REVIEW ARTICLE

EFFECT OF CONVENTIONAL AND COX-2 SELECTIVE NON-STEROIDAL ANTIINFLAMMATORY DRUGS ON BONE HEALING

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SUMMARY

In the present literature review, experimental and clinical studies of the last 15 years concerning the effects of conventional and COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) on bone healing were reported. Most of the data pertaining to conventional NSAIDs have shown to cause delayed fracture healing and impairment of spinal fusion in animal studies, as well as a negative interference on spinal fusion rate in human beings. In spite of the established importance of prostaglandin E2, synthesized by osteoblasts under COX-2 stimulation, in controlling bone formation, the results regarding the potential inhibitory effects of selective NSAIDs on experimental bone healing are still controversial and there is no clinical data to confirm that they interfere negatively with repairing bone formation.

Keywords: *Prostaglandins; COX-2; Non-steroidal anti-inflammatory drugs; Bone healing*

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INTRODUCTION

Among the several roles played by prostaglandins, the local control of bone metabolism can be described. Therefore, it is expected that the long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandins synthesis, interferes on a normal bone's structure and function, as well as on the development of some bone pathologies. In this literature review, experimental and clinical studies conducted in the last 15 years addressing the effects of conventional and cycloxygenase-2 enzyme (COX-2) selective NSAIDs on reparative bone formation are listed. As a supplementary explanation, data on the different COX isoforms involved on prostaglandins formation and on the role of prostaglandins on the control of normal bone metabolism have been provided. All the studies listed on references section resulted from a search on PubMed (US National Library of Medicine).

Prostaglandins, cyclooxygenase enzymes and NSAIDs

Eicosanoids are formed as a response to various stimuli that are able to activate phospholipase A_2 enzyme, which hydrolyzes phospholipids of cell membranes releasing arachidonic acid into the cytoplasm, which will, in turn, serve as a byproduct to two different enzymatic paths, the COX path – ultimately leading to thromboxanes and prostaglandins formation, and the lipooxygenase path – leading to the formation of leukotrienes and other compounds. The so-called constitutive prostaglandins are usually expressed in a variety of tissues and organs, with well-known physiological activities: digestive mucosa protection, renal blood flow control and homeostasis, among others. U]The so-called inductive prostaglandins are mainly expressed as a response to inflammatory stimuli and contribute to the development of edema, hyperalgesia and fever[1]. In the early 1990's, the existence of tow COX enzyme isoforms was evidenced, both with similar structures and essentially catalyzing the same reaction. It was then assumed that the COX-1 isoform catalyzed the inductive prostaglandins synthesis. More recently, however, the inexistence of such a precise division of activities of both isoforms has been proven, meaning that the COX-1 enzyme seems to play a significant role on inflammation as well, especially on hyperalgesia, and the COX-2 enzyme is constitutively expressed in many organs, being an important mediator of renal, reproductive and nervous functions, also contributing to the protection of digestive mucosa cells and to homeostasis control[2].

The involvement of prostaglandins in a large number of human pathologies was the driver for NSAIDs development and accounts for the fact of these drugs being included among the most frequently prescribed agents worldwide. NSAIDs can be indicated in a number of conditions, including fever and pain control, both for treating postoperative and post-trauma acute pain and for relief in cases of chronic pain associated to musculoskeletal disorders, to osteoarthritis and to rheumatoid arthritis. In the 1960's and 1970's, a number of anti-inflammatory and analgesic drugs were made available to market. Those conventional NSAIDs, however, present, in addition to their therapeutic actions, some undesirable side effects, especially for digestive tract and kidneys. Today, NSAIDs therapeutic action is known to be especially due to COX-2 enzyme inhibition, while undesirable effects are especially due to COX-1 inhibition[3, 4].

With the discovery of the type 2 of COX, in 1991, pharmaceutical industry started to massively invest in the development of COX-2-selective NSAIDs, pursuing a powerful therapeutic action but without the undesired side effects. These drugs – known as coxibs – were first introduced to the market in 1999[5], providing an effective anti-inflammatory action and significantly lower risks of gastrointestinal toxicity as compared to conventional NSAIDs, promising a solution for the

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morbidity associated to the long-term use of anti-inflammatory agents. More recently, the long-term use of selective cox-2 inhibitors have been emerging also as a preventive and therapeutic alternative for some non-inflammatory diseases that result in increased COX-2 expression, as seen in some kinds of cancer, notably those of epithelial source, and in Alzheimer's disease[2]. Nevertheless, the long-term use of some of these selective NSAIDs has been shown to be deleterious to renal function and homeostasis, offering an increased risk of thrombosis and infarction[5]. Therefore, rofecoxib (Vioxx®) was recalled in September 2004 and valdecoxib (Bextra®) in April 2005. Only celecoxib ,(Celebra®, Pfizer) remains available in market, but with a black-strip package, as well as a second-generation coxibs such as etoricoxib (Arcoxia®, Merck) and parecoxib (Dynastal®, Pfizer – a veldecoxib pro-drug), marketed in the United States and in 45 other countries, and lumiracoxib (Prexige®, Novartis), approved for use in the United Kingdom[5].

Prostaglandins and Bone Tissue

Bone modeling, remodeling and repair are controlled by hormones and local factors that must act in accurate strengths, simultaneously or sequentially, establishing synergic or antagonic interactions in order to assure a full and appropriate cell function, accountable for matrix formation and absorption in a speed and duration required for a normal bone tissue. The skull is an abundant source of prostaglandins, which are important local regulators of bone metabolism, sometimes with stimulatory effects, sometimes inhibitive, playing critical roles both for its physiology and for some pathological changes.

Prostaglandins, especially PGE_2, are produced by osteoblasts under a permanent COX-2 stimulus, of which expression is regulated by hormones, cytokines and growth factors that control bone remodeling. A major physiological function of prostaglandins on bone tissue is to mediate its increased formation as a response to mechanical stimuli, both in animals and human beings. Exogenous PGE_2 is known to strongly increase bone formation in experimental animals, and this anabolic effect can be mimicked by applying mechanical stimuli on bone surface, a condition also stimulating PGE2 production in human beings. Furthermore, in several experimental models, NSAIDs have been proven to delay bone injuries and fractures repair, which evidences the role of prostaglandins on reparative bone formation[3, 4, 6].

In some circumstances, notably those of pathological nature, prostaglandins (especially PGE_2) can stimulate bone absorption increasing the amount and functional activity of osteoclasts. Many bone absorption factors are known to stimulate prostaglandins production by inducing COX-2 enzyme. In situations like those, gene blockage to COX-2 results in damaged osteoclastogenesis. Bone absorption stimulation by prostaglandins plays a potential role on bone loss occurring in inflammatory diseases (arthritis and periodontal diseases), on bone response to long-term immobilization, and possibly on estrogen deficiency, the key pathogenic mechanism for osteoporosis[6].

NSAIDs and Bone Repair

Apparently, the use of NSAIDs, yet for long periods, is rarely associated to adverse effects on normal bone metabolism. Furthermore, clinical observations suggest the therapeutic use of NSAIDs for preventing bone loss and treating osteoporosis in elderly women[1, 6]. Additionally, beneficial effects of NSAIDs have been evidenced, halting heterotopic ossification [7, 8]. The potential deleterious effects of these drugs on bone repair, however, has been targeted in several investigations, with results still controversial.

Conventional NSAIDs: experimental and clinical studies

Indomethacin has been used as a standard for non-selective NSAID and as a positive control in studies testing the activity of new drugs in this class. The majority of the studies show that its long-term use delays long bones repair process and spinal fusion in experimental animals[9, 10, 11, 12, 13]. An exception to this is a recent study[14] where neither indomethacin nor other selective and non-selective NSAIDs (ibuprofen, ketorolac, rofecoxib and celecoxib) significantly interfered on tibial repair of mice. The authors discuss that the selection of the dosages of the different NSAIDs was based on literature and pharmacological data, targeting doses corresponding to the ones used for clinical treatment in human beings, and justify their negative results for having used young animals, while literature points out to a delayed repair in more mature animals. It is worthy to highlight, however, that in that experiment, drugs were incorporated to meals, and no data was available regarding individual intake rates during the experimental period. The other conventional NSAIDs (diclofenac, ibuprofen, naproxen, ketorolac) have been shown to be able to affect reparative bone neoformation, inhibiting long-bones fracture repair and spinal fusion in most of the experimental studies[9, 15, 16, 17, 18].

Regarding clinical studies, yet many of these are retrospective and other uncontrolled factors may be interfering on repair process[18], literature suggests, with rare exceptions[19], that conventional NSAIDs can negatively interfere on spinal fusion rate[20, 21, 22, 23, 24], additionally to be effective in preventing heterotopic ossification[8].

Nevertheless, three letters to the editor published on the British Medical Journal in late 1990's illustrate the controversy around this topic. Varghese and cols.[25] stressed that, although pre-clinical studies show deleterious effects of NSAIDs on fractures repair and spinal fusion, those drugs are still widely employed in clinical orthopaedics for postoperative pain relief. The authors mention the high rate of patients submitted to hip prosthesis placement and using NSAIDs for long periods, and recommend that, should these drugs must be used, this should be done at the lowest possible dosage and for the shortest possible time. As a response, Stone and Richards[26] admit that many, but not all animal studies showed deleterious effects of NSAIDs on bone repair, and report that they are aware of only two studies with human beings, one of these corroborating and the other denying NSAIDs adverse effects on bone repair. The authors warned about the need to control postoperative pain and recommended that, in the absence of conclusive clinical experiments, the use of NSAIDs should not be suspended, although care should be taken in cases of proven risk of non-union. Subsequently, Godden[27] strongly contradicted the suggestion by Stone and Richards[26] that further clinical studies are required on this topic, stating that journals focusing maxillofacial surgery have published a number of studies addressing the use of NSAIDs for pain relief associated to third molar extraction and that, although not making reference to studies specifically addressing bone repair, the authors would be obliged to report any adverse effects, with no reported cases of delayed repair. The author, in a reference to the letter by Varghese and cols.[25], said that the results achieved on rodents should

not be extended to clinical environment, and discouraged further clinical studies on this topic, for being unnecessary and ethically questionable.

Selective COX-2 NSAIDs: experimental and clinical studies

The number of experimental results concerning the effects of selective COX-2 NSAIDs on bone repair is quite smaller, recent (from 2002 on) and also controversial. In addition to the evidences showing that rofecoxib, celecoxib and parecoxib inhibit long bones repair in rats and rabbits[12, 17, 18, 28], there are some reports stating that rofecoxib and celecoxib do not interfere on long bones' fracture repair and on spinal fusion rates in these species [11, 13, 14]. Analyzing experimental details, it is not possible to explain these controversies by differences between dosages, forms and time of administration of drugs, by differences between animal species, kind of bone and method of reparative bone tissue assessment.

Some authors suggest that the key factors interfering on results achieved with selective NSAIDs are dose and treatment period[14], as well as intra- and inter-species differences regarding sensitivity to drugs, potential local and systemic compensatory factors, interference of parameters such as age, bone remodeling pace, and associated diseases, and also these drugs' pharmacokinetics in rodents versus human beings[1].

Criticisms to experimental models showing the deleterious effects by the use of selective NSAIDs on reparative bone formation include the need of further information about pharmacological dosages for comparing them with human-intended therapies, and also the use of apparently too high doses and for a very long term, considering its clinical use for intraoperative acute pain control[4,18,29]. Nevertheless, one should keep in mind the long-term use of these drugs for controlling chronic pain associated to musculoskeletal disorders, osteoarthritis and rheumatoid arthritis, common conditions in clinical medical practice[4, 18].

Another experimental model that seeks to clarify the importance of COX-1 and COX-2 enzymes for reparative bone formation refers to the use of knockout mice for correspondent genes. By comparing X-ray images for bone repair in wild and knockout mice, a significant delay on bony callus formation was shown for COX-2 knockout animals, but not for COX-1[30]. The validation of this experimental model, however, was also questioned, once the gene absence for COX-2 causes severe renal dysfunction in mice, and this pathology could cause biased results[18].

Although controversial, the question raised from pre-clinical experimental results is whether patients requiring reparative bone formation, including fracture repair, spinal fusion, and orthopaedic implants union conditions could be safely treated with selective COX-2 NSAIDs or not[4, 29]. Despite being rare, as far as we could check, there is no evidence proving that these drugs interfere on reparative bone neoformation in human beings[24, 31], differently from what is seen for conventional NSAIDs.

CONCLUSION

The majority of studies described in literature show that conventional NSAIDs can delay long-bones fracture repair and spinal fusion in experimental animals, and negatively interfere on spinal fusion rate in human beings. Despite of the proven importance of prostaglandin E_2 synthesized by osteoblasts under COX-2 stimulation for bone formation, experimental results concerning the potential inhibitory effects of selective NSAIDs on bone repair are both rare and still controversial, and there is no evidence that they interfere on reparative bone neoformation in human beings.

REFERENCES

1- Radi ZA, Khan NK. Effects of cyclooxygenase inhibition on bone, tendon and ligament healing. Inflamma Res 2005; 54:358-366.
2- Carvalho WA, Carvalho RDS, Rios-Santos F. Analgésicos inibidores específicos da ciclooxigenase-2: avanços terapêuticos. Rev Bras Anestesiol 2004; 54:448-464.
3- Gajraj NM. The effect of cyclooxygenase-2 inhibitors on bone healing. Regional Anesthesia and Pain Medicine 2003; 28:456-465.
4- Gerstenfeld LC, Einhorn TA. COX inhibitors and their effects on bone healing. Expert Opin Drug Saf 2004; 3(2):1-6.
5- Melnikova I. Future of COX2 inhibitors. Nature Reviews Drug Discovery 2005; 4:453-454.
6- Raisz LG. Potential impact of selective cycloxygenase-2 inhibitors on bone metabolism in health and disease. Am J med 2001; 110:43S-45S.
7- Kjaersgaard-Andersen P, Nafei A, Teichert G, Kristensen O, Schmidt SA, Keller J, Lucht U. Indomethacin for prevention of heterotopic ossification. A randomized controlled study in 41 hip arthroplasties. Acta Orthop Scand 1993; 64(6):639-642.
8- Moore KD, Goss K, Anglen JO. Indomethacin versus radiation therapy for prophylaxix against heterotopic ossification in acetabular fractures: a randomized, prospective study. J Bone Joint Surg Br 1998; 80(2):259-263.
9- Altman RD, Latta LL, Keer R, Renfree K, Hornicek FJ, Banovac K. Effect of nonsteroidal anti-inflammatory drugs on fracture healing: a laboratory study in rats. J Orthop Trauma 1995; 9(5):393-400.
10- Dimar JR 2nd, Ante WA, Zhang YP, Glassman SD. The effect of nonsteroidal anti-inflammatory drugs on posterior spinal fusions in the rat. Spine 1996; 21(16):1870-1876.
11- Long J, Lewis S, Kuklo T, Zhu Y, Riew KD. The effect of cyclooxygenase-2 inhibitors on spinal fusion. J Bone Joint Surg Am 2002; 84:1763-1768.
12- Simon AM, Manigrasso MB, O'Connor JP. Cyclo-oxygenase 2 function is essential for bone fracture healing. J Bone Mineral Res 2002; 17:963-976.
13- Brown KM, Saunders MM, Kirsch T, Donahue HJ, Reid JS. Effect of COX-2-specific inhibition on fracture-healing in the rat femur. J Bone Joint Surg Am 2004; 86:116-123.
14- Mullis BH, Copland ST, Weinhold PS, Miclau T, Lester GE, Bos GD. Effect of COX-2 inhibitors and non-steroidal anti-inflammatory drugs on a mouse fracture model. Injury, Int J Care Injured 2006;
15- Ho ML, Chang JK, Wang GJ. Antiinflammatory drug effects on bone repair and remodeling in rabbits. Clin Orthop Relat Res 1995; 313:270-278.
16- Martin GJ, Boden SD, Titus L. Recombinant human bone morphogenetic protein-2 overcomes the inhibitory effect of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), on posterolateral lumbar intertransverse process spine fusion. Spine 1999; 124(21):2188-2193.
17- Goodman S, Ma T, Trindade M, Ikenoue T, Matsuura I, Wong N, Fox N, Genovese M, Regula D, Smith RL. COX-2 selective NSAID decreases bone ingrowth in vivo. J Orthop Res 2002; 20(6):1164-1169.
18- Gerstenfeld LC, Thiede M, Seibert K, Mielke C, Phippard D, Svagr B, Cullinane D, Einhorn TA. Differential inhibition of fracture healing by non-selective and cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs. J Orthopaedic Res 2003; 21:670-675.
19- Pritchett JW. Ketorolac prophylaxix against heterotopic ossification after hip replacement. Clin Orthop Relat Res 1995; 314:162-165.
20- Deguchi M Rapoff AJ, Zdeblick TA. Posterolateral fusion for isthmic spondylolisthesis in adults: analysis of fusion rate and clinical results. J Spinal Disord 1998; 11(6):459-464.
21- Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ, De Boer P. Nonunion of the femoral diaphysis. The influence of reaming and non-steroidal anti-inflammatory drugs. J Bone Joint Surg Br 2000; 82(5):655-658.
22- Glassman SD, Rose SM, Dimar JR, Puno RM, Campbell MJ, Johnson JR. The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. Spine 1998; 23(7):834-838.
23- Burd TA, Hughes MS, Anglen JO. Heterotopic ossification prophylaxis with indomethacin increases the risk of long-bone nonunion. J Bone Joint Surg Br 2003; 85(5):700-705.
24- Reuben SS, Ablett D, Kaye R. High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. Can Anaesth 2005; 52(5):506-512.
25- Varghese D, Kodakat S, Patel H. Non-steroidal anti-inflammatories should not be used aftr orthopaedic surgery. British Medical Journal 1998; 316(7141):1390.
26- Stone PG, Richards E. NSAIDs need not usually be withheld after orthopaedic surgery. British Medical Journal 1998; 317(7165):1079.
27- Godden D. Effects of NSAIDs on bone healing have been widely reported in maxillofacial journals. British Med J 1999; 318(7191):1141.
28- Goodman S, Ma T, Mitsunaga L, Mivanishi K, Genovese M, Smith RL. Temporal effects of a COX-2 selective NSAID on bone ingrowth. J Biomed Mater Res 2005; 72(3):279-287.
29- Seidenberg AB, An YH. Is there an inhibitory effect of COX-2 inhibitors on bone healing ? Pharmacol Res 2004; 50:151-156.
30- Zhang X, Schwarz EM, Young DA, Puzaz JE, Rosier RN, O'Keef RJ. Cyclooxygenase-2 regulates mesenchymal cell differentiation into the osteoblast lineage and is critically involved in bone repair. J Clin Invest 2002; 109:1405-1415.
31- Reuben SS, Ekman EF. The effect of cyclooxygenase-2 inhibition on analgesia and spinal fusion. J Bone Joint Surg Am 2005; 87(3):536-542.