Dose-Response of Ketorolac as an Adjunct to Patient-Controlled Analgesia Morphine in Patients After Spinal Fusion Surgery

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This randomized, blind study was designed to determine the appropriate dose of ketorolac (a drug used as a supplement to opioids) to administer to patients who have undergone spinal stabilization surgery. The ketorolac was administered every 6 h, in addition to patient-controlled analgesia (PCA) with morphine, to 70 inpatients undergoing spine stabilization by one surgeon. The study was performed to determine the analgesic efficacy and incidence of side effects with different doses of ketorolac. The patients were divided into seven groups. They were given either IV saline (control group) or IV ketorolac (5, 7.5, 10, 12.5, 15, or 30 mg) every 6 h. The outcomes measured included pain scores, 24-h morphine usage, level of sedation, and side effect profile six times during the first 24 h postoperatively. The total dose of morphine was significantly larger in the control and 5 mg ketorolac groups than in the other five groups. Morphine consumption was similar in all groups receiving ≥7.5 mg of ketorolac. The pain scores were significantly higher in the control group than in some of the larger dose groups at three of the study intervals. The 5 mg group had higher pain scores than the other groups at most of the time intervals studied. There were no significant differences in pain scores among the other five groups. Sedation scores were higher (i.e., patients were more sedated) in the control group than in the other six groups at three of the time periods. We conclude that the administration of ketorolac 7.5 mg every 6 h has a morphine-sparing effect equivalent to that of larger doses in patients undergoing spine stabilization surgery. Using larger doses of ketorolac did not result in less somnolence, lower morphine use, or less pain. We recommend that ketorolac 7.5 mg be given every 6 h to patients undergoing spinal fusion surgery in addition to PCA morphine.
Implications: Using smaller doses of ketorolac (e.g., 7.5 mg every 6 h) as a supplement to morphine patient-controlled analgesia is as effective as larger doses in patients who have undergone spine stabilization surgery.
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Ketorolac is a useful analgesic adjunct for the multimodal management of postoperative pain. Ketorolac potentiates patient-controlled analgesia (PCA) with morphine (1–8). We have previously shown that ketorolac 15 mg every 6 h decreases pain, decreases morphine use, and reduces sedation compared with placebo (9). The appropriate dose of ketorolac to use in conjunction with PCA morphine has yet to be determined. This placebo-controlled study was conducted to evaluate the analgesic efficacy and incidence of side effects when varying doses of ketorolac were given, in addition to PCA morphine, to patients after spinal fusion surgery.

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Methods

After institutional review board approval, informed, written consent was obtained from 70 patients scheduled to undergo elective decompressive lumbar laminectomy with spinal fusion by a single surgeon. Patients were eligible for participation if they spoke English, they were at least 18 yr of age, they weighed >40 kg, and they could operate a PCA device. Exclusion criteria included known allergy, sensitivity, or contraindications to morphine or any nonsteroidal antiinflammatory drug (NSAID); renal insufficiency; a history of peptic ulcer; a history of a bleeding diathesis; and pregnancy.

Anesthesia was induced with propofol (2 mg/kg), fentanyl (5 μg/kg), and vecuronium (0.1 mg/kg) and was maintained with isoflurane in 70% N_2O in O_2. Neuromuscular blockade was antagonized with neostigmine (50 μg/kg). Patients were connected to a PCA pump (Abbott PCA Plus; Abbott Park, IL) on

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arrival in the postanesthesia care unit (PACU). The PCA solution contained morphine 1 mg/mL. The initial incremental dose was 1.5 mL with a lockout interval of 8 min and a 4-h limit of 30 mL. The incremental dose was increased to 2.0 mL and the 4-h limit was increased to 45 mL if analgesia was inadequate after 1 h. If analgesia remained inadequate after an additional hour, the incremental dose was further increased to 2.5 mL.

All patients received PCA morphine. The patients were assigned to one of seven treatment groups in a double-blind, randomized manner. Group 1 (K_0) received an IV injection of saline every 6 h. Group 2 (K_5) received an IV injection of ketorolac 5 mg every 6 h. Group 3 ($K_{7.5}$) received an IV injection of ketorolac 7.5 mg every 6 h. Group 4 (K_{10}) received an IV injection of ketorolac 10 mg every 6 h. Group 5 ($K_{12.5}$) received an IV injection of ketorolac 12.5 mg every 6 h. Group 6 (K_{15}) received an IV injection of ketorolac 15 mg every 6 h. Group 7 (K_{30}) received an IV injection of ketorolac 30 mg every 6 h.

Patients were asked to quantify their pain on a verbal analog pain scale between 0 and 10, with 0 representing no pain and 10 representing the worst imaginable pain. Pain assessments were made 4, 8, 12, 16, 20, and 24 h after surgery. Sedation was recorded every 4 h and rated by a blind observer on a numerical scale (1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, and 5 = asleep and not responsive to any stimulus). Postoperative nausea, vomiting, pruritus, respiratory depression (defined as a respiratory rate <10 breaths/min), and urinary retention were recorded throughout the 24-h postoperative period.

Demographic data (age, height, and weight), procedure duration, and doses of morphine required are expressed as mean ± SD and were analyzed using analysis of variance. Pain scores and level of sedation were analyzed by using the Kruskal-Wallis test. If a significant result was obtained, the Wilcoxon signed rank test was performed to determine between which groups there was significance; Bonferroni's correction was made for multiple comparisons. Presence of pruritus and nausea were analyzed by using a contingency table. Significance was determined at the $P < 0.05$ level.

Results

There were no significant differences among the treatment groups with respect to age, height, weight, or duration of surgery (Table 1).

The total dose of morphine (Figure 1) and the cumulative doses for each of the six time periods were significantly different among the groups ($P < 0.001$). The morphine doses were higher in the K_0 and K_5 group than in the other five groups (Table 2). There were no significant differences in the doses administered among the other five groups.

The pain scores were different among the groups 4 h ($P < 0.006$), 8 h ($P < 0.001$), 12 h ($P < 0.002$), 16 h ($P < 0.004$), 20 h ($P < 0.0001$), and 24 h ($P < 0.0005$) after surgery. At 8 h, the pain scores were significantly higher in the K_0 group than in the K_{10} group. At 20 and 24 h, the pain scores were significantly higher in the K_0 group than in the $K_{7.5}$ and K_{30} groups. At each of the time intervals, the K_5 group had higher pain scores than most of the larger dose groups. There were no differences in pain scores among the other five groups.

There was no significant difference with respect to the incidence of pruritus or in the incidence of nausea/vomiting among any of the groups (Table 3).

There were no instances of respiratory depression. The sedation scores were higher (i.e., patients were

Table 1. Demographic Data

Group	Age (yr)	Height (in)	Weight (lb)	Procedure time (min)
K0	42 ± 12	67 ± 5	172 ± 43	282 ± 53
K5	42 ± 6	68 ± 4	161 ± 25	271 ± 36
K7.5	44 ± 10	67 ± 4	165 ± 35	274 ± 43
K10	45 ± 12	69 ± 4	172 ± 25	279 ± 26
K12.5	43 ± 11	69 ± 4	167 ± 43	270 ± 43
K15	42 ± 5	69 ± 4	178 ± 28	274 ± 44
K30	48 ± 9	66 ± 3	160 ± 28	271 ± 37

There were no significant differences among the groups.
K0 = no ketorolac, K5 = 5 mg of ketorolac every 6 h, K7.5 = 7.5 mg of ketorolac every 6 h, K10 = 10 mg of ketorolac every 6 h, K12.5 = 12.5 mg of ketorolac every 6 h, K15 = 15 mg of ketorolac every 6 h, K30 = 30 mg of ketorolac every 6 h.

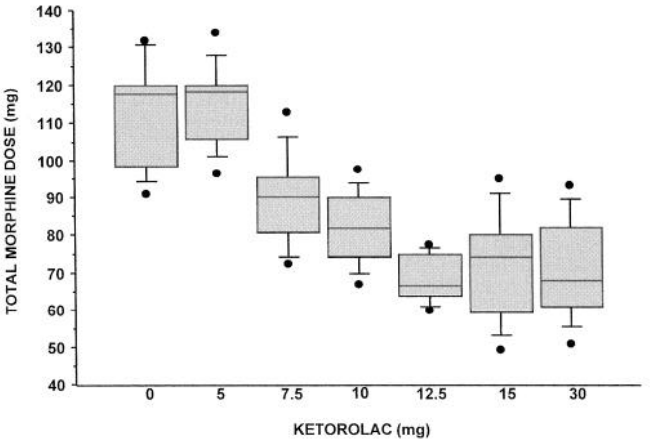

Figure 1. Comparison of the morphine consumption of the seven groups. The box represents the 25th–75th percentile; the dark line is the median; the extended bars represent the 10th–90th percentiles; and the circles represent values outside this range.

Table 2. Morphine Consumption, Pain Scores, and Sedation Scores for the Six Evaluation Periods

Group	Evaluation 1 (Hours 0–4)	Evaluation 2 (Hours 4–8)	Evaluation 3 (Hours 8–12)	Evaluation 4 (Hours 12–16)	Evaluation 5 (Hours 16–20)	Evaluation 6 (Hours 20–24)
Morphine administered (mg per time period)*						
K0	24 ± 4	21 ± 5	20 ± 4	19 ± 4	16 ± 4	14 ± 2
K5	27 ± 3	23 ± 4	19 ± 3	20 ± 4	15 ± 3	13 ± 4
K7.5	25 ± 3	20 ± 3	13 ± 3	15 ± 7	9 ± 3	8 ± 3
K10	22 ± 6	18 ± 6	13 ± 4	12 ± 4	8 ± 2	8 ± 2
K12.5	19 ± 5	16 ± 4	10 ± 3	9 ± 2	8 ± 2	7 ± 3
K15	17 ± 4	15 ± 3	11 ± 2	12 ± 4	10 ± 4	8 ± 5
K30	19 ± 4	15 ± 4	10 ± 4	10 ± 4	8 ± 3	7 ± 3
Pain scores						
K0	4.2 ± 1.1	3.8 ± 0.8	2.8 ± 0.6	2.8 ± 0.9	2.5 ± 0.7	2.3 ± 0.5
K5	4.6 ± 0.7	4.0 ± 0.7	3.2 ± 0.4	3.2 ± 0.6	2.8 ± 0.4	2.5 ± 0.5
K7.5	3.6 ± 0.8	2.9 ± 0.7	2.4 ± 0.5	2.0 ± 0.8	1.2 ± 0.4‡	1.3 ± 0.5‡
K10	2.8 ± 1.2	2.3 ± 0.9†	2.2 ± 0.6	1.8 ± 0.8	1.6 ± 0.5	1.7 ± 0.5
K12.5	3.1 ± 1.4	2.7 ± 0.9	2.1 ± 0.6	2.3 ± 0.6	1.6 ± 0.5	1.7 ± 0.5
K15	3.2 ± 1.1	2.7 ± 0.8	2.1 ± 0.3	1.9 ± 0.6	1.8 ± 0.4	1.6 ± 0.5
K30	3.0 ± 0.7	2.8 ± 0.6	2.2 ± 0.6	2.0 ± 0.7	1.5 ± 0.5‡	1.3 ± 0.5‡
Sedation scores						
K0	3.1 ± 0.7§	2.1 ± 0.6	1.7 ± 0.5	1.8 ± 0.8	2.0 ± 0.7§	1.8 ± 0.6§
K5	2.8 ± 0.4	2.1 ± 0.6	1.6 ± 0.7	1.6 ± 0.7	1.4 ± 0.5	1.5 ± 0.5
K7.5	1.7 ± 0.7	1.6 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	1.1 ± 0.3	1.0 ± 0
K10	2.0 ± 0.7	1.8 ± 0.6	1.3 ± 0.5	1.1 ± 0.3	1.4 ± 0.5	1.0 ± 0
K12.5	2.1 ± 0.6	1.7 ± 0.5	1.1 ± 0.3	1.3 ± 0.5	1.0 ± 0	1.0 ± 0
K15	2.0 ± 0.5	1.4 ± 0.5	1.2 ± 0.4	1.4 ± 0.7	1.1 ± 0.3	1.0 ± 0
K30	2.0 ± 0.7	1.9 ± 0.3	1.4 ± 0.7	1.3 ± 0.5	1.1 ± 0.3	1.1 ± 0.3

Evaluations were performed every 4 h postoperatively and were obtained at the end of the time period.
* Morphine doses were significantly higher in the K0 and K5 group than in the other five groups ($P < 0.001$).
At each of the time intervals the K5 group had higher pain scores than the majority of the higher dose groups.
† The pain scores were higher in the K0 group than in the K10 group.
‡ The pain scores were higher in the K0 group than in the K7.5 and K30 groups.
§ The patients were more sedated in the K0 group than in the other six groups ($P < 0.02$).
Patients received 0 mg (K0), 5 mg (K5), 7.5 mg (K7.5), 10 mg (K10), 12.5 mg (K12.5), 15 mg (K15), or 30 mg (K30) of ketorolac every 6 h.

Table 3. Side Effects

Group	Nausea/vomiting	Pruritis
K0	7	5
K5	8	6
K7.5	6	6
K10	4	2
K12.5	4	3
K15	3	5
K30	4	4

There was no significant difference with respect to the incidence of pruritus or in the incidence of nausea/vomiting among any of the groups.
Patients received 0 mg (K0), 5 mg (K5), 7.5 mg (K7.5), 10 mg (K10), 12.5 mg (K12.5), 15 mg (K15), or 30 mg (K30) of ketorolac every 6 h.

more sedated) in the K_0 group than in the other six groups 4, 20, and 24 h postoperatively ($P < 0.02$).

Discussion

A multimodal analgesic approach is currently recommended for the management of perioperative pain (10,11). Unless contraindicated, the pharmacological management should include a NSAID (10). Ketorolac, the only parenteral NSAID available in the United States, is frequently used in the perioperative setting. When used as an analgesic adjunct, ketorolac has been shown to significantly reduce PCA morphine use (1–9). We demonstrated in the present study an approximate one-third reduction in PCA morphine use when ketorolac was added to the analgesic regimen.

Although the combination of PCA opioids and adjunctive NSAIDs reduces self-administration attempts and total opioid dose, improvements in analgesic efficacy and reduction in side effects are observed less often (3,5,8,9). We, likewise, were unable to demonstrate a decrease in the incidence of pruritus, nausea, or vomiting. We were able to demonstrate a decrease in pain scores and a decreased level of sedation at three of the evaluations with the addition of ketorolac. We believe that the reason the sedation scores were not significantly different at three evaluations is because sedation is simply a surrogate for morphine consumption; statistically significant morphine differences do not always translate into clinically significant sedation differences.

The appropriate analgesic dose of ketorolac is controversial. Premarketing clinical investigations demonstrated that 30–90 mg of ketorolac provided postoperative analgesia similar to 6–12 mg of morphine and 50–100 mg of meperidine (12–14). Recent studies,

however, have revealed that ketorolac is ineffective as the sole postoperative analgesic in the management of moderate to severe postoperative pain (15,16). Since ketorolac has been marketed, there have been reports of deaths due to gastrointestinal and operative site bleeding (17). As a consequence, the drug's license was suspended in Germany and France (18). In a response to these adverse events, the drug's manufacturer recommended reducing the dose of ketorolac from 150 to 120 mg per day (19). The European Committee for Proprietary Medicinal Products recommended a further maximal daily dose reduction to 60 mg for the elderly and to 90 mg for the nonelderly (20). The appropriate dose of ketorolac to use as an analgesic adjunct has yet to be determined. Ketorolac, like other NSAIDs, exhibits an analgesic ceiling effect. Like other clinical investigations involving either bolus doses (4,8,9) or IV infusions of ketorolac (6), our study revealed that increasing the dose of ketorolac failed to provide any additional analgesia. Previous studies revealed that 10–15 mg of IM (8) or IV ketorolac (4,9,12) administered every 6 h was as effective as 30 mg in reducing 24-h PCA opioid requirements. Furthermore, Sevarino et al. (4) stated that an examination of smaller doses (5–7.5 mg) of ketorolac should be undertaken. Our study revealed that smaller doses of ketorolac (7.5 mg) are similar in analgesic efficacy to a 30-mg dose. Because ketorolac side effects seem to be dose-related (17), using this smaller dose of ketorolac may be safer.

A further theoretical concern is the effect of a NSAID on wound healing—specifically, the effect on bone repair in the present patient population. One investigation found that NSAIDs decreased the rate of fracture healing (21), whereas others found no significant effect on osteoblast or osteoclast activity (22). An interesting study in rabbits did, however, show a dose-dependent inhibitory effect of ketorolac on bone repair. In this study, 2 mg/kg ketorolac daily for 6 wk did not have a measurable effect on bone repair, whereas 4 mg/kg produced a deterioration in the mechanical properties of the bone matrix (23). This possible dose-dependent bone repair effect lends further credence to the use of the smallest possible clinically effective dose, which we established in the present study to be 7.5 mg every 6 h in patients who underwent spinal stabilization surgery.

We recommend that ketorolac be used as an adjunct to PCA morphine in patients undergoing spine stabilization surgery. This results in decreased morphine consumption, decreased somnolence, and enhanced analgesia compared with those in patients who do not receive ketorolac. Furthermore, we were unable to demonstrate that a dose of 7.5 mg every 6 h was any less effective than larger doses. We thus recommend that ketorolac 7.5 mg every 6 h should be added to a pain management regimen of PCA morphine in patients undergoing spine stabilization surgery.

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