The effect of ketoprophen on lumbar spinal fusion healing in a rabbit model

Laboratory investigation

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Object. Several reports have shown that nonsteroidal antiinflammatory drugs (NSAIDs) have an inhibitory effect in osteogenesis and reduce heterotopic ossification in humans. A deleterious effect of NSAIDs in posterolateral intertransverse process fusion has also been suggested. The authors used a validated rabbit model to try to determine the influence of the NSAID ketoprophen on the fusion rate in lumbar spinal arthrodesis.

Methods. Thirty New Zealand male rabbits underwent posterolateral (intertransverse process) bilateral spinal fusions at a single level, using autologous bone graft obtained from both iliac crests. The animals were randomized after the operation, so that 15 rabbits received ketoprophen as a postoperative analgesic and the other 15 received the postoperative analgesic tramadol. The animals were killed 8 weeks after surgery, and fusion status was determined by inspection, palpation, anteroposterior radiographs, and histological analysis.

Results. A solid fusion was obtained in eight rabbits (53%), and pseudarthrosis in seven rabbits (47%) in each group.

Conclusions. These findings suggest that the use of ketoprophen after intertransverse spinal fusion at a single level does not decrease the fusion rate, compared with tramadol. (DOI: 10.3171/SPI-07/12/631)

KEY WORDS • arthrodesis • ketoprophen • nonsteroidal antiinflammatory drug • rabbit model • spine fusion • tramadol

Posterolateral spinal fusion is performed to treat many spinal conditions related to degenerative disorders, tumors, infections, trauma, and deformities of the spine. The technique most frequently used in the lumbar spine is posterolateral intertransverse process fusion. Despite the frequency of use of this technique, the percentage of patients experiencing pseudarthrosis has been reported to be between 10 and 60%. Factors influencing fusion healing include the disease for which the fusion was indicated, type of graft used (autograft or allograft), number of levels fused, fusion technique, presence of instrumentation, patient smoking habits, metabolic abnormalities, and others.1,2,3,10,12,18,20,22,34,45,48,51

There has been much research directed at trying to recognize factors influencing consolidation of lumbar spinal fusions. Basic research study of instrumentation and its biomechanics is very costly because it requires the use of animals of similar size to human beings. Other lines of research try to establish answers to biological events that may affect the consolidation, and for these types of research it is possible to use experimental models of lower cost and size that simulate consolidation in humans.5,6,8,9,12,42,43

Since the 1970s, clinical reports have demonstrated that NSAIDs have an inhibitory effect on heterotopic ossification in humans.2,5,10,12,18,20,22,34,45,48,51 Additionally, authors of some studies suggest that NSAIDs exert a negative biological effect on osteogenesis.1,2,3,6,10,12,13,14,16,19,21,25–29,38–40,44,46

During the 1990s, reports describing an inhibitory effect of NSAIDs on lumbar spinal fusion consolidation were published.11,13,14,19,30,31 The evidence supporting this hypothesis, however, is scarce, consisting of two published retrospective clinical studies and three papers involving animal experimental models. This evidence, in our opinion, does not allow definitive conclusions to be drawn. More recently, other papers12,36,37 have shown that the effect of NSAIDs on spinal fusion may be dependent on the particular NSAID used,32 the length of time it is administered,37 and the dose received by the study participant.36

We performed this randomized double-blind study to try to determine the influence of ketoprophen, a frequently used NSAID in clinical practice, on the fusion rate of lumbar spinal fusion.
Materials and Methods

Thirty New Zealand male rabbits, weighing between 2100 and 4200 g, underwent posterolateral (intertransverse process) bilateral spinal fusions at a single level, using autologous bone graft obtained from both iliac crests. The animals were weighed prior to surgery and randomized after the operation, so that 15 rabbits received ketoprophen in the dosage recommended for veterinary use as a postoperative analogesic (ketoprophen group) and the other 15 received the postoperative analogesic tramadol, a non-NSAID analogesic (tramadol group).

Approval from the institutional review board for animal research was obtained for this study. We did not use a control group receiving a placebo in view of the necessity of administering an analgesic to animals subjected to a surgical intervention such as the one described. Ketoprophen was administered at 2 mg/kg subcutaneously every 12 hours for 5 days and then every 24 hours for 3 days (the dose recommended for veterinary use). Tramadol was administered at 4 mg/kg subcutaneously every 12 hours for 5 days, and then every 24 hours for 3 days. The administration of both drugs began during the hour after the conclusion of the operation. In both groups, antibiotic prophylaxis was used in the form of enrofloxacin 5 mg/kg administered subcutaneously every 24 hours for 7 days.

The animals were coded, and the administration of the drugs was performed by personnel other than the surgeons and evaluators. The researchers did not know which drug was given.

The animals were killed 8 weeks after the operation. The complete lumbar spine and the sacrum, stripped of soft tissue and muscle, were harvested. Two researchers determined fusion healing by inspection and palpation, assessing flexion/extension movement as described by Boden and colleagues. During the evaluation stage, the examiners were not aware which drug had been administered.

An anteroposterior radiograph was obtained of each specimen after removal from the animal. The fusion was assessed by palpation; radiographs were used to confirm fused specimens based on the presence of a continuous bone mass on the radiographs, crossing both transverse processes, without radiolucent lines. A histological analysis was also performed on each specimen, to confirm the presence of a bone bridge (consolidation) or pseudarthrosis. To consider a specimen as fused, it had to have absence of movement on the palpation test in addition to bone bridging noted on radiographs and on histological analysis.

The sample size estimation was based on data from a previous study by Martin and colleagues. The hypothesis was that the ketoprophen group would have a fusion rate 50% lower than the tramadol group. With a significance level of 5% and a power of 80%, the smallest appropriate sample size was 15 animals in each group. The statistical analysis of the data obtained was performed using the Mann–Whitney and Kruskal–Wallis nonparametric tests. A probability value of less than 0.05 was considered a statistically significant difference.

Results

The animals were of similar size in both groups. The average weight of the animals in the ketoprophen group was $3126 \pm 515$ g (range 2500–4200 g), and in the tramadol group it was $2985 \pm 602$ g (range 2100–3900 g), with a probability value greater than 0.05 between the two groups.

The fusion rate was the same in the ketoprophen group as in the tramadol group. Using the criteria of the absence of mobility in flexion/extension in addition to bone bridging between the transverse processes on radiographs (Fig. 1) and on histological analysis (Fig. 2), fusion was noted in eight rabbits (53%) and pseudarthrosis in seven rabbits (47%) in each of the groups (Fig. 3). A bone bridge (solid fusion) was found bilaterally in three rabbits (20%) and unilaterally in five rabbits (33%) in both the ketoprophen group and the tramadol group. The average weights of the animals according to the degree of consolidation were 3071 g for rabbits with pseudarthrosis, 3101 g for rabbits with the unilateral bone bridge, and 2943 g for rabbits with the bilateral bone bridge (p > 0.05). There was no statistical difference between the average weight of the group with consolidation (3042 g) and the group with pseudarthrosis (3071 g).

Discussion

Nonsteroidal antiinflammatory drugs are used extensively in the management of pain from many different sources, including postoperative pain.

There are a number of publications related to the role of

Fig. 1. Radiographs showing a unilateral fusion mass (A), a bilateral intertransverse fusion (B), and a nonunion (C).
NSAIDs in bone formation. There is evidence that NSAIDs reduce heterotopic ossification in animals. Clinical studies have shown that the NSAID indomethacin reduces heterotopic ossification in patients undergoing hip arthroplasty. This effect was also reported to occur even if the patients were only treated with indomethacin in the first weeks following the operation.

There are also studies describing the influence of NSAIDs in osteogenesis. The effect of indomethacin on osteogenesis has been widely studied, and it has been shown to reduce the formation of fracture callus in rats and increase the rate of pseudarthrosis. Additionally, this NSAID inhibits the transformation of collagen into osseous tissue, thereby affecting the resistance of the callus to stress. The mechanisms that have been suggested to be responsible for this effect on bone formation include a decrease in remodeling and formation of bone, inhibition of calcification of the bone matrix, a reduction in blood flow, and alteration of the inflammatory response at the fracture site.

Considering that consolidation of lumbar spinal fusion is similar to the osteogenesis process that occurs in heterotopic ossification and fracture healing, it was suggested that NSAIDs could also affect healing in lumbar spinal fusions. In 1994, Lebwohl and colleagues presented a paper on the effect of ibuprofen on rabbits subjected to spinal fusion at multiple levels. There was a trend in this study showing that ibuprofen produced a negative effect, but the difference lacked statistical significance.

There are limited data from published papers suggesting the possibility of a harmful effect of NSAIDs in the consolidation of lumbar spinal fusions. Dimar and associates used an experimental model of multilevel fusion in rats, which showed a significantly deleterious effect of NSAIDs on the fusion rate in lumbar spinal fusions. The model used in that study, however, had a number of disadvantages. First, the dose of NSAIDs was close to the toxic dose, and 18% of the animals in the group under treatment died due to complications from the NSAIDs. Second, the bone autograft obtained was of vertebral origin because it was difficult to obtain enough graft material from the iliac crest to perform the segmented fusion. Bone graft material of vertebral origin contains a different proportion of cortical and cancellous bone and therefore its biological behavior is different from that of an iliac crest graft. Finally, the surgical fusion technique used was posterior fusion, a technique that is less frequently used in humans, with posterolateral fusion the current preferred technique.

Glassman and coworkers found a negative effect of NSAIDs on the fusion rate in a retrospective study of patients who underwent lumbar spinal fusions. In this study as well, however, there are difficulties with accepting the evidence provided as conclusive. First, because it was a retrospective study, the patients were not randomized by use.
or nonuse of NSAIDs; the use of NSAIDs in some patients might be related to some factor influencing the rate of pseudarthrosis. Additionally, these patients had instrumentation inserted, which limits the interpretation of the radiological results. When instrumentation is present, radiography has an accuracy rate of no more than 60% in evaluating the consolidation of a posterolateral fusion.

In another retrospective clinical study, Deguchi et al.\textsuperscript{13} evaluated patients with isthmic spondylolisthesis who underwent decompressive surgery in addition to posterolateral spinal fusion. In this report, patients who continued taking NSAIDs for 3 months after surgery showed a significantly higher rate of pseudarthrosis and poorer clinical results than the other patients. Due to the actual design of the study, it is not possible to attribute the higher percentage of pseudarthrosis to the more prolonged use of NSAIDs because there were other variables, such as the presence or absence of instrumentation, patient smoking habits, and the number of levels involved in the operation that could also have affected the results and which were not evaluated specifically in the context of their relationship to the prolonged use of NSAIDs. The extended use of NSAIDs in the postoperative period may also have been secondary to inferior results (pain) associated with the surgery, and not the reverse. In this study there is no reference to the reason for the prolonged use of NSAIDs in this group of patients. Also relevant to this study is the difficulty of evaluating the consolidation in the presence of instrumentation.

Other studies have used the same rabbit model as we did. Martin and colleagues\textsuperscript{33} reported a deleterious effect of ketorolac compared with the use of saline solution in the consolidation of lumbar spinal fusions in rabbits. This negative effect was reversed by the use of bone morphogenetic protein type-2. This study compared the use of ketorolac and saline solution in the postoperative period, whereas our study which compared an NSAID with a non-NSAID analgesic. We do not know whether the use of another analgesic might affect the results, but it does not seem possible to leave human patients without an analgesic during the postoperative period. There is no reference in the study of Martin et al.\textsuperscript{33} to the use of some other form of analgesia. Also, the ketorolac dosage used in the study of Martin et al. was the one previously shown to produce a significant inhibition of consolidation of the ulna in a rabbit model, whereas the dose chosen for our treatment group was that recommended for veterinary use. Riew and coworkers\textsuperscript{37} compared the effect of indomethacin, beginning 2 or 4 weeks postoperatively, to that of saline. They found that the earlier that indomethacin was administered postoperatively, the greater was its negative effect on fusion. These results suggest that NSAIDs may have a deleterious effect on fusion that is time dependent. Long and colleagues,\textsuperscript{32} using this same rabbit model, compared the effect of celecoxib and indomethacin to that of saline solution after fusion of intertransverse processes. A significant difference between the control and indomethacin groups, but not between the celecoxib and control groups, was found. These results suggest that celecoxib does not significantly inhibit the rate of spinal fusion in rabbits. Thus, different NSAIDs appear to have a different effect on spinal fusion healing. The authors of this paper believe that the inhibitory effects of NSAIDs on bone healing are probably mediated by inhibition of cyclooxygenase-1, which is something that has yet to be proven. Indomethacin is the drug most widely described to inhibit bone formation, as previously discussed, and other noncyclooxygenase-2 selective NSAIDs may not have the same effects.

More recently, Reuben and associates\textsuperscript{6} published a paper showing that the short-term perioperative administration of celecoxib, rofecoxib, or low-dose ketorolac did not have significant deleterious effects on spinal fusion, but in contrast, higher doses of ketorolac did show this effect. As previously noted, several papers that have demonstrated a deleterious effect of NSAIDs on the healing of spinal fusions in animals had used a dose already known to produce a negative effect on bone formation. In our paper, we decided to use a veterinary recommended dose, which may explain the lack of an inhibitory effect observed.

In our paper we used the model described by Boden and associates,\textsuperscript{6} because in different publications it is considered the lower animal model most comparable to humans, because of both the surgical technique and the rate of consolidations. Our study showed 53% fusion for both groups, comparable with the rate of consolidation (between 40 and 70%) that has been reported in studies in which this model.
associated with autograft, has been used. This comparable rate suggests that the model was well reproduced, and that our results are, therefore, valid.

**Conclusions**

A deleterious effect of NSAIDs on the healing of posterolateral (intertransverse process) fusion has been suggested, but the evidence is not definitive. Different NSAIDs appear to have a different effect on spinal fusion healing. The NSAID dose and the time of drug administration are factors that may influence the fusion rate as well. Ketoprophen, used in a veterinary recommended dose, did not affect the fusion rate in a lumbar spinal arthrodesis model in rabbits, compared with a non-NSAID analgesic.

**References**


**J. Neurosurg: Spine / Volume 7 / December, 2007**

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