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# Ketorolac and Spinal Fusion

## Does the Perioperative Use of Ketorolac Really Inhibit Spinal Fusion?

Ben B. Pradhan, MD, MSE,* Robert L. Tatsumi, MD,† Jason Gallina, MD,‡ Craig A. Kuhns, MD,§ Jeffrey C. Wang, MD,¶ and Edgar G. Dawson, MD‖

**Study Design.** Retrospective review.

**Objective.** To evaluate the effect of postoperative use of ketorolac (Toradol) on spinal fusion in humans.

**Summary of Background Data.** The value of parenteral ketorolac in postoperative analgesia has been well documented across surgical specialties. However, some studies have shown that ketorolac may adversely affect osteogenic activity and fracture healing.

**Methods.** A total of 405 consecutive patients who underwent primary lumbar posterolateral intertransverse process fusion with pedicle screw instrumentation were included in this retrospective study. A subtotal of 228 patients received Toradol after surgery for adjunctive analgesia. Each patient received a mandatory dose of 30 mg intravenously every 6 hours for 48 hours. The same surgeon performed the fusion procedure on all of these patients. Historical controls included 177 patients who did not receive Toradol after surgery. The minimum follow-up period was 24 months. Nonunions were diagnosed by analyzing sequential radiographs, flexion-extension radiographs, and computed tomography with multiplanar reconstructions. The gold standard of surgical exploration was performed in symptomatic patients with diagnostic ambiguity or nonunions diagnosed by imaging.

**Results.** There were no smokers in the study population. Pseudarthrosis was identified in 12 of 228 patients (5.3%) who received Toradol after surgery, and in 11 of 177 patients (6.2%) who did not. There was no significant difference detected in the nonunion rates between the two groups ($P > 0.05$, $\chi^2$ method).

**Conclusion.** Use of ketorolac after spinal fusion surgery in humans, limited to 48 hours after surgery for adjunctive analgesia, has no significant effect on ultimate fusion rates.

**Key words:** spinal fusion, pseudoarthrosis, ketorolac, nonsteroidal analgesics. **Spine 2008;33:2079–2082**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain control and are the most often prescribed class of medication around the world.[1] The benefits of NSAIDs include reduced pain, improved postoperative ambulation, shorter hospitalization and decreased nausea, emesis and sedation.[2–4] NSAIDs have documented efficacy when administered as the sole analgesic after minor surgical procedures and adjuvants to other analgesics after major surgery.[5,6] Ketorolac (Toradol, Roche Laboratories, Nutley, NJ), approved by the Food and Drug Administration in November 1989 for the control of postoperative pain, enhances the effect of narcotics, and decreases narcotic requirement.[2,4,7–15] Empirically the authors have observed a more comfortable postoperative hospital course in spinal fusion patients who received parenteral Ketorolac at our institution without any attendant increase in complications.

NSAIDs, however, have a myriad of undesirable side effects especially in the perioperative period and includes gastrointestinal bleeding or ulcers, wound healing problems or bleeding, and renal failure.[7,16–25] NSAIDs may also adversely affect osteogenic activity and fracture healing.[26–29] Regarding spinal surgery, a number of studies have shown adverse effects on fusion rates in animals.[30–33] This may occur through any one or all of several mechanisms.[28,31,34] Glassman *et al*[35] examined the influence of ketorolac on spinal fusion in humans and concluded that this drug significantly inhibited fusion at doses typically used for postoperative pain control and that NSAIDs should be avoided in the early postoperative period.

The goal of this retrospective study was to determine the nonunion rate at 34 months after spine surgery in patients who were given a short-term amount of ketorolac after surgery.

## Materials and Methods

Nonsmoking patients who underwent 1, 2, or 3 level lumbar posterolateral intertransverse process fusion with pedicle screw instrumentation and decompression by a single surgeon (EGD) were given ketorolac intravenously as a mandatory drug, and not as a *prn* (as needed) drug. Every patient received the same dose and duration of the drug–30 mg intravenously every 6 hours for a total of 48 hours (total 240 mg). No loading dose was given. Patient's were contraindicated to have ketorolac if they had a documented allergy to NSAIDs, history of peptic ulcer disease, congestive heart failure, liver disease, bleeding disorder, serum creatinine >1.5 mg/dL, or age >65 years.

Patient's who underwent the same procedure by the senior author (EGD) before November 1989 (before the introduction of ketorolac) and by another surgeon (JCW) were not given Ketorolac after surgery. All patients were given patient con-

From the *Risser Orthopaedic Group, Pasadena, CA; the †Pacific Spine Specialists, Tualatin, OR; ‡New York, NY; the §University of Missouri School of Medicine, Columbia, MO; ¶UCLA School of Medicine, Los Angeles, CA. ‖Edgar G. Dawson, MD, is deceased.
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Address correspondence and reprint requests to Ben B. Pradhan, MD, MSE, Risser Orthopaedic Group, 2627 East Washington Boulevard, Pasadena, CA 91107; E-mail: bpradhanb@hotmail.com

**Table 1. Patient Demographics**

| | Toradol Treated Group | Non-Toradol Treated Group |
|---|---|---|
| Patients | 228 | 177 |
| Males | 88 | 57 |
| Females | 140 | 120 |
| Smokers | 0 | 0 |
| Prior spinal surgery | 0 | 0 |
| Mean age (yr) | 56.3 | 56.0 |
| Mean height (in) | 67.9 | 65.6 |
| Mean weight (lbs/kg) | 165.3/75.1 | 166.6/75.7 |
| 1–2 level fusions | 203 | 151 |
| 3-level fusions | 25 | 26 |
| Iliac crest bone graft | 125 | 153 |
| Local bone ± allograft | 103 | 24 |
| Mean follow-up (mo) | 27.4 (24–66) | 34.1 (24–107) |

**Table 2. Nonunion Results**

| | Toradol Group | Non-Toradol Group | *P* |
|---|---|---|---|
| Nonunions | 12/228 (5.3%) | 11/177 (6.2%) | >0.05 |
| Nonunions in 1-level fusions | 5/126 (4.0%) | 5/80 (6.3%) | >0.05 |
| Nonunions in 2-level fusions | 5/77 (6.5%) | 3/71 (4.2%) | >0.05 |
| Nonunions in 3-level fusions | 2/25 (8.0%) | 3/26 (11.5%) | >0.05 |
| Nonunions with iliac crest bone graft | 10/25 (8.0%) | 10/153 (6.5%) | >0.05 |
| Nonunions with local bone ± allograft | 2/103 (1.9%) | 1/24 (4.2%) | >0.05 |
| Nonunions in patients of surgeon 1 | 12/228 (5.3%) | 7/85 (8.2%) | >0.05 |
| Nonunions in patients of surgeon 2 | | 4/92 (4.3%) | |

trolled analgesia transitioned to *prn* acetaminophen and opioid tablets. No oral NSAIDs were given after surgery.

The status of the fusion was determined based on anteroposterior and flexion-extension radiographs or computerized tomography at the time of 1-year follow-up. Pseudarthrosis (nonunion) was defined as the absence of bridging bone formation without trabeculation, >2° of motion on flexion-extension radiographs, and/or radiolucency around the hardware.

Demographic data (age, sex, height, weight), the level of fusions, and the use of iliac crest bone graft (ICBG) were analyzed with analysis of variance (Table 1). The incidence of pseudarthrosis was evaluated by a $\chi^2$ analysis.

## ■ Results

Four hundred five patients underwent primary lumbar posterolateral intertransverse process fusion with pedicle screw instrumentation and decompression. Two hundred twenty-eight patients received ketorolac and 177 patient's did not receive this drug and these patients were split approximately equally between 2 surgeons, (EGD) and (JCW).

There was no significant difference between the 2 groups for age, gender, height, weight, or number of levels fused. There was also no significant difference detected between the 2 groups for pseudarthrosis or any differences between the 2 surgeons. Nonunion was diagnosed in 12 of 228 (5.3%) patients who received Toradol, and in 11 of 177 (6.2%) of patients who did not receive ketorolac (Table 2). When comparing the patients the senior surgeon (EGD) operated on, there was a higher nonunion rate when he did not use ketorolac; however, this difference was not significant under statistical analysis. There was a trend toward higher nonunion rates with 3 level fusions as opposed to 1–2 levels, however, there was limited data to find statistical significance.

A large proportion of patients in this study did not receive autogenous ICBG to augment fusion. The percentage of patients receiving ICBG was significantly lower in the Toradol treated group than in the non-Toradol treated group (54.8% *vs.* 86.4%, $P < 0.05$).

## ■ Discussion

The use of posterolateral fusion in the treatment of degenerative, traumatic, and other unstable spinal disorders has been one of the most popular methods in spine surgery.[36–38] Pseudarthrosis rates for posterolateral lumbar spine fusions has been quoted to be anywhere from 3% to 35% in the literature.[39–42] The addition of instrumentation has not eliminated this problem.[43–45] Various factors may contribute to pseudarthrosis which may include smoking and long-term NSAID usage. Smoking has been shown to increase pseudarthrosis rates 2- to 5-fold.[39,41,46,47] Long-term, high dose, NSAID use after fusion surgery has been shown to adversely affect fusion rates in animals.[30–33,48,49]

NSAIDs are commonly used for pain control and are the most often prescribed class of medications around the world.[1] Ketorolac has been used in the perioperative period frequently and safely in many surgical procedures.[12,50–55] A number of studies have specifically examined the use of ketorolac after orthopaedic and spine surgery, finding no increase in complications.[2,4,8,11–14,56,57] Aubrun *et al*[13] detected no difference in perioperative complications with intravenous ketoprofen use after adult spinal fusion surgery. Munro *et al*[15] and Vitale *et al*[58] found no increase in complication rates after pediatric scoliosis fusion surgery. Le Roux and Samudrala[14] arrived at similar findings after lumbar disc surgery. Gora-Harper *et al*[59] noted less morbidity and lower cost after joint and spine procedures treated with ketorolac.

The adverse effects of NSAIDs on spinal fusion seen in animal studies are likely dose and duration-dependent.[30,60,61] The dose of ketorolac for humans in this study was approximately 1.5 mg/kg/d for the first 48 hours only. Studies involving spinal fusions in animals have dosed NSAIDs anywhere from 3 mg/kg/d to 10 mg/kg/d for durations from 7 days to 12 weeks.[30–33,60,62] Ho *et al*[60] discovered that while 4 mg/kg/d of ketorolac given for 6 weeks delayed endochondral ossification in rabbit ulnar fractures, a dosing schedule of 2 mg/kg/d for 6 weeks seemed to have little or no effect. The latter in fact is one of the lowest dosing schedules in the literature. Table 3 lists the breakdown of the cumulative doses of NSAIDs administered in

**Table 3. Cumulative Doses of NSAIDs on Bone Formation**

| Study | Dosing (mg/kg/d) | Duration | Cumulative Dose (mg/kg) |
|---|---|---|---|
| Riew *et al*, 2003 | 10 | 4 wk | 280 |
| Gerstenfeld *et al*, 2003 | 4 | 6 wk | 168 |
| Long *et al*, 2002 | 10 | 8 wk | 560 |
| Martin *et al*, 1999 | 4 | 7 d | 28 |
| Ho *et al*, 1998 | 4 | 6 wk | 168 |
| Dimar *et al*, 1996 | 3 | 12 wk | 252 |
| Reuben *et al*, 1998 (minimum effective postoperative dose) | 0.4 | 24 h | 0.4 |
| Current study | 1.5 | 48 h | 3 |

d indicates days; h, hours; wk, weeks.

various studies in the literature. It is notable that in this study, the ketorolac dose amounted to approximately 1.5 mg/kg/d for 2 days. It seems, however, that this dose can still be lowered without compromising results. Reuben *et al*[4] performed a study on the analgesic effects of ketorolac specifically after spinal fusion surgery, and concluded that the minimum effective dose of ketorolac was 15 mg every 6 hours for 24 hours, which translates to approximately 0.4 mg/kg/d for a day assuming a 70 kg patient.

To our knowledge, there has been only one clinical study that has evaluated the effects on bone formation by ketorolac use during the perioperative period after spinal fusion surgery in humans.[35] The purpose of our study was to demonstrate that limited use of ketorolac for immediate postoperative analgesia after spinal fusion, does not necessarily lead to increased pseudarthrosis rates. There are several improvements in our study method compared to Glassman *et al*.[35] One of the major shortcomings in the previous study was that Toradol administration was not indiscriminate-it was given as a PRN medication and patients with more pain received higher accumulated dosages of this medication. Thus, the variable dosage amount might be a confounding factor when one is evaluating the effect of nonunion. Furthermore, in the aforementioned study, there were additional confounding factors that could affect spinal fusion rates such as a high population of smokers (50%) and multiple surgeons performing the fusion procedures.

In this study, the patients who were given Toradol after surgery were operated on by a single surgeon in a nonsmoking population. Based on the findings in this study, and in contrast to the previous study, we conclude that limited use of ketorolac for analgesia after lumbar spinal fusion surgery had no significant effect on fusion. To minimize other complications, we suggest screening the patients for risk factors and to use the minimum effective dose and duration per surgeon discretion.

### ■ Key Points

- Ketorolac has been safely used in the perioperative period for many surgical procedures.
- Ketorolac is a good adjuvant with other analgesics after major surgical procedures.
- The use of ketorolac after primary lumbar spinal fusion surgery in humans did not affect fusion rates when compared with surgical patients who did not receive the same drug.

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