *Acta Orthopaedica*, investigated the major inhibitory period that COX-2 inhibitors has on a rat fracture model by altering the time period of administration from early to late (4).

The study used twenty 12 week old Wistar rats weighing between 250 and 300g. The rats were housed individually in a room that was both temperature and humidity controlled. All rats had free access to both food and water. To begin the study all 20 rats were anesthetized with sodium pentobarbital given at 50mg/kg subcutaneously. The capsule of the knee joint was incised, exposing the intertrochanteric space and the distal femur. A 0.8-mm K-wire was inserted between the

femur condyles and mid-shaft fractures were made to both femurs of all 20 rats.

Once the fracture were made, the rats were assigned to one of four groups each made up of 5 rats per group: group I received etodolac at a dose of 20 mg/kg/day for three weeks; group II, the early administration group, received the same dose of medication from the day of operation to day 7 post-op; group III, the late administration group, received the same dose but on days 14 to 21 post-op; and the last group, group IV, the control group, received injections of 0.5% methyl cellulose solution.

Immediately after surgery, and subsequently at 1, 2, and 3 weeks post surgery, posterior-anterior radiographs were taken of the femurs to evaluate callus formation and bone healing. Radiographs were evaluated on three categories: periosteal reaction, bone union, and remodeling. The maximum score that could be given in both the periosteal reaction and bone union categories were 3, whereas the maximum score that could have been given in the remodeling category was 2. To evaluate the radiographs, two orthopedic radiologists were selected to perform randomized blinded selection of films. Three weeks following surgery, rats were put down with sodium pentobarbital, and the femurs were harvested from all of the rats, and all of the soft tissue and K wires were removed. Unilateral femurs from all of the rats were selected at random to be kept at -20° C until mechanical testing took place.

Evaluations for mechanical testing used a three point bending test. Each femur was placed on a metal holding device and bending force was applied midway between the supports of the anterior surface at a speed of 10mm/min until failure of the bone.

Once all data was collected, researchers applied a one-way ANOVA and Fisher's protected least significant difference test. P-values that were less than 0.05 were considered significant.

At 3 weeks, researches noted bone union in groups III and IV, but observed that bone union was poor in groups I and II. The one way ANOVA tests proved that this finding was significant, calculating a P-value less than 0.05. The radiographic score of groups I and II were also lower than those of groups III and IV. Results from looking at both bone union and radiographic scores showed that bone union and callus formation were both delayed by administration of etorolac early on after surgery.

For mechanical evaluations to be performed, unilateral femurs were selected at random from each of the groups. Ultimate strengths were measured using the three point bending system. Scores from mechanical evaluation revealed that from group I and II were less than those for group III and IV. Stiffness of the femurs was also tested using the three point bending system. Again the results were the same; stiffness for groups I and II was less than that for groups three and four.

In the end, results from the study showed that administration of a COX-2 inhibitor delayed fracture healing, and the effects were more evident within the early administration groups. Radiographic and mechanical studies of the study revealed that groups receiving COX-2 inhibitors in the late phase showed similar results as the control group. Ultimately, this study showed that there is a time dependency in the effect of COX-2 specific inhibitors on fracture healing.

The study did use a randomized, blinded design and therefore the results can be classified under level II evidence. Specifics on how rats were randomly assigned into each group was not identified by the authors, however, it is blatantly stated by the authors that the rats were randomly assigned into one of four groups.

However, downfalls of the study were the small sample size of the population used. A larger sample size would have made the results more significant. Another downfall to this particular study was that it only used one particular COX-2 inhibitor and did not compare etodolac to other COX-2 inhibitors or other NSAIDs. As a result, this may raise the question of whether or not etodolac itself is the only drug of its kind to have such deleterious effects on fracture healing, or whether NSAIDs in general cause this effect.

The third study entitled "Effect of COX-2 Specific Inhibition on Fracture Healing in the Rat Femur" was published in the Journal of Bone and Joint Surgery (6). The goal of this study was to determine whether postoperative administration of a COX-2 specific inhibitor affected fracture healing to the same degree as did other conventional NSAIDs.

Researchers of this study used fifty-seven Wistar rats weighing 300g. The 57 rats were randomly divided into three groups of nineteen. A non-displaced unilateral fracture was made to the lateral right femur in all the rats. One group, the control, received no treatment, the second group received indomethacin, a non-selective NSAID at a dose 1

mg/kg/day, and the third group received celecoxib, a COX-2 inhibitor, at a dose of 3 mg/kg/day beginning on postoperative day 1. All dosages were determined to be within the average recommended dosage for humans. The drug was mixed with chocolate and fed to the rats daily. Dosages were adjusted with respect to weight gain.

To create the fracture, the rats were anesthetized with and intraperitoneal injection of ketamine at a dose of 60 mg/kg. Once anesthetized, the skin over the femur was shaved. To prevent infection, a dose of 0.05 mg of procaine penicillin was administered intramuscularly in the left thigh. A 20 gauge

needle was then used to insert a 0.045 inch non-threaded Kirschner wire. The proximal end of the wire was isolated with the aide of a second incision, and the end was bent, cut, and buried beneath the muscle. The left femora served as controls. The right femora were placed in the abduction position and external rotation in a standard three point bending apparatus fixed to the testing machine. The fracture was created under displacement control while fracture load was recorded with a load cell. Once the fracture was made, the femoral skin incisions were stapled closed, and the rats were allowed to recover and permitted to eat and walk as they pleased.

Subsets from each group of rats were killed using a lethal dose of sodium pentobarbital at four, eight, and twelve weeks postoperatively. Both femora were disarticulated from the hip. The femora were radiographed, wrapped in cloth, soaked with saline solution, and stored at -20° C for mechanical and histologic studies.

In order to determine whether or not the use of COX-2 inhibitors resulted in radiographic evidence of delayed fracture healing, anteriorposterior and lateral x-rays were taken of all femora. Each radiograph was analyzed with respect to callus formation and maturity and bridging bone formation. All radiographs were graded by two independent observers blinded to the treatment group.

Histologic analysis consisted of researches taking each fracture with its callus and fixing it in 4% paraformaldehyde in a phosphate buffered solution at 4° C for fourteen to twenty-one days. Grade of healing was determined on the relative percentage of fibrous tissue, cartilage, woven bone, and mature bone in the callus. All histologic analyses were graded by two independent observers who were blinded to the treatment groups.

Mechanical analysis was done by measuring both the femur and fracture callus strength. Before testing began, each femur and its corresponding callus were measured. In order to perform the three point bending test, the bone ends were fixed and positioned in such a way to create a fracture, and the diaphysis and callus were loaded with the aide of a curved loading ram until a fracture occurred. Once the fracture was accomplished, researchers recorded load, displacement, bending stiffness, failure load, bending moment, and fracture location. Once all tests were performed, all data was grouped and analyzed with and unpaired two tailed t tests.

Radiographic analysis showed that at four weeks, there was a smaller mean amount of bridging bone formation in the indomethacin group than in either the celecoxib or control groups. At eight weeks, radiographs showed similar results. However, due to high variability of bone healing, neither finding was statistically significant.

Histologic analysis found that at four and eight weeks, both the indomethacin and celecoxib groups demonstrated more fibrous tissue and less woven bone formation as opposed to the control group. At twelve weeks, however, there were no significant differences among the three groups.

With respect to mechanical analysis, mechanical strength and fracture stiffness were determined by three point bending. Values were expressed as a percentage of mechanical strength of the fractured right femur as compared to the intact left femur. At four weeks, both strength and stiffness in the indomethacin group were significantly decreased as compared to the control group. The celecoxib group showed a decrease in mean stiffness and strength at four weeks and decreased mean stiffness at eight weeks as compared to the control group, but these findings were not statistically significant.

Researchers of this study found that at four and eight weeks, fibrous healing, endochondral bone formation, and immature bone formation were more prevalent in the celecoxib and indomethacin groups than they were in the control group. Biomechanically, this translated into decreased strength and stiffness in the indomethacin group. This finding was not statistically significant within the celecoxib group.

Researches concluded that administration of indomethacin does in fact decrease bone healing. However, researchers of the study found that administration of a COX-2 inhibitor does not significantly affect radiographic or biomechanical

parameters of fracture healing.

This final study had many positives. The results of this study fall under level II evidence. The population was randomly selected into three groups. However, specifics on how groups were randomly selected were revealed by the authors. Once in a group results of the study were judged by independent researches that were blinded to the treatment. Another positive to the study was the fact that it used both a nonselective NSAID and a COX-2 inhibitor to compare the effects each had on fracture healing.

Some of the negative aspects of the study were that fact that they used only one example of each type of drug. This lack of variety of drugs leads to the assumption that indomethacin is the only NSAID to cause fracture inhibition while celecoxib is the only COX-2 inhibitor to not delay fracture healing. Perhaps using two or three different drugs of the same type might have resulted in more significant results. The sample size of this study was large, however, a larger sample size would have provided data that would have been more standardized to the entire population.

CONCLUSION

The studies discussed above performed experiments to test whether or not the use of COX inhibitors will have a detrimental effect on fracture healing.

All but one of the three studies found with statistical significance that the use of COX-1 inhibitors during fracture healing delays callus formation and decreases the strength of the new forming bone. The study done by Bos et al, found compelling data to suggest that COX-1 inhibitors do negatively affect fracture healing, however, their findings were not statistically significant (2).

The next question is if all COX inhibitors have this effect on fracture healing, or whether it's a matter of selectivity. All but one of the studies found that COX-2 inhibitors do not affect fracture healing in any significant way when compared to COX-1 inhibitors. The study by Brown et al found that celecoxib, a COX-2 inhibitor, does not have the detrimental effect on fracture healing when compared to the

traditional NSAID indomethacin (6). The only study to do so was the one by Egawa et al. however, their population size was very small and a bigger population size would have probably contradicted their findings (4).

It has been shown by these studies that use of COX-2 inhibitors have an advantage over COX-1 inhibitors when dealing with pain during fracture healing. COX-2 inhibitors, because of their selectivity, do not adversely affect fracture healing as significantly as COX-1 inhibitors do. Another advantage of using COX-2 inhibitors is the lack of side effects that are caused by the use of COX-1 inhibitors, namely GI bleeding and prolonging clotting time. As a result of this finding, clinicians should advise their patients on the use of COX-2 inhibitors for pain during fracture healing.

References

1. Wheeler, P, Batt ME Do Non-Steroidal Anti-Inflammatory Drugs Adversely Affect Stress Fracture Healing? A Short Review British Journal of Sports Medicine. 2005; 39; 65-69. Available <http://bjsm.bmj.com/cgi/content/full/39/2/69>. Accessed 24, February 2008
2. Bos, GD, Mullis, BH, Copland ST, Weinhold, PS, Miclau, T, Lester Effect of COX-2 Inhibitors and Non-Steroidal Anti-Inflammatory Drugs on a Mouse Fracture Model INJURY International Journal of the Care of the Injured. 2006; 37; 827-837. Available
Accessed 24, February 2008
3. Gerstenfeld, LC, Al-Ghawas, M, Alkhairy, YM, Cullinane, DM, Krall, EA, Fitch, JL, Webb, EG, Thiede, MA, Einhorn, TA Selective and Nonselective Cyclooxygenase-2 Inhibitors and Experimental Fracture Healing Journal of Bone and Joint Surgery. 2007; 89 (1); 114-125. Available
Accessed 24, February 2008
4. Egawa, H, Endo, K, Sairyo, K, Komatsubara, S, Sasa, T, Ogawa, T, Yonekura, D, Murakami, R, Yasui, N Cyclooxygenase-2 Inhibitor Delays Fracture Healing in Rats Acta Orthopaedica. 2005; 76; 470-472. Available
Accessed 24, February 2008
5. Vuolteenaho, K, Moilanen, T, Moilanen E Non-Steroidal Anti-Inflammatory Drugs, Cyclooxygenase-2 and the Bone Healing Process Basic & Clinical Pharmacology and Toxicology. 2008; 102; 10-14. Available
Accessed 24, February 2008
6. Brown, KM, Saunders, MM, Kirsch, T, Donahue, HJ, Reid, JS Effect of COX-2 Specific Inhibition on Fracture Healing in the Rat Femur Journal of Bone & Joint Surgery, American Volume. 2004; 86 (1); 116-123. Available
Accessed 24, February 2008

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