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Comparison of Ketorolac and Morphine as Adjuvants during Pediatric Surgery

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The intraoperative use of opioid analgesics decreases the volatile anesthetic requirement and provides for pain relief in the early postoperative period. In a randomized double-blind, placebo-controlled study involving 95 ASA physical status 1 or 2 children (ages 5–15 yr) undergoing general anesthesia for elective operations, we compared postoperative analgesia following the intraoperative intravenous (iv) administration of ketorolac, a nonsteroidal antiinflammatory drug or morphine, an opioid analgesic. After induction of general anesthesia and before the start of the surgical procedure, children received equal volumes of saline, morphine (0.1 mg · kg^{-1}, iv) or ketorolac (0.9 mg · kg^{-1}, iv). Postoperative pain was evaluated by the child using a 10-cm linear visual analog scale (VAS) and by a blinded observer using both a VAS and an objective pain scale (OPS) in the postanesthesia care unit (PACU). There were no statistically significant differences in the VAS and OPS scores in the PACU or in the postoperative analgesic requirements in children receiving morphine or ketorolac. The placebo group had a significantly higher VAS and OPS score and required earlier and more frequent analgesic therapy in the PACU compared to the two analgesic groups. Patients receiving ketorolac had less postoperative emesis than those receiving morphine. We conclude that ketorolac (0.9 mg · kg^{-1}) is an effective alternative to morphine (0.1 mg · kg^{-1}) as an iv adjuvant during general anesthesia, and in the dose used in this study, is associated with less postoperative nausea and vomiting in children. (Key words: Analgesics: antiinflammatory drugs; ketorolac; nonsteroidal; opioids. Anesthesia: pediatrics. Pain: postoperative.)

THE INTRAOPERATIVE USE of opioids decreases the volatile anesthetic requirement and provides for early postoperative pain relief, which is often inadequate in children.[1–3] However, opioid analgesics can produce postoperative respiratory depression and vomiting.[4,5] Nonsteroidal antiinflammatory drugs (NSAID) have been used for both prophylaxis and therapy of postoperative pain, but most compounds in this drug group have a "ceiling" effect with respect to analgesia and are inadequate for control of moderate-to-severe pain occurring in the early postoperative period.[5–11]

Ketorolac tromethamine (Toradol®) is a NSAID that has been reported to provide greater and longer-lasting pain relief than morphine.[12–15] It is also reported to be free of any respiratory depressant effect.[16,17] However, few data are available regarding the efficacy of parenteral ketorolac in children.[18] This randomized, double-blind, placebo-controlled study was designed to compare the perioperative analgesic effect of intravenously (iv) administered ketorolac and morphine in children undergoing elective operations.

Materials and Methods

We studied 95 healthy ASA physical status 1 or 2 children, ages 5–15 yr, undergoing surgical procedures known to be associated with moderate-to-severe postoperative pain (*e.g.*, tonsillectomy or orthopedic and plastic surgical procedures). The study was approved by the Washington University Human Studies Committee, and written informed consent was obtained from the parents of each child. We excluded patients less than 5 yr of age, children with known bleeding or platelet disorders, renal, cardiac or hepatic disease, those undergoing emergency surgery, and children who were scheduled to be discharged from the hospital on the day of surgery. During the preoperative visit we explained the visual analog scale (VAS) that would be used to assess pain and tested the child's understanding by asking them to mark points on a 10-cm line indicating the intensity of pain following a mosquito bite, a fall from a bicycle, and a needle injection.[19]

No patient received preanesthetic medication. Anesthesia was induced with halothane and nitrous oxide *via* a face mask or iv with propofol 2 mg · kg^{-1}, according to the preference of the patient. In the patients who underwent an inhalational induction, halothane was discontinued immediately after the establishment of intravascular access, and a bolus of propofol, 2 mg · kg^{-1} iv, was administered over 30–60 s. The time from the start of induction until the end-tidal halothane concentration decreased to less than 0.15% after discontinuation of the agent was recorded.

All patients underwent tracheal intubation facilitated with atracurium 0.5 mg · kg^{-1} iv. Anesthesia was initially maintained with nitrous oxide 66% in oxygen and an iv infusion of propofol 150 μg · kg^{-1} · min^{-1}, varied as necessary to prevent signs of light anesthesia (*e.g.*, tachycardia, hypertension, or lacrimation). Neuromuscular blockade

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was maintained with additional atracurium, 0.1 mg · kg^{-1}, as needed.

Patients were randomly assigned to one of three treatment groups. Prior to surgical incision, all patients received equal volumes of study medication. One group received saline (iv); a second group received morphine 0.1 mg · kg^{-1} iv; and a third received ketorolac 0.9 mg · kg^{-1} iv. The dose of ketorolac was based on the larger volume of distribution in children compared to adults.[18] At the end of the surgical procedure, neuromuscular blockade was antagonized with edrophonium and atropine; nitrous oxide and propofol were discontinued; and the trachea extubated after awakening. The total dose of propofol used and the duration of surgery and anesthesia were recorded along with the time from the end of surgery to tracheal extubation, spontaneous eye opening, and response to commands (which was evaluated by asking the child to "squeeze my hand" at 30–60-s intervals after eye-opening).

In the postanesthesia care unit (PACU), pain was assessed by both the patient and an observer who was unaware of group assignments. Pain was assessed at 10–15-min intervals using a linear VAS.[19,20] In addition, the observer evaluated pain using an objective pain scale (OPS) as described by Hannallah *et al.*[21] and Broadman *et al.*[22] If the patient VAS was greater than 60 mm or the OPS pain score was greater than 6 on two consecutive assessments at 5-min intervals, the patient received morphine 0.05 mg · kg^{-1} iv, which was repeated as needed until the patient was comfortable. The patients, parents, and nurses remained unaware of the study group assignments. Following discharge from the PACU, patients assessed their own pain, and received oral acetaminophen 10–15 mg · kg^{-1} for mild pain and morphine 0.05 mg · kg^{-1} iv for moderate-to-severe pain. These medications were repeated at 4-h intervals as needed. The number of analgesic doses administered within 6 and 24 h after discharge from the PACU was compared in the three groups.

Statistical Analysis

The age, weight, duration of anesthesia and surgery, mean propofol infusion rate, the time from the start of induction until the end-tidal halothane concentration was < 0.15%, the time from end of surgery to tracheal extubation, eye-opening, and response to commands, and the VAS pain scores were compared between the three groups by a one-way analysis of variance. If the null hypothesis was rejected, intergroup differences were examined by the Student-Newman-Keuls test and by Scheffé's test. The ASA physical status, types of surgical procedures, and anesthetic induction techniques were compared between the three groups by a chi-square test. The OPS scores and the number of doses of analgesic medication administered in the first 6- and 24-h postoperative period were compared by a nonparametric analysis of variance (Kruskal-Wallis). Intergroup comparisons were made by a Mann-Whitney U-test with corrections for multiple comparisons. In the statistical analysis of pain scores, no correction was made for "rescue" therapy, and patients receiving postoperative analgesic therapy were not assigned the last pain score prior to therapy for the remaining points in the analysis.

In each group, the number of patients who required a rescue by morphine within an arbitrarily chosen interval of 12 min of arrival in the PACU, the number requiring more than one rescue dose of morphine in the PACU, and the number of patients who vomited in the immediate 24-h postoperative period were compared by Fisher's exact test and by a chi-square test with a Yates correction. A P value of < 0.05 was considered statistically significant.

Results

The three groups were similar with respect to age, weight, ASA physical status, anesthetic technique, type of operation, and duration of surgery and anesthesia (table 1). The surgical procedures included otorhinolaryngologic procedures such as tonsil/adenoidectomy, orthopedic procedures (*e.g.*, bone biopsies and grafts, open reduction with internal fixation of a fracture, or osteotomies) and plastic reconstructive procedures (*e.g.*, revision of cleft lip and nose repair with rib or ear cartilage grafts, or external ear reconstruction). There were no statistically significant differences between the three groups in the times from the start of induction until the end-tidal halothane concentration was < 0.15%. There were also no differences between the three groups in the end-tidal nitrous oxide concentration, the mean infusion rate of pro-

TABLE 1. Demographic Data, Types of Surgical Procedures, Anesthetic Induction Techniques, and Duration of Surgery and Anesthesia

	Placebo	Morphine	Ketorolac
Number (n)	32	31	32
Age (yr)	10.0 ± 3.6	8.5 ± 3.7	8.3 ± 3.8
Weight (kg)	45.2 ± 23.8	36.2 ± 22.0	35.5 ± 18.9
Height (cm)	140 ± 22	129 ± 27	133 ± 24
ASA physical status (1/2)	23/9	28/3	24/8
Surgical procedure			
Tonsil/ adenoidectomy	20	21	22
Orthopedic	11	8	7
Plastic reconstructive	1	2	3
Induction technique			
Halothane + N_2O	23	24	25
Propofol	9	7	7
Surgical time (min)	53 ± 38	48 ± 37	45 ± 32
Anesthesia time (min)	87 ± 50	87 ± 56	77 ± 42

Values for weight, height, and surgical and anesthesia times are mean ± SD.

TABLE 2. Comparison of Intraoperative Anesthetic Techniques and Data on Emergence Times

	Placebo	Morphine	Ketorolac
Time from induction to end-tidal halothane concentration <0.15% (min)	13 ± 10	17 ± 13	14 ± 9
End-tidal N_2O concentration (%)	67 ± 2	67 ± 2	66 ± 3
Mean infusion rate of propofol ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	198 ± 67	206 ± 41	213 ± 53
Time to extubation (min)	11.3 ± 6.0	12.4 ± 9.5	9.5 ± 6.1
Time to eye-opening (min)	13.4 ± 6.9	14.1 ± 8.8	13.1 ± 9.1
Time to obeying commands (min)	16.7 ± 6.8	19.1 ± 12.4	16.5 ± 10.7
Time in PACU (min)	46.0 ± 14.2	39.7 ± 19.4	35.8 ± 10.7*

All times are in minutes from the end of surgery unless otherwise stated. Values are mean ± SD.

PACU = postanesthesia care unit.
* $P < 0.05$ compared to placebo group.

pofol, or the times from the end of surgery to tracheal extubation, eye-opening, and response to verbal commands (table 2). Patients receiving ketorolac were discharged from the PACU sooner than patients who received saline.

There was no correlation between the duration of surgery and the VAS or OPS pain scores in any of the three groups. There were no significant differences in the VAS and OPS scores in the groups receiving ketorolac and morphine. VAS and OPS scores were significantly higher in the placebo group compared to the other two groups at 10 min after arrival in the PACU (table 3). Pain scores were not corrected for postoperative analgesic therapy, and by 30 min, the VAS and OPS scores in the three groups did not differ because all patients in moderate-to-severe pain had received morphine "rescue" therapy (tables 3 and 4).

The number of patients who required a "rescue" dose of morphine within 12 min after arriving in the PACU and the number of children who required more than one "rescue" dose of morphine in the PACU were significantly greater in the placebo group compared to the other two groups, but not between the groups receiving morphine or ketorolac (table 4). The median number of analgesic treatments provided within 6 and 24 h after discharge from the PACU did not differ between the groups receiving morphine and ketorolac but were significantly lower in both groups compared to the placebo group.

TABLE 3. Postoperative Pain Evaluation Following Arrival in the PACU

	Placebo	Morphine	Ketorolac
VAS by patient			
0–5 min (mm)	62 ± 34	49 ± 35	49 ± 31
10 min (mm)	76 ± 20	45 ± 31*	46 ± 31*
30 min (mm)	49 ± 32	38 ± 32	31 ± 20
Median OPS (range)			
0–5 min	4 (0–9)	2 (0–9)	1 (0–9)
10 min	4 (0–8)	3 (0–9)*	2 (0–8)*
30 min	2 (0–7)	2 (0–5)	2 (0–9)

Mean visual analog scale (VAS) by the patient (±SD). Median objective pain scale (OPS) with range in parentheses.
* $P < 0.05$ compared to the placebo group.

However, in all three groups, patients undergoing orthopedic procedures required morphine "rescue" therapy more frequently than those undergoing tonsillectomy–adenoidectomy. Finally, the incidence of emesis in the first 24 h after surgery was significantly less in the ketorolac group compared to the morphine group (table 4).

Discussion

This study demonstrated that an intraoperative dose of ketorolac 0.9 $mg \cdot kg^{-1}$ iv, provided postoperative analgesia similar to that achieved with morphine 0.1 $mg \cdot kg^{-1}$ iv. The lack of a significant difference between the three treatment groups with respect to pain scores on arrival in the PACU may be explained by the effects of residual concentrations of anesthetic agents used intraoperatively. Despite the intraoperative administration of either morphine or ketorolac, patients in both groups required supplemental opioids in the postoperative period. However, patients who received a placebo required morphine earlier and more frequently in the PACU than those who received intraoperative ketorolac or morphine.

TABLE 4. Comparison of Analgesic Therapy and Emesis in the Postoperative Period

	Placebo	Morphine	Ketorolac
Patients requiring first morphine "rescue" treatment within 12 min of arrival in PACU (%)	66%	34%*	34%*
Patient requiring more than 1 morphine "rescue" treatment in the PACU (%)	60%	29%*	25%*
Median number of analgesic treatments during the first 6 h after discharge from PACU (range)	2 (0–6)	1* (0–2)	1* (0–3)
Median number of analgesic treatments during the first 24 h after discharge from the PACU (range)	4 (1–9)	2* (0–7)	2* (0–4)
Emesis during the first 24 h after surgery (%)	37%	59%	25%†

PACU = postanesthesia care unit.
* $P < 0.05$ compared to the placebo group.
† $P < 0.05$ compared to the morphine group.

These data suggest that intraoperative ketorolac, like morphine, decreases the postoperative analgesic requirements in children.

The dose of ketorolac that was administered to these children was based on 1) the available pharmacokinetic data, which suggests a greater volume of distribution and clearance per unit body weight of ketorolac in children compared to adults,[18] and 2) an earlier clinical study suggesting that 0.5 $mg \cdot kg^{-1}$ ketorolac was less effective as an analgesic in the 1st h postoperatively compared to morphine 0.1 $mg \cdot kg^{-1}$ in children.[18] It is possible that ketorolac, like other NSAIDs, has a "ceiling" analgesic effect, and although it may decrease the requirements for supplemental opioids, it does not completely eliminate the need for opioid analgesic supplementation.[12-15,23] The lack of data on the dose–response relationship for intraoperative ketorolac is a limitation of this preliminary study. It is possible that ketorolac in doses between 0.5 $mg \cdot kg^{-1}$ and 0.9 $mg \cdot kg^{-1}$ may produce a similar degree of pain relief to that which was reported in our study. Further studies on the dose-response relationship of ketorolac in children are required.

While all NSAID compounds inhibit platelet aggregation by a reversible block of prostaglandin synthetase, increased surgical blood loss has been reported only with the use of indomethacin and not with diclofenac or ketorolac.[12,15,24-26] Although ketorolac has been associated with prolongation of bleeding time in adults, increased perioperative bleeding has not been demonstrated.[12,15] In our study, only 1 of 63 patients undergoing tonsillectomy–adenoidectomy procedures had to return to the operating room for the treatment of excessive bleeding. This patient was assigned to the placebo group, and reoperation was performed on the fifth postoperative day. Although ketorolac may not be associated with excessive bleeding in patients with normal coagulation, patients with subclinical hemostatic defects may be "at risk" of increased perioperative blood loss if ketorolac is used as an adjuvant during surgery.

The lower incidence of emesis in the group receiving iv ketorolac compared to the morphine group cannot be attributed to variations in the anesthetic technique. Although different techniques were used to induce anesthesia, the number of patients who underwent induction *via* face mask or iv injection did not differ between the treatment groups. Although propofol is associated with decreased postoperative emesis, any effect on emesis would have been the same in all three groups as the propofol maintenance infusion rates were similar.[27] Furthermore, all patients received nitrous oxide 66% in oxygen. Additional studies are necessary to determine the incidence of emesis and satisfactory analgesia when ketorolac is administered during maintenance anesthesia with halothane and nitrous oxide.

A major advantage of ketorolac (and other NSAIDs) over opioid analgesics is its lack of respiratory depression.[15-17] Opioids act on specific receptors in the central nervous system to attenuate nociception.[23] Ketorolac inhibits prostaglandin synthesis to minimize the activation and sensitization of peripheral nociceptors by bradykinin and other mediators, thus reducing pain and inflammatory responses to surgery.[5,12,15] Because ketorolac and opioids act at different sites, a combination of these agents may provide additive, if not synergistic pain relief.[23] If satisfactory analgesia is obtained with lower doses of each drug when used in combination, the incidence of side effects may be decreased.[23]

In summary, this study demonstrated that an intraoperative dose of ketorolac, 0.9 $mg \cdot kg^{-1}$ iv, provided postoperative analgesia similar to that associated with morphine 0.1 $mg \cdot kg^{-1}$ iv, but was associated with significantly less emesis. Thus, ketorolac is a useful alternative to morphine for providing prophylactic analgesia in children undergoing elective operations.

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References

1. Hoffman JC, DiFazio CA: The anesthesia sparing effect of pentazocine, meperidine and morphine. Arch Int Pharmacodyn Ther 186:261–268, 1970
2. Mather L, Mackie J: The incidence of postoperative pain in children. Pain 15:271–282, 1983
3. Shannon M, Berde CB: Pharmacologic management of pain in children and adolescents. Pediatr Clin N Am 36:855–871, 1989
4. Maunuksela E-L, Korpela R, Olkkola KT: Double-blind multiple dose comparison of buprenorphine and morphine in postoperative pain of children. Br J Anaesth 60:48–53, 1988
5. Reasbeck PG, Rice ML, Reasbeck JC: Double blind controlled trial of indomethacin as an adjunct to narcotic analgesia after major abdominal surgery. Lancet 2:115–118, 1982
6. Maunuksela E-L, Olkkola KT, Korpela R: Does prophylactic intravenous infusion of indomethacin improve the management of postoperative pain in children? Can J Anaesth 35:123–127, 1988
7. Moore MA, Wandless JG, Fell D: Pediatric postoperative analgesia: A comparison of rectal diclofenac with caudal bupivacaine after inguinal herniotomy. Anaesthesia 45:156–158, 1990
8. Owen H, Glavin JR, Shaw NA: Ibuprofen in the management of postoperative pain. Br J Anaesth 58:1371–1375, 1986
9. Dommerby H, Rasmussen OR: Diclofenac (Voltaren®): pain relieving effect after tonsillectomy. Acta Otolaryngol (Stockh) 98: 185–192, 1984
10. Hodsman NBA, Burns JW, Blyth A, Kenny GNC, McArdle CS, Rotman H: The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia 42:1005–1008, 1987
11. Moffat AC, Kenny GNC, Prentice JW: Postoperative nefopam and diclofenac: Evaluation of their morphine-sparing effect after upper abdominal surgery. Anaesthesia 45:302–305, 1990
12. Buckley MMT, Brogden RN: Ketorolac: A review of its phar-

macodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 39:86–109, 1990

13. Yee JP, Koshiver JE, Albon C, Brown CR: Comparison of intramuscular ketorolac tromethamine and morphine sulphate for analgesia of pain after major surgery. Pharmacotherapy 6:253–261, 1986
14. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D: Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 41:556–561, 1987
15. Kenny GNC: Editorial: Ketorolac trometamol: A new non-opioid analgesic. Br J Anaesth 65:445–447, 1990
16. Murray AW, Brockway MS, Kenny GNC: Comparison of the cardiorespiratory effects of ketorolac and alfentanil during propofol anaesthesia. Br J Anaesth 63:601–603, 1989
17. Brandon Bravo LJC, Mattie H, Spierdijk J, Bovill J, Burm AG: The effects on ventilation of ketorolac in comparison with morphine. Eur J Clin Pharmacol 35:491–494, 1988
18. Maunuksela E-L, Olkkola KT, Kokki H: Pharmacokinetics of intravenous ketorolac and its efficacy in relieving postoperative pain in children (abstract) J Pain Symptom Manage 6: 143, 1991
19. Berde CB, Lehn BM, Yee JD, Sethna NF, Russo D: Patient-controlled analgesia in children and adolescents: A randomized prospective comparison with intramuscular administration of morphine for postoperative analgesia. J Pediatr 118:460–466, 1991
20. McGrath PA: An assessment of children's pain: A review of behavioral, physiological and direct scaling techniques. Pain 31: 147–176, 1987
21. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS: Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for the control of post-orchiopexy pain in pediatric ambulatory surgery. ANESTHESIOLOGY 66:832–835, 1987
22. Broadman L, Rice LJ, Hannallah R: Evaluation of an objective pain scale for infants and children. Reg Anesth 13:45, 1988
23. Dahl JB, Kehlet H: Non-steroidal anti-inflammatory drugs: Rationale for use in severe postoperative pain. Br J Anaesth 66:703–712, 1991
24. Bricker SRW, Savage ME, Hanning CD: Perioperative blood loss and non-steroidal anti-inflammatory drugs: An investigation using diclofenac in patients undergoing transurethral resection of the prostate. Eur J Anaesthesiol 4:429–434, 1987
25. Engel C, Lund B, Kristensen SS, Axel C, Nielsen JB: Indomethacin as an analgesic after hysterectomy. Acta Anaesthesiol Scand 33: 498–501, 1989
26. Rorarius MGF, Baer GA, Metsa-Ketela J, Miralles J, Palomaki E, Vapaatalo H: Effects of perioperatively administered diclofenac and indomethacin on blood loss, bleeding time and plasma prostanoids in man. Eur J Anaesthesiol 6:335–342, 1989
27. Doze VA, Shafer A, White PF: Propofol-nitrous oxide *versus* thiopental-isoflurane-nitrous oxide for general anesthesia. ANESTHESIOLOGY 69:63–71, 1988