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Article

Long-term physiological effects of NSAIDS on bone properties

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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) are the most often prescribed category of painkiller for mild to severe pain and inflammation. Through the inhibition of the COX-2 enzyme, NSAIDs inhibit the production of prostaglandins in the tissue. While this reduces the pain sensation, it also delays a fundamental step in bone remodeling. Recent studies have shown that medicating with NSAIDS following acute bone trauma can have detrimental effects on bone repair and quality. There is not yet a clear consensus as to whether or not NSAIDs inhibit proper bone healing and repair. This review aims to gather data from different studies on bone health and quality following NSAID use to come to a consensus as to whether or not existing data shows that there is a deleterious effect. The research was gathered from studies comparing healing time, bone strength, stiffness, and histological quality following acute trauma to bone and subsequent medication of NSAIDS. The data gathered in this review shows that NSAIDs consistently have a negative effect on healing and healed bones. Although there is no evidence that NSAIDs cause a longer healing time, bone strength, stiffness, and quality have all been shown to be reduced following NSAIDS medication compared to a control group.

Keywords: NSAIDS, Fracture, Bone Healing, COX-1, COX-2, Prostaglandins, Inflammation, Histology, Bone Strength, Bone Stiffness, Repair, Tibial Fracture, Long-Term Effects, Pain, Post-Operative, Recovery

1. Introduction

In an era of tremendous pharmaceutical growth, it is often easy to over-simplify complex pharmaceuticals. Furthermore, letting short term benefits outweigh the long-term effects of certain drugs can be a growing problem. Non-steroidal anti-inflammatory drugs, or NSAIDs, are a perfect example of this issue. With an expanding number of NSAIDS becoming available, all claiming to work in different ways with different side effects, it is important to understand the fundamental nature and mechanism of NSAIDS. NSAIDs are often prescribed by clinicians following an operation in order to control patient pain, swelling, fever, or inflammation. NSAIDs can also be obtained without a prescription for personal use usually to aid in the suppression of mild aches and pains. However, growing evidence is suggesting that these NSAIDs may actually be detrimental to a proper bone recovery if taken sometime following acute bone trauma. The basic workings of these drugs are that they inhibit enzymes that play an important role in the inflammation cascade following acute bone trauma such as a tibia fracture [1]. Like any medication, over-prescription of a drug to the population can have various unwanted and sometimes unexpected effects. A small study in Canada showed that NSAIDs were unnecessarily prescribed by physicians in 41.7 percent of their visits. At the same clinic, reports of gastropathy, a stomach disease affecting the mucosal lining of the stomach and a potential side effect of NSAIDs, was correctly diagnosed as being related to NSAIDS in an astounding 93.4 percent of cases [2,3]. Situations like these are often attributed to looking for short-term relief without taking regard to the possibility of long-term consequences. As stated earlier, there are a variety of NSAIDs on the market, each with their own mechanism on how they inhibit pain and inflammation. Just like antibiotics, overusing an NSAID can relieve the pain it was intended to, but have drastic consequences elsewhere on the body [4,5]. Unfortunately, the reported number of people purchasing over-the-counter NSAIDS without a prescription is on the rise [6]. More importantly than the unintended side effects of these NSAIDS is their possibility to hinder bone healing.

Although NSAIDS effect on bone healing is not completely understood, there is enough of a concern for physicians in the US to tend to avoid their use in bone fracture cases [7]. Orthopedic surgeons in the US tend to

prescribe opioids to deal with pain management post-procedure. There is no research showing opioids to have the same effect of slowing or hindering bone healing that NSAIDs do, however, this comes at the cost of opioids have a greater number of side effects and the property of being a highly addictive drug [7,8,9]. Since opioids have addictive properties that are detrimental to the well-being of the person taking them, it is important to research and understand whether NSAIDs do in fact cause problems in bone healing in humans; and if so, what aspect of them is the central issue. This would allow pharmaceutical companies to work on developing future forms of NSAIDs that can alleviate pain and inflammation while avoiding the deleterious effects seen in bone healing of animal studies. This review looks at the existing information of the relationship between NSAIDs and bone healing to come to a conclusion if there is enough evidence to deem NSAIDS harmful to bone healing. We look at the mechanisms of the inflammation cascade following acute bone trauma such as a fracture, followed by the basic mechanisms of NSAIDS and how they inhibit the body's natural response to injury. We then look at existing research following NSAIDs application and whether or not they have an effect on the healing time of bones, as well as the physical properties of the bones themselves such as stiffness, load bearing strength, breaking point, and the composition of the bone following NSAID use compared to a no use.

2. Methods

Research for this review was gathered using the bibliographic management software models RefWorks and Endnote. Using RefWorks through the Texas A&M medical sciences library all articles deemed to be potentially used were saved and ordered. Google scholar was the search engine used to find peer-reviewed articles outside of using RefWorks and Endnote. Databases accessed include Pubmed, MEDLINE, CINAHL complete, SPORTDiscus, and EMBASE. Through these databases terms related to the topic were searched in broad and then narrowed down to fit a more specific criterion. Phrases searched include a plethora of terms and phrases related to NSAIDS and long bone fractures. The most used phrases, however, include: "NSAIDS effect on bone, bone healing, inflammation cascade, effects of NSAIDs on bone healing, effects of NSAIDs on bone composition, etc." Using primarily Pubmed, MEDLINE, and Google Scholar, additional studies were searched to understand the pathway bones take to heal as well as the mechanisms that allow NSAIDS to achieve pain alleviation. These searches were more straight forward in nature consisting of searches such as: "mechanism of inflammation, mechanism of NSAIDS, different types of enzymes, enzymes vs glucocorticoids, etc." Journal entries of experiments were mainly used as information resources for this review. Entries were chosen for use if they provided information regarding the effects of NSAIDs on bone healing in any aspect. RefWorks was used to store citations and create a bibliography of referenced works in this review.

3. The Mechanisms of Inflammation and NSAIDS

3.1 The inflammation cascade and bone healing

As painful as it is, inflammation is the bodies first response to acute trauma, sickness, infection and a host of other ailments [10]. Inflammation is the bodies way of bringing a host of different cell types, nutrients, blood flow, enzymes and proteins to the area of damage, in the case of a bone fracture, that is necessary for the rebuilding process of the bone. The immediate response following a fracture is a momentary vasoconstriction to ensure large amounts of blood arent loss in the scenario it is an open wound or a compound fracture. Following vasoconstriction is quick vasodilation to flood the area with blood, which forms an edema between the fractured bone pieces. This edema is filled with high levels of mature granulocytes, macrophages, and cytotoxic lymphocytes. Along with these cells are high amounts of inflammatory cytokines [11,12]. The inflammatory response, which usually lasts 2-9 days post-injury is onset by an accumulation of cytokines, prostaglandins, growth factors, and other inflammation mediators. Neutrophils and macrophages work to clear bone debris that may have broken off the bone. Eventually, capillaries grow into the shrinking hematoma. Along with these capillaries come fibroblasts that initiate the "reparative phase" of healing. Mesenchymal cells from surrounding soft tissue accumulate at the hematoma cite and, in the form of osteoblasts, start to lay down "woven bone." After the woven bone has spanned the gap of the fracture, osteoblasts begin to lay down trabecular bone from the outside of the bone inwards. Between weeks two and three and until around four months, this trabecular bone is replaced by lamellar bone in a series called ossification where the soft and spongy trabecular bone is replaced by mature, solid, weight-bearing bone. Overall bone remodeling continues for months to years but is mechanically stable at forty days [13].

3.2 NSAIDS mechanism of pain relief

Cytokines and growth factors are two of the main mediators by which bone resorption is managed. This resorption, which is done by the neutrophils and macrophages, is one of the first steps to cleaning the wounded area [13]. Prostaglandins (PGs) are potent stimulators of cytokines and growth factors. PGs are a number of compounds with varying hormone-like properties. One of the side effects of PGs is that they drastically increase the sensitization of pain receptors [13]. This is the mechanism that causes severe pain in the site of a bone fracture. This is also the mechanism NSAIDS are involved in impeding. When there is tissue damage, the enzyme Phospholipase A2 catalyzes the formation of arachidonic acid. Cyclooxygenase enzymes, COX-1 and COX-2, breakdown arachidonic acid into prostaglandins. Cytokines and growth factors present during inflammation stimulate the COX-2 enzymes which induce PGs in the area causing severe pain [14]. NSAIDs work by binding to the COX-2 enzyme before it binds to the arachidonic acid thus reducing the number of PGs. This has shown to be a viable source of pain relief, however, prostaglandins are needed to stimulate cytokines and growth factors to mediate bone resorption. This hindrance of a fundamental step in bone healing has caused concern in recent years for the integrity of the bone itself. Limiting needed substances for bone healing could damage the bone or at the least lead to prolongation of bone repair [15].

3.3 COX-1 vs COX-2 inhibition

COX-1 is an enzyme expressed by many tissues and organs. While COX-1 enzymes lead to the formation of PGs like COX-2, COX-1 works in different areas of the body. PGs induced by COX-1 have functions such as protecting the gastrointestinal mucosa from stomach acid, promote clotting by activating blood platelets, and controlling renal blood flow [1,16]. The usual target of NSAIDs is the COX-2 enzyme which initiates the production of PGs responsible for increased sensitization to pain [14]. While many prescribed NSAIDS are selective for COX-2 enzymes, some inhibit both COX-1 and COX-2. These NSAIDs are known as "traditional NSAIDS." As mentioned earlier, over-prescription of traditional NSAIDS has led to the unintentional interruption of systems that COX-1 is associated with such as gastropathy. The detrimental effects of inhibiting the COX-1 enzyme is well documented and will not be focused on in this review. Rather, solely focusing on the effects of selective COX-2 NSAIDs on bone repair and healing.

4. COX-2 Inhibition and Bone Healing

4.1 Bone Healing TIme

COX-2 selective NSAIDs target the production of PGs in that they reduce their concentration in the hematoma of a bone fracture. While this does relieve pain, it prolongs the recovery of the bone by stalling the early resorption step [15]. This can be an issue in that the bone may take longer to fully heal or even proceed to heal and rebuild incorrectly without properly removing unwanted bone from the area. Fader et al. looked into the possibility that COX-2 selective NSAIDs increased the healing time for diaphyseal tibia fractures. Fader points out that in the US, most physicians prescribe opioids for pain involving fractures. She also points out that this is not the standard practice outside the US. In Chile, physicians still prescribe NSAIDs for post-operative pain. Fader's goal was to study the healing time of the same tibia fracture between patients taking opioids and those taking NSAIDs. Her study consisted of 190 Chilean patients taking NSAIDs and 182 US patients taking opioids. She only included tibial fractures that met a certain classification to normalize that data. Healing time was defined as the time it took for there to be cortical bridging in at least 3 of 4 cortices seen on lateral radiographs. The results showed that the mean healing time for the opioid population was 185 ± 108 days. The healing time for the NSAIDS population was 180.5 ± 76 days. Independent t-test determined the difference in healing time to not be statistically significant. Although no significant difference was found, Fader points out that it is important to understand that there were most likely many more factors at play that can affect healing rates such as smoking, diabetic status, and baseline nutrition [17]. Fader's work suggests NSAIDS may be safely used without any effect on the healing time of bones, however, this only applies to the time of healing and does not address the differences, if any, in the quality of the bone.

4.2 Mechanical Strength of Healed Bone

Multiple studies have looked into the mechanical effects NSAIDs have on the bones in animal studies. Bissinger et al. studied the effects of Diclofenac, a traditional NSAID. Bissinger assigned 33 rats to different groups; those taking diclofenac, those taking Prednisolon (a glucocorticoid), and a control group. After the mice were anesthetized, a fracture was produced in the tibia via the three-point bending technique [18]. Over the next three week period, rats in the diclofenac group were given 5 mg/kg BW per day. After three weeks the rats were again anesthetized and the tibia tested again. Breaking load (N) and stiffness (N/mm) of the tibia bone

were recorded and compared amongst the three groups [19]. The breaking load of the diclofenac group was 15.68 N lower on average than the control group and the stiffness was 65.13 N/mm lower. This data shows that there was a significant difference in the quality of the bone. This leads to the conclusion that the NSAIDs had a substantial impairment in fracture healing [20]. Altman et al. performed a similar study using the three-point bending technique. Altman looked to see if the duration of taking NSAIDs had a significant effect and mechanical strength. He tested rats who had taken ibuprofen for four weeks following tibial fracture, rats who had taken Ibuprofen for twelve weeks, and a control group. He also tested the breaking load of the healed bone. He tested the strength of the tibia every two weeks for twelve weeks. He found there was no significant difference between the two groups who had taken ibuprofen for four and twelve weeks throughout the entire duration of the twelve weeks. No significant difference was seen between the two ibuprofen groups and the control group until the ten-week mark. At that point, the mechanical strength was seen to be significantly greater in the control group. Both these trials show that there is substantial evidence to suggest that NSAIDs do have a negative effect on the mechanical properties of bones post-fracture [21].

4.3 Histological Differences in Bones

Aside from measuring the mechanical strength of post-fractured bones, both Bissinger and Altman also took a histological approach comparing the bones in their studies. Bissinger looked at bone volume, bone mineral content, and bone surface as well as other aspects of bone histology. He found that in all three of these categories, the diclofenac group had lower values than the control group. This showed that the bone, although being classified as healed, had less mass and less mineral content than the same healed bone of the control group [20]. In the study done by Altman, the criteria by which they scored the histological data were not made clear. They did state, however, that the scores of histological healing in the ibuprofen-treated groups were consistently lower than the control group. This data concludes that it is not just a reduction in mass and mineral content, but also a change to the cells of the bone themselves [21]. Lastly, a study by Glassman et al. showed that in patients undergoing spinal fusion form the L4 to the sacrum, those who took NSAIDS post-operatively were five times more likely to demonstrate non-union of the bones. This data too shows that there is an effect of NSAIDs on the normal growth and repair of bone even in non-traumatic scenarios [22].

5. Summary and Practical Applications

The study of short and long-term effects of commonly prescribed NSAIDS is becoming more available in recent years. The majority of current studies are animal subjects but the data is still viable and useful. Conclusions from these animal studies can be drawn and a consensus reached that NSAIDs do have an adverse effect on the bone healing process. Fader concluded that there was no difference in the healing time between patients treating pain with NSAIDs vs opioids. Although the difference in time to heal was not different, questions on the integrity of the bones themselves arise. All other studies have shown that mechanical integrity and histological makeup are worse in groups taking NSAIDS than control.

The timing of the onset of NSAID medication also needs to be studied. Altman showed that taking NSAIDs at the onset of inflammation for only four weeks as opposed to twelve weeks showed no difference in the strength of the bone nor the reduction in bone mass and the decreased quality of the mineral content. We can draw the conclusion that taking NSAIDS immediately following acute bone trauma results in the same result no matter how long the NSAIDs are taken for afterward.

Future studies should begin to look at human subjects when possible. Healing time has been looked at but the physical and histological properties remain unknown. Another area of future research should investigate whether delaying the onset of NSAIDS by days or weeks has an effect on the healing process. Theoretically, by delaying the onset of NSAIDS, the bone resorption process mediated by PGs would be able to complete its process allowing the bone to move on to the next step in the healing process unhindered.

Information on human studies as well as studies into the effects of the delayed onset of NSAID medications could provide healthcare providers a better understanding of the safety of NSAIDS in pain management and its place in the therapeutic field. For now, enough evidence is present to continue to avoid the prescription of NSAIDs following acute bone trauma until further evidence in human trials is achieved.

Conflicts of Interest: Authors have no competing interests to declare. Comments and conclusions drawn do not constitute endorsement by the authors and/or the institution. The authors independently reviewed, analyzed and interpreted the results from this review and have no financial interests in the results of this study.

References

1. Fracon, R. N., Teófilo, J. M., Satin, R. B., & Lamano, T. (2008). Prostaglandins and bone: potential risks and benefits related to the use of nonsteroidal anti-inflammatory drugs in clinical dentistry. Journal of oral science, 50(3), 247-252.
2. Tamblyn, R., Berkson, L., Dauphinee, W. D., Gayton, D., Grad, R., Huang, A., ... & Snell, L. (1997). Unnecessary prescribing of NSAIDs and the management of NSAID-related gastropathy in medical practice. Annals of internal medicine, 127(6), 429-438.
3. Hawkey, C. J. (2000). Nonsteroidal anti-inflammatory drug gastropathy. Gastroenterology, 119(2), 521-535.
4. Chinedum, I. E. (2005). Microbial resistance to antibiotics. African journal of Biotechnology, 4(13).
5. Lounkine, E., Keiser, M. J., Whitebread, S., Mikhailov, D., Hamon, J., Jenkins, J. L., ... & Shoichet, B. K. (2012). Large-scale prediction and testing of drug activity on side-effect targets. Nature, 486(7403), 361.
6. Stosic, R., Dunagan, F., Palmer, H., Fowler, T., & Adams, I. (2011). Responsible self-medication: perceived risks and benefits of over-the-counter analgesic use. International Journal of Pharmacy Practice, 19(4), 236-245.
7. Fader, L., Whitaker, J., Lopez, M., Vivace, B., Parra, M., Carlson, J., & Zamora, R. (2018). Tibia fractures and NSAIDs. Does it make a difference? A multicenter retrospective study. Injury, 49(12), 2290-2294.
8. Volkow, N. D., McLellan, T. A., Cotto, J. H., Karithanom, M., & Weiss, S. R. (2011). Characteristics of opioid prescriptions in 2009. Jama, 305(13), 1299-1301.
9. Beck, A., Salem, K., Krischak, G., Kinzl, L., Bischoff, M., & Schmelz, A. (2005). Nonsteroidal anti-inflammatory drugs (NSAIDs) in the perioperative phase in traumatology and orthopedics effects on bone healing. Operative Orthopadie und Traumatologie, 17(6), 569-578.
10. Scott, A., Khan, K. M., Cook, J. L., & Duronio, V. (2004). What is "inflammation"? Are we ready to move beyond Celsus?. British journal of sports medicine, 38(3), 248-249.
11. Lisowska, B., Kosson, D., & Domaracka, K. (2018). Positives and negatives of nonsteroidal anti-inflammatory drugs in bone healing: The effects of these drugs on bone repair. Drug Design, Development and Therapy, 12, 1809-1814. doi:10.2147/DDDT.S164565
12. Hoff, P., Gaber, T., Strehl, C., Schmidt-Bleek, K., Lang, A., Huscher, D., ... & Buttgereit, F. (2016). Immunological characterization of the early human fracture hematoma. Immunologic research, 64(5-6), 1195-1206.
13. Riechman, Steven. (2018). Steps of fracture healing. [PowerPoint slides].
14. Gajraj, N. M. (2003). The effect of cyclooxygenase-2 inhibitors on bone healing. Regional anesthesia and pain medicine, 28(5), 456-465.
15. Zhang, X., Schwarz, E. M., Young, D. A., Puzas, J. E., Rosier, R. N., & O'Keefe, R. J. (2002). Cyclooxygenase-2 regulates mesenchymal cell differentiation into the osteoblast lineage and is critically involved in bone repair. The Journal of clinical investigation, 109(11), 1405-1415.
16. Parente, L. (2001). Pros and cons of selective inhibition of cyclooxygenase-2 versus dual lipoxygenase/cyclooxygenase inhibition: is two better than one?. The Journal of rheumatology, 28(11), 2375-2382.
17. Kurmis, A. P., Kurmis, T. P., O'Brien, J. X., & Dalén, T. (2012). The effect of nonsteroidal anti-inflammatory drug administration on acute phase fracture-healing: a review. JBJS, 94(9), 815-823.
18. Bonnarens, F., & Einhorn, T. A. (1984). Production of a standard closed fracture in laboratory animal bone. Journal of Orthopaedic Research, 2(1), 97-101.
19. Turner, C. H., & Burr, D. B. (1993). Basic biomechanical measurements of bone: a tutorial. Bone, 14(4), 595-608.

20. Bissinger, O., Kreutzer, K., Götz, C., Hapfelmeier, A., Pautke, C., Vogt, S., . . . Prodinger, P. M. (2016). A biomechanical, micro-computertomographic and histological analysis of the influence of diclofenac and prednisolone on fracture healing in vivo. BMC Musculoskeletal Disorders, 17(1), 383. doi:10.1186/s12891-016-1241-2
21. Altman, R. D., Latta, L. L., Keer, R., Renfree, K., Hornicek, F. J., & Banovac, K. (1995). Effect of nonsteroidal antiinflammatory drugs on fracture healing: A laboratory study in rats. Journal of Orthopaedic Trauma, 9(5), 392-400.
22. Glassman, S. D., Rose, S. M., Dimar, J. R., Puno, R. M., Campbell, M. J., & Johnson, J. R. (1998). The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. Spine, 23(7), 834-838.