Low-dose ketorolac improves analgesia and reduces morphine requirements following posterior spinal fusion in adolescents

[Une faible dose de kétorolac améliore l'analgésie et réduit les besoins de morphine à la suite d'une spondylodèse postérieure chez des adolescents]

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Purpose: To determine if low-dose ketorolac would improve analgesia while minimizing unwanted side effects in adolescents following posterior spinal fusion (PSF).

Methods: A prospective randomized double-blind placebo-controlled trial assessed the analgesic effects of low-dose ketorolac following PSF. Thirty-five adolescents aged 11–17 yr were randomly assigned to receive placebo or 0.5 $mg \cdot kg^{-1}$ ketorolac (maximum of 15 mg) six hourly postoperatively for 36 hr in conjunction with standard morphine patient controlled analgesia (PCA). Pain and sedation were assessed twice daily for the first three postoperative days (POD). The incidence of side effects related to both non-steroidal anti-inflammatory agents and opioids were recorded.

Results: Adolescents in the ketorolac group received an average dose of 0.2 $mg \cdot kg^{-1}$ (average exposure 1.2 $mg \cdot kg^{-1}$), had lower pain scores on POD one and two ($P < 0.05$) and consumed less morphine in the postanesthesia care unit and on POD two. There was no difference in the incidence of pruritus, nausea, vomiting or constipation, but patients in the ketorolac group tolerated activity better on POD one ($P < 0.05$). There were no differences between groups with regard to postoperative blood loss or transfusion requirements. Fourteen patients were followed for two years and the incidence of curve progression, hardware failure or back pain at final follow-up was not different.

Conclusion: Low-dose ketorolac in conjunction with morphine PCA improved the quality of analgesia and reduced morphine requirements following PSF compared to placebo without increasing the incidence of non-steroidal anti-inflammatory side effects.

Objectif : *Déterminer si une faible dose de kétorolac améliore l'analgésie tout en réduisant les effets secondaires chez des adolescents qui ont subi une spondylodèse postérieure (SDP).*

Méthode : *Un essai à double insu, randomisé et contrôlé contre placebo a permis d'évaluer les effets analgésiques d'une faible dose de kétorolac administrée après une SDP. Trente-cinq adolescents de 11–17 ans ont été répartis de manière aléatoire et ont reçu, soit un placebo, soit 0,5 $mg \cdot kg^{-1}$ de kétorolac (maximum de 15 mg) toutes les six heures après l'opération et ce, pendant 36 h en conjonction avec de la morphine normale en analgésie autocontrôlée (AAC). La douleur et la sédation ont été évaluées deux fois par jour pour les trois premiers jours postopératoires (JPO). L'incidence d'effets secondaires reliés aux anti-inflammatoires non stéroïdiens (AINS) et aux opioïdes a été notée.*

Résultats : *Les sujets qui ont eu du kétorolac ont reçu une dose moyenne de 0,2 $mg \cdot kg^{-1}$ (exposition moyenne de 1,2 $mg \cdot kg^{-1}$), ont présenté des scores de douleur plus faibles aux JPO un et deux ($P < 0,05$) et ont pris moins de morphine à la salle de réveil et au deuxième JPO. L'incidence de prurit, nausées, vomissements ou constipation était comparable dans les deux groupes, mais les mouvements étaient mieux tolérés avec le kétorolac au premier JPO ($P < 0,05$). La perte sanguine postopératoire et les besoins de transfusion ont été comparables. Quatorze patients ont été suivis pendant deux ans et l'incidence de la progression de la courbe, de la défaillance du matériel ou de la douleur au dos n'était pas différente au dernier examen de suivi.*

Conclusion : *Une faible dose de kétorolac, administrée avec de la morphine en AAC, améliore la qualité de l'analgésie et réduit les besoins de morphine à la suite d'un SDP, en comparaison avec un placebo, et sans augmenter l'incidence d'effets secondaires des AINS.*

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POSTERIOR spine fusion (PSF), a common operative treatment for adolescent idiopathic scoliosis, is associated with postoperative pain that is frequently difficult to manage. We have observed that these patients often describe their pain as being worse than anticipated and require high doses of opioids for pain relief. Opioid analgesia, especially in high doses, is associated with adverse effects that include nausea, vomiting, pruritus, urinary retention and respiratory depression. Ketorolac tromethamine, a parenteral non-steroidal anti-inflammatory analgesic (NSAID), has been shown to be as effective as morphine in the treatment of mild to moderate postoperative pain in both children and adults.[1–3] Ketorolac has also been shown to enhance analgesia when used as an adjuvant of morphine patient controlled analgesia (PCA) in adult patients undergoing spine stabilization surgery.[4] Yet concerns related to inhibition of platelet aggregation[5] and the potential to increase intraoperative and postoperative bleeding have limited its use for management of pain after surgery. In addition, ketorolac has been shown to decrease spinal fusion in an animal model[6] and inhibit spinal fusion in adults.[7] Since ketorolac exhibits a ceiling analgesic effect while the adverse effects may be dose-dependent,[8] we hypothesized that low-dose ketorolac in conjunction with morphine PCA would improve analgesia while reducing morphine requirements and opioid side effects without causing undesirable NSAID complications.

Methods

Following approval from the University of Michigan Institutional Review Board, written informed consent from the parents and assent from the patient, 38 ASA physical status I and II children aged between 11 and 17 yr, scheduled for elective correction of idiopathic scoliosis were studied in a double-blinded, randomized, controlled fashion. Exclusion criteria included known allergies to morphine or ketorolac, hepatic or renal insufficiency, a history of peptic ulceration, bleeding diathesis and respiratory insufficiency. Patients currently taking NSAIDs were not excluded.

All patients were instructed on the postoperative use of PCA, as well as the numeric and verbal pain scales to be used in the assessment of their pain and sedation. A midazolam premedication was given at the discretion of the anesthesiologist. All patients received a standardized general anesthetic. Following either an inhalational or *iv* induction, all children received a bolus of fentanyl 2–4 $\mu g \cdot kg^{-1}$ *iv* and pancuronium 0.1 $mg \cdot kg^{-1}$ *iv* to facilitate tracheal intubation. Anesthesia was maintained with isoflurane/nitrous oxide and a fentanyl infusion of 1–4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. The fentanyl infusion was terminated 30–45 min prior to the completion of surgery and following tracheal extubation, all patients were admitted to the postanesthesia care unit (PACU).

Patients were randomly assigned to one of two groups. Group I received 5 mL normal saline *iv* and Group II received ketorolac 0.5 $mg \cdot kg^{-1}$ *iv* (made up to 5 mL to a maximum dose of 15 mg at the completion of surgery. Each patient then received repeat dosing of the same solution every six hours for a total of six doses. All personnel administering the drugs and evaluating the patients for pain and side effects were blinded to the contents of the syringes. Morphine PCA was instituted as follows: an initial loading dose of 0.05–0.1 $mg \cdot kg^{-1}$ with a continuous infusion of 0.01 $mg \cdot kg^{-1} \cdot hr^{-1}$ and a demand dose of 0.02 $mg \cdot kg^{-1}$. Adjustments in dose were made by the acute pain service on daily rounds. Acetaminophen 10–20 $mg \cdot kg^{-1}$ *po* and diazepam 0.05–0.1 mg *iv* were prescribed as needed for supplemental analgesia and muscle spasm respectively and administered at the discretion of the bedside nurse. Postoperative nausea and vomiting were treated as indicated with ondansetron or metoclopramide.

Each patient was evaluated by a trained observer for pain and sedation on emergence from anesthesia in PACU, in the evening of the operative day, and twice daily on postoperative days one to three. The patients rated their pain numerically on a scale of 0 to 10 (0 = no pain, 10 = worst imaginable pain). Pain on "activity" was scored when the patient was moved from side to side as per nursing protocols, or on sitting out of bed and ambulating on postoperative day three. Sedation was scored from 0 to 5 (0 = does not arouse with significant stimulation, 1 = asleep, requires vigorous stimulation to arouse, 2 = asleep but arouses with mild stimulation, 3 = sleepy, easily aroused, 4 = awake and alert, 5 = agitated, uncontrollable, excessive motion). Patients also rated their degree of muscle spasm on a scale of 0 to 4 (0 = no spasms, 1 = minimal, 2 = occasional, every shift, 3 = consistent when moved, 4 = frequent, occurs without movement). Total morphine consumption, as well as acetaminophen, diazepam and anti-emetic use per day were recorded. The hematocrit was followed intraoperatively and daily postoperatively until the surgical drain was removed. Packed red blood cells were transfused if the hematocrit fell below 25 or if there was hemodynamic instability. Intraoperative and postoperative blood loss and transfusion requirements were documented.

We examined curve progression, back pain and hardware failure as possible indicators of failure of a solid posterior spinal fusion. One blinded observer measured

standing spine radiographs. The radiographs were measured using the Cobb method preoperatively, postoperatively and at annual follow-up for a minimum of two years. Curve progression was designated when a curve at annual follow up increased 10° from the first postoperative radiograph. At the final follow-up clinic the incidence of back pain was determined by a single practitioner. Hardware failures were noted.

Statistical methods

A power analysis was performed to determine the number of patients in each group. Based on pilot data of differences in pain scores between the groups (i.e., placebo = 7 ± 2.5; ketorolac = 5 ± 1.9) and given that alpha = 0.05 and beta = 0.2, we determined that 15 patients per group would be required.

Demographic data were compared using Chi-square or unpaired t tests as appropriate. Discrete data were compared using Chi-square and Fisher's exact tests where applicable. The Mann-Whitney U test was used to compare data from the outcome scales. Unpaired t tests were used to compare differences in pain scores at discrete time points between the two groups. Analysis of variance with repeated measures and post hoc paired t tests with Bonferroni corrections were used to evaluate changes in pain scores over time. Statistical significance was accepted at the 5% level ($P < 0.05$).

Results

Of the 38 patients enrolled, three patients in the placebo group were excluded due to protocol violations or incomplete data. Data were analyzed on the remaining 35. There were no differences between groups with regard to age, sex, weight, number of spinal levels fused, length of surgery or length of stay in PACU (Table I).

The patients who received ketorolac consistently rated their pain lower than those patients who received placebo. A statistically significant difference in pain scores was present on day one and on the afternoon of day two (Figure). There was however, no significant time effect for pain scores in either group through day three. Additionally, children in the placebo group used more morphine in the PACU and on POD two (Table II). There were no differences between the groups with respect to acetaminophen or diazepam usage (Table II). The incidence of muscle spasms was similar for children in both groups and was highest on POD one, 25% and 28% for the ketorolac and placebo groups respectively. The patients' tolerance of activity on each postoperative day is detailed in Table III. Although there was a trend toward better tolerance of activity in patients who received ketorolac through POD three, this difference reached statistical significance on POD one only.

Intraoperative blood loss was similar in both groups, (11.3 mL·kg^{-1} in Group I *vs* 14.3 mL·kg^{-1} in Group II). Postoperative blood loss as measured from surgical drains revealed no differences between groups

TABLE I Demographic and perioperative data [mean ± SD or median (range)]

	Placebo (n = 15)	*Ketorolac (n = 20)*
Age (yr)	14.1 ± 1.2	13.9 ± 1.3
Sex (male/female)	0/15	2/18
Weight (kg)	56.4 ± 14.3	58.7 ± 22.0
# of levels fused	12 (10–13)	12 (10–13)
Length of surgery (min)	331 ± 62	301 ± 63
Length of PACU stays (min)	108 ± 36	109 ± 19

PACU = postanesthesia care unit.

TABLE II Intraoperative and postoperative medications [mean dose ± SD (*n*/%)]

	iv Morphine (mg·kg^{-1}·day^{-1})		*Diazepam (mg·kg^{-1}·day^{-1})*		*Acetaminophen (mg·kg^{-1}·day^{-1})*	
	Placebo	*Ketorolac*	*Placebo*	*Ketorolac*	*Placebo*	*Ketorolac*
Intraoperative	1 ± 0.4 (15/100%)	1 ± 0.5 (20/100%)	NA	NA	NA	NA
PACU	0.09 ± 0.05* (11/73%)	0.06 ± 0.3 (11/55%)	0	0	0	0
POD zero	0.3 ± 0.1 (15/100%)	0.3 ± 0.1 (20/100%)	0.1 ± 0.01 (2/13%)	0	12.5 ± 1.9 (4/27%)	11.8 ± 0.9 (2/10%)
POD one	0.9 ± 0.4 (15/100%)	0.8 ± 0.3 (20/100%)	0.23 ± 0.2 (3/20%)	0.06 ± 0.01 (3/15%)	22 ± 11 (11/73%)	28 ± 21 (9/45%)
POD two	1 ± 0.5* (15/100%)	0.7 ± 0.4 (20/100%)	0.4 ± 0.4 (4/27%)	0.06 ± 0.03 (5/25%)	27.2 ± 19.9 (12/80%)	29 ±14 (14/70%)
POD three	0.7 ± 0.5 (14/93%)	0.6 ± 0.4 (16/80%)	0.17 ± 0.15 (5/33%)	0.09 ± 0.07 (4/20%)	34 ± 18.5 (15/100%)	52 ± 29.9 (17/85%)

PACU = postanesthesia care unit; POD = postoperative day; *$P \leq 0.05$ compared to ketorolac group.

TABLE III Pain with activity [*n* (%)]

	Placebo (*n* = 15)	*Ketorolac* (*n* = 20)
Eve of POD zero		
No discomfort	3 (20%)	9 (45%)
Moderate discomfort	7 (47%)	10 (50%)
Severe discomfort/refuses to move	2 (13%)	1 (5%)
POD one		
No discomfort	3 (20%)	10 (59%)*
Moderate discomfort	8 (53%)	7 (41%)
Severe discomfort/refuses to move	3 (20%)	0
POD two		
No discomfort	3 (20%)	9 (45%)
Moderate discomfort	6 (40%)	8 (40%)
Severe discomfort/refuses to move	1 (7%)	1 (5%)
POD three		
No discomfort	2 (13%)	8 (40%)
Moderate discomfort	4 (26%)	8 (40%)
Severe discomfort/refuses to move	0	2 (10%)

POD = postoperative day; *$P \leq 0.05$ compared to placebo group.

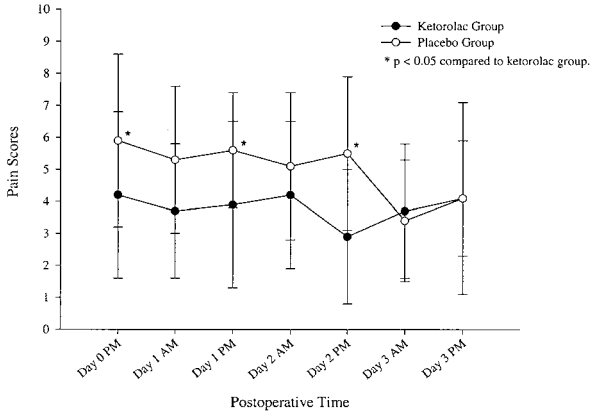

FIGURE Postoperative pain scores.

(Group I = 3.5 mL·kg^{-1}·day^{-1}, Group II = 2.9 mL·kg^{-1}·day^{-1}). In the placebo group 3/15 (20%) received a blood transfusion postoperatively compared to 4/20 (20%) in the ketorolac group.

We found no differences between groups in the incidence of side effects of opioid analgesics administered postoperatively, which included nausea, vomiting, pruritus and respiratory depression. The incidence of postoperative nausea and vomiting on POD one through three in Group I was 27%, 21% and 31% respectively, compared with 40%, 37% and 37% in Group II. Very few patients complained of pruritus in either group and there were no reports of respiratory depression.

The time to first void was similar between groups, however the mean number of hours until clear liquids were tolerated, though not statistically significant, tended to be shorter in the ketorolac group (17 *vs* 29 hr, $P = 0.08$). The length of hospital stay was similar for both groups (6.2 days in the placebo group *vs* 6.0 days in the ketorolac group).

Fourteen patients were followed for at least two years. The two groups had similar thoracic and lumbar curve magnitude preoperatively and curve progression postoperatively. Of the eight patients in the ketorolac group, five had stable curves, and three patients had at least 10° of curve progression. Five of the six patients in the placebo group had stable curves with one having curve progression. There was no difference in the incidence of curve progression between the two groups (Fischer's exact test, $P = 0.58$). Clinic notes at final follow-up in the ketorolac group documented that six patients had no back pain, and two had occasional back pain. In the placebo group, two patients had moderate to severe back pain, two occasional back pain, and two had no back pain. There was no difference between the two groups in terms of the incidence of occasional or moderate back pain ($P = 0.15$). There was one hardware failure in the ketorolac group which required further surgery, and one hardware failure in the placebo group, which did not require re-operation. Regarding hardware failure, there was no difference between the two groups ($P > 0.99$).

Discussion

This study examined the effects of low dose ketorolac in adolescents undergoing posterior spinal fusion for correction of idiopathic scoliosis. Ketorolac, used in a wide range of doses, has been shown to be an effective analgesic for adult and pediatric surgery. It is thought that ketorolac has a ceiling analgesic effect and that adverse effects associated with its use may be dose-dependent.[8] A recent study demonstrated that a dose as low as 7.5 mg (approximately 0.1 mg·kg^{-1}) every six hours decreased morphine consumption and somnolence while enhancing analgesia in adults undergoing decompressive lumbar laminectomy.[8] A dose of 0.5 mg·kg^{-1} (maximum of 15 mg) was used in this study, however as the mean weight in our sample was 57 kg the average dose was approximately 0.2 mg·kg^{-1}. We hypothesized that this lower dose would reduce the unwanted side effects of NSAIDs while providing effective supplemental analgesia.

The analgesic action of ketorolac is primarily achieved at the peripheral nociceptor site through its

inhibition of cyclooxygenase and therefore prostaglandin synthesis, resulting in diminished transmission of noxious stimuli along sensory afferent fibres.[9] Ketorolac can therefore provide analgesia of longer duration than morphine without causing the pruritus, nausea, vomiting, constipation, sedation or respiratory depression commonly associated with opioids. When used in conjunction with morphine PCA, ketorolac has been shown not only to be morphine sparing, but also to reduce the incidence of the unwanted side effects mentioned above.[10] In our study, we were able to show that morphine usage in the immediate postoperative period was reduced in the ketorolac group, and that more effective analgesia, as evidenced by lower pain scores for the first two postoperative days was obtained. The concurrent use of acetaminophen and diazepam has the potential to decrease opioid use in this setting. We postulate that the difference in pain scores seen on POD two after ketorolac had been discontinued was attributable to early pain control that facilitated early mobilization. We did not, however, demonstrate a reduction in nausea, vomiting or pruritus. Burns *et al.* had similar findings in adult patients having upper abdominal surgery.[11] Despite reduced morphine requirements in the ketorolac group, they found no reduction in postoperative nausea and vomiting. Sutters *et al.*[12] found that when using higher doses of ketorolac in children undergoing orthopedic procedures, the ketorolac group used fewer PCA doses but had the same opioid side effects as the control group. Eberson *et al.* using a higher dose of ketorolac in children undergoing long bone and foot osteotomies found that the dosage of morphine in the ketorolac group was decreased, there were less gastrointestinal side effects and a shorter length of hospitalization.[13] The use of ketorolac as an adjuvant to opioid therapy may have a role in the pain management of children who are at risk for pulmonary or gastrointestinal complications. Improved comfort, ease of positioning and turning and an early return to a regular diet are all positive outcomes for children undergoing major spinal surgery.

The use of NSAIDs following major orthopedic surgery remains controversial for two main reasons. Firstly, ketorolac inhibits collagen-induced platelet aggregation and may prolong bleeding time with the potential to increase postoperative bleeding.[5] Rusy *et al.* studied the effect of ketorolac 1 $mg \cdot kg^{-1}$ for pediatric tonsillectomy and showed that bleeding times were significantly increased and hemostasis was more difficult to obtain.[14] Conversely, Thwaites *et al.* showed that despite near complete abolition of thromboxane B_2 production, platelet function remained normal following a single *iv* dose of ketorolac in patients undergoing knee arthroscopy.[15] Unlike aspirin, the effect of ketorolac on platelet function is transient and platelet aggregation returns to normal 24–48 hr after discontinuing the drug. We did not see any clinical evidence of increased bleeding postoperatively as measured by surgical drain loss and postoperative transfusion requirements. This finding concurs with multiple other clinical trials that have failed to demonstrate a clinically significant increase in bleeding associated with the use of ketorolac.

Secondly, NSAIDs have been shown to inhibit fracture healing and decrease heterotopic ossification.[16] In addition, NSAIDs have been shown to decrease spinal fusion in an animal model.[6] Recently, a retrospective analysis of 167 adult patients who underwent instrumented posterior spinal fusion and who had received ketorolac in the perioperative period demonstrated a fivefold greater likelihood of non-union compared to patients who received no NSAIDs (4/121 *vs* 29/167).[7] We administered ketorolac in a pediatric population and evaluated spinal fusion at the two-year follow-up. In a small subset of patients (n = 14), we found no difference in our ketorolac and placebo groups with respect to curve progression, back pain, or hardware failure.

In conclusion, this study showed that low-dose ketorolac provided safe and effective supplemental analgesia following PSF in adolescents. Although the small number of patients studied does not allow definitive conclusions, the use of ketorolac was not associated with increased postoperative blood loss or pseudoarthrosis at the two-year follow-up.

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