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A Randomized, Double-blind Evaluation of Ketorolac Tromethamine for Postoperative Analgesia in Ambulatory Surgery Patients

Hak Y. Wong, M.B.B.S., Randall L. Carpenter, M.D.,† Dan J. Kopacz, M.D.,† Robert J. Fragen, M.D.,‡ Gale Thompson, M.D.,§ Thomas J. Maneatis, M.D.,‖ Lincoln J. Bynum, M.D.‖*

Background: **Given he trend toward early discharge of patients after surgery and the inherent adverse effects of opioid analgesics, we compared a new nonsteroidal antiinflammatory drug, ketorolac tromethamine, given intravenously (iv) and then orally, with two commonly prescribed opioid analgesics in ambulatory patients for up to 1 week after surgery.**

Methods: **In this study incorporating a double-blind, multidose design, 221 patients who had moderate or severe pain after surgery were randomized to one of three treatment groups: group K30 received 30 mg iv ketorolac twice, then 10 mg iv every 30 min as required to control pain, up to six doses, followed by 10 mg oral ketorolac every 4–6 h; group F50 received 50 μg iv fentanyl at the same time intervals as in group K30, followed by 60 mg codeine plus 600 mg acetaminophen (C + A) orally every 4–6 h; and group F10 received the same combination as did group F50, but only 10 μg fentanyl per dose.**

Results: **Compared with 50 μg fentanyl iv, 30 mg iv ketorolac provided delayed but otherwise equivalent analgesic effects and was associated with similar side effects. Compared with C + A, 10 mg oral ketorolac was associated with a lower incidence of nausea and somnolence and earlier return of bowel function but not better pain relief, drug tolerability, quality of life, or psychologic well-being.**

Conclusions: **Ketorolac, when used in an iv and then oral sequence, is a safe and effective analgesic in the ambulatory surgery setting. It has a slower onset than fentanyl, but causes fewer side effects than C + A. (Key words: Analgesia: postoperative. Analgesics, nonsteroidal antiinflammatory drug: acetaminophen; ketorolac. Analgesics, opioid: codeine; fentanyl. Surgery: ambulatory.)**

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* Clinical Associate in Anesthesia, Department of Anesthesia, Northwestern University Medical School and Northwestern Memorial Hospital.

† Staff Anesthesiologist, Department of Anesthesiology, Virginia Mason Clinic.

‡ Professor of Clinical Anesthesia, Department of Anesthesia, Northwestern University, Medical School and Northwestern Memorial Hospital.

§ Chief of Anesthesiology, Department of Anesthesiology, Virginia Mason Clinic.

‖ Syntex Laboratories, Inc.

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Address reprint requests to Dr. Wong: Department of Anesthesia, Northwestern University Medical School, 303 East Superior, Room 360, Chicago, Illinois 60611.

INCREASING numbers of surgical operations are now performed on an ambulatory basis, with the patient discharged from the surgical facility within a few hours after the procedure. Provision of effective and safe analgesia is one of the many new challenges precipitated by this shift in health care practice. Despite many well known side effects, the opioids remain the mainstay of postoperative analgesia because of their efficacy and ability to be administered parenterally. Ketorolac tromethamine is a new nonsteroidal antiinflammatory drug that is available in both parenteral and oral forms. It has negligible effects on ventilatory control,[1] hemodynamics,[2,3] and psychomotor control,[4] making it an attractive alternative to the opioids for the ambulatory surgical patient. Previous authors reported the use of ketorolac in either parenteral[5-11] or oral[12,13] form for postoperative pain. The objective of the current study was to evaluate the analgesic efficacy and adverse effects of ketorolac as the sole postoperative analgesic (both intravenous and oral) for patients in an ambulatory surgical setting. Intravenous (iv) fentanyl and oral codeine plus acetaminophen were used as comparative analgesics.

Table 1. Dose Schedule of Analgesic Drugs for Three Treatment Groups

Group	Intravenous Phase		Oral Phase (days 1–7)
	Dose 1 and 2*	Dose 3–8	
K30	Ketorolac 30 mg every 15 min	Ketorolac 10 mg every 30 min	Ketorolac 10 mg every 4–6 h
F50	Fentanyl 50 μg every 15 min	Fentanyl 50 μg every 30 min	Codeine 60 mg + acetaminophen 600 mg every 4–6 h
F10	Fentanyl 10 μg every 15 min	Fentanyl 10 μg every 30 min	Codeine 60 mg + acetaminophen 600 mg every 4–6 h

* All doses after dose 1 were given as needed for pain.

Methods

The study was a multicenter, double-blind, randomized, parallel, multidose study conducted concurrently at two clinical sites. The study protocol was approved by the institutional review boards of both institutions. The subjects were recruited from patients scheduled to undergo surgery under general anesthesia who would be discharged from the hospital the same day. All subjects gave written informed consent to participate in the study. Exclusion criteria included: 1) known allergy or contraindication to any opioid analgesic or nonsteroidal antiinflammatory drug, 2) known alcohol or drug abuse, 3) preexisting analgesic or psychotropic drug therapy, including sedatives and anxiolytic drugs, 4) known bleeding diathesis or active peptic ulcer, and 5) inability or unwillingness to complete recordings and complete a questionnaire at home and return for follow-up evaluation.

Of all the patients recruited before surgery, only those who rated their pain as moderate or severe on emergence from anesthesia were entered into one of the three treatment groups (table 1). Randomization was carried out at a central site by computer generation using a block size of nine (three subjects per treatment group), and the two clinical sites used separate randomization schedules. To maintain the blinding of both subjects and investigators, and because injectable ketorolac is amber in color, the iv medication was drawn up in amber syringes by the hospital pharmacist at each site. The oral medications, in capsule form, were prepared and packaged in identical blister cards by the manufacturer of ketorolac (Syntex Laboratories). Sample size calculation was based on the analgesic effect (measured as TOTPAR#) obtained in a pilot study and the assumption that difference between treatment was clinically significant when the effect size¶ was at least 0.5. Power analysis showed that a sample size of 70 per treatment group should provide 80% power (assuming two-tail tests at $\alpha = 0.05$ level) to detect differences between treatment groups of an effect size of 0.50.

All patients recruited for the study were taught the use of the categorical pain rating scale and the pain relief scale (table 2) and were informed about the medication dosing schedule. They received no preanesthetic sedation or prophylactic antiemetics. All were given general anesthesia consisting of thiopental induction, maintenance with nitrous oxide and a volatile anesthetic, and appropriate muscle relaxants. Fentanyl, up to 200 μg, was used at the discretion of the anesthesia team during induction of anesthesia but not afterward during the course of the anesthetic. To ensure that patients would be able to follow the postdischarge protocol, benzodiazepines were specifically excluded from the anesthetic regimen.

Protocol: IV Phase

The study began in the recovery room when the patient complained of pain and rated baseline pain intensity as moderate or worse. The assigned medication was given by a blinded nurse evaluator, who then recorded the patient's rating of pain and pain relief at 15 and 30 min and 1, 2, 3, and 4 h thereafter. The level of observed drowsiness and other untoward effects such as nausea and vomiting were recorded at the same times. Additional doses of the study medication could be administered iv per protocol (table 1), if requested by the patient, until the patient was ready to resume oral intake. At the end of the 4-h period from the first iv dose, or when the patient was ready to resume oral intake, whichever was earlier, both the patient and the nurse evaluator were asked to make a subjective, overall assessment of the pain relief achieved, and overall rating and tolerability of the drug (table 2) during this period, defined and referred to as the "IV phase."

See table 3 and section on Data Transformation.

¶ Effect size is defined as measured difference between group means divided by standard deviation of values.

Table 2. Categorical Rating Scales Used in the Study

Pain Intensity	Pain Relief	Overall Rating and Drug Tolerability	Level of Drowsiness
None = 0	None = 0	Poor = 0	1 = Asleep, and does not respond to any stimuli
Mild = 1	A little = 1	Fair = 1	2 = Asleep, but responds to tactile stimulus
Moderate = 2	Some = 2	Good = 2	3 = Asleep, but responds easily to verbal stimulus
Severe = 3	A lot = 3	Very good = 3	4 = Awake, but drowsy
Very severe = 4	Complete = 4	Excellent = 4	5 = Completely awake

Answers to quality of life assessment questions a–f were rated as follows: None = 0; A little = 1; Some = 2; A lot = 3; Severe = 4. Questions were as follows: (a) Problems with work? (b) Problems looking after the home? (c) Problems with ability to care for yourself? (d) Problems with social life? (e) Problems with home life? (f) Problems with interests and hobbies?

The time taken for the patient to reach several "recovery milestones" in the hospital was noted. These recovery milestones included: discharge from postanesthesia recovery room, return of audible bowel sounds, ability to tolerate oral liquid, ambulation with assistance, ambulation without assistance, spontaneous micturition, and readiness to leave the hospital. First bowel movement also was recorded as a milestone, but in all patients this occurred after discharge from the hospital.

Protocol: Oral Phase

The oral phase of the study started when the patient resumed and tolerated oral intake (a prerequisite before discharge from the hospital) and ended on the seventh day after surgery, or when the patient had stopped taking analgesic medication for 24 h, whichever came first. The patient received a 7-day supply of oral medication with instruction to take the medication as needed for pain at appropriate intervals. A prescription for a conventional oral analgesic, chosen by the patient's surgeon, also was provided as a backup if the study medication should fail.

Every night the patient rated on a preprinted diary the overall relief of pain throughout the day on a categorical scale (table 2) and the extent to which quality of life was affected (table 2). At the end of the oral phase, the patient also completed a psychologic general well-being index questionnaire.[14]

Protocol: Termination from the Study

During the iv phase, patients could withdraw from the study after the first dose of medication for any reason, and in particular if an alternative (open label) analgesic was administered. These subjects would not proceed to the oral phase.

During the oral phase, patients could withdraw from the study for any reason, including taking the alternative medication because of inadequate pain relief or adverse effects.

Data and Statistical Analysis

Data Transformation: Four analgesic measures were computed from the pain intensity and pain relief data recorded during the 4 h after the first iv dose of medication: PID, SPID, PAR, TOTPAR (table 3).[15] Two drowsiness indices also were computed: DID, SDID (table 3).

When patients left the study because of inadequate analgesia, the worse of the baseline rating or the last determined value for pain intensity, and none for pain relief, were extrapolated for the missing values. When patients left the study because of other reasons, the last determined values were extrapolated for the missing values. For drowsiness indices, the last determined value of drowsiness was extrapolated.

Table 3. Computed Variables for Data Analysis

Analgesic efficacy
- PID = Pain intensity difference, the difference between baseline pain intensity and the intensity recorded at each timepoint
- SPID = Summed PID scores (hourly), which are weighted sums of PID from all preceding time points
- PAR = Pain relief score recorded at each timepoint
- TOTPAR = Summed pain relief score (hourly), defined as weighted sums of PAR from all preceding time points

Observer-rated drowsiness
- DID = Drowsiness intensity difference, the difference between baseline drowsiness level and the drowsiness level recorded at each timepoint
- SDID = Summed DID scores, which are weighted sums of DID at each hour

PGWB index
- Answers for each question in the psychological general well-being questionnaire rated from 0 to 5, with 5 as the best rating
- PGWB index = Summation of rating from all questions (range 0–105)

Table 4. Demographic and Baseline Characteristics of Treatment Groups

	Group K30	Group F50	Group F10
Number	73	76	72
Sex, N (%)			
Male	25 (34)	29 (38)	31 (43)
Female	48 (66)	47 (62)	41 (57)
Race, N (%)			
White	64 (88)	67 (88)	65 (90)
Black	7 (10)	5 (7)	3 (4)
Other	2 (2)	4 (5)	4 (6)
Height* (cm)	171.6 ± 8.8	170.2 ± 9.6	172.2 ± 11.8
Weight* (kg)	73.8 ± 17.4	72.8 ± 16.0	76.3 ± 18.7
Duration of surgery* (h)	0.8 ± 0.4	0.9 ± 0.4	0.8 ± 0.4
Intraoperative fentanyl used* (μg)	125.0 ± 54.0	127.0 ± 76.0	117.0 ± 46.0
Baseline pain, N (%)			
Moderate	48 (66)	46 (60)	51 (71)
Severe	24 (33)	27 (36)	19 (26)
Very severe	1 (1)	3 (4)	2 (3)
Baseline drowsiness N (%)			
Completely awake	11 (15)	11 (14)	15 (21)
Awake but drowsy	42 (57)	36 (48)	37 (51)
Responsive to vocal stimulus	20 (27)	29 (38)	20 (28)
Responsive to tactile stimulus	1 (1)	0	0

* Values are mean ± SD.

For the oral phase, the psychologic general well-being index was calculated (table 3). Sums of subsets of items on the scale were used to measure various subscales: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. A higher score denotes a more positive result. Variables on quality of life were averaged over all days with recorded data.

Statistical Analysis: Statistical analyses were performed using Statistical Analysis Systems for Personal Computer. Interval and ordinal variables were analyzed by analysis of variance and least significant difference test for multiple comparisons. Data were analyzed for the effects of treatment, site, and treatment-by-site. After ascertaining the lack of treatment-by-site effect, variables were pooled across sites. Significant differences were verified by the Cochran-Mantel-Haenszel test, which also was used to analyze categorical variables.

The Kaplan-Meier procedure was used to estimate the cumulative proportions of patients achieving a given event, and the generalized Wilcoxon (Gehan) test was used to compare the three treatment groups for each event. Statistical significance was set at P value $\leq .05$.

Table 5. Distribution of Surgical Procedures

Procedure	Group K30	Group F50	Group F10
Arthroscopy	30 (41%)	29 (38%)	26 (36%)
Laparoscopy	9 (12%)	8 (11%)	5 (7%)
Other orthopedic	7 (10%)	12 (16%)	9 (13%)
Breast biopsy	12 (16%)	15 (20%)	16 (22%)
Other breast procedures	7 (10%)	4 (5%)	4 (6%)
Hernia repair	5 (7%)	6 (8%)	7 (10%)
Other procedures	3 (4%)	2 (3%)	5 (7%)
Total	73 (100%)	76 (100%)	72 (100%)

Results

Table 4 summarizes the basic demographic characteristics, length of surgery, mean dose of fentanyl received intraoperatively, and baseline pain and drowsiness levels of the 221 patients who entered the study, and table 5 tabulates the types of surgical procedures performed. There was no statistically significant difference between the three treatment groups for these variables.

Table 6 summarizes the course of the cohorts in the study, the number and reasons for early termination, and the average number of doses of medication taken. The majority of early termination during the IV phase occurred during the first 40 min.

IV Phase

Patients in group F50 stayed in the IV phase longer than did the other two groups ($P = .017$ during the

Table 6. Course of Patients in Study

	Group K30	Group F50	Group F10
No. of patients in iv phase	73	76	72
Duration of iv phase (h)*	2.1 ± 1.3	2.7 ± 1.3§¶	2.1 ± 1.3
No. of iv doses	2.4 ± 1.0	2.5 ± 1.0	2.2 ± 1.0
No. received >1 dose	57	64	51
Interval between iv doses (min)	23.8 ± 18.3	29.0 ± 16.6**	21.6 ± 10.9
Withdrew during iv phase			
Reasons			
Ineffectiveness	21 (28%)	15 (19%)	23 (31%)
Adverse event†	2	3	3
Administrative problem	0	2	0
No. entering oral phase	50	56	46
No. who took oral drug	49	55	46
Duration of oral phase (h)	81.6 ± 55.7	61.4 ± 52.6	63.1 ± 53.7
No. of doses taken	10.6 ± 8	7.9 ± 8	7.5 ± 8
Withdrew during oral phase	9	7	5
Reason			
Ineffectiveness	5 (10%)	3 (5%)	3 (6%)
Adverse event	3	1	1
Intercurrent illness‡	1	1	0
Administrative problem	0	2	1
No. who completed study	40	48	41

* This period was determined by either patient withdrawal or readiness of patients to resume oral intake.

† Six of seven patients requested termination due to nausea–vomiting; the remaining one patient (in group F10) has postextubation pulmonary edema.

‡ One patient fell on ice, and one had leg cramps requiring admission.

§ P = .0040 *versus* group K30.

¶ P = .0052 *versus* group F10.

** P = .0097 *versus* group F10.

third hour). Also, they were more likely to request second or third doses than were patients in groups F10 and K30. However, the overall withdrawal rates were not statistically different among the three groups.

The analgesic efficacy of the treatments was assessed with SPID and TOTPAR scores each hour for 4 h after the first dose (figs. 1 and 2). During all 4 h, SPID scores were significantly higher in the F50 than in the F10

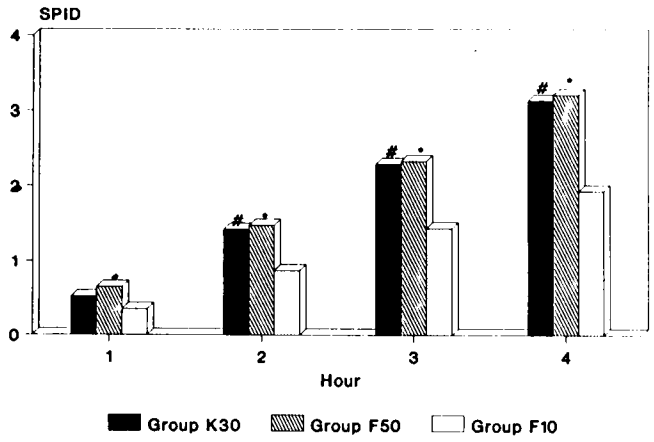

Fig. 1. Summed pain intensity difference (SPID) during the 4 h after first intravenous dose of medication. * = difference between groups F50 and F10, $P \leq .030$; # = difference between groups K30 and F10, $P \leq .05$.

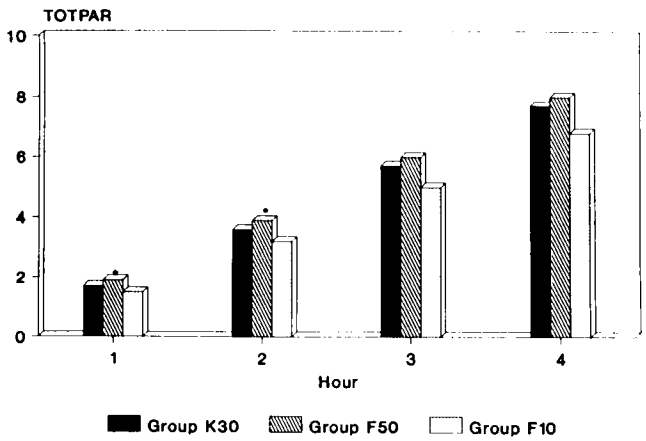

Fig. 2. Summed pain relief score (TOTPAR) during the 4 h after first intravenous dose of medication. * = difference between groups F50 and F10, $P \leq .04$.

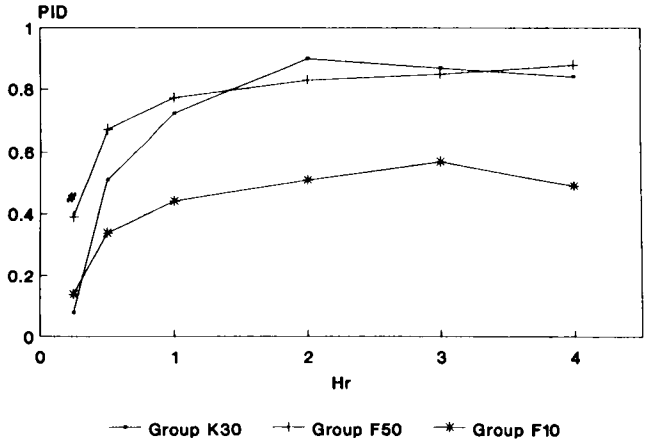

Fig. 3. Pain intensity difference (PID) score during the 4 h after first intravenous dose. # = difference between groups F50 and group K30, $P = .012$. Groups F50 and F10 were significantly different except during hour 3.

group ($P \leq .030$). Likewise, TOTPAR scores were significantly higher in the F50 than in the F10 group, but only during the first 2 h. Group K30 had higher SPIDs but not TOTPAR scores than did group F10 during the second, third, and fourth hours ($P \leq .05$). There was no significant difference between groups K30 and F50 when the hourly SPID and TOTPAR scores were compared. However, comparison of the PID and PAR scores shows that F50 achieved better PIDs and PARs than did K30 during the first 15 min after the first iv dose (fig. 3). This difference disappeared by 30 min.

The peak analgesic effect, as measured by the group average of the highest PID score achieved during the 4 h, was 1.3, 1.1, and 0.9 in groups F50, K30, and F10, respectively, the difference between groups F50 and F10 being significant ($P = .0049$). However, the time to reach peak analgesia was similar for all three groups (55.2–60.7 min).

In all three groups, there was a trend toward increase with time of observer-rated drowsiness, but there was no difference between groups. Table 7 summarizes adverse effects reported by patients that were considered to be probably or possibly related to the study medications. Complaints of somnolence, headache, and dizziness occurred with similar frequencies among the three treatment groups. The incidence and severity of nausea were similar among the three groups.

The patients' overall evaluation of pain relief and the overall rating of study medication during the IV phase favored group F50 over group F10 ($P = .012$) but did not distinguish between groups K30 and F10 or between groups F50 and K30. The observer's overall evaluation of pain relief favored group F50 over both F10 and K30 groups ($P \leq .007$), but the observer's overall evaluation of the study medication favored group F50 over group F10 only ($P = .014$).

The time taken to reach various recovery milestones was not different between groups.

Table 7. Adverse Effects Possibly or Probably Related to Study Medications

	Group K30	Group F50	Group F10
Intravenous phase			
Number			
N	73	76	72
Somnolence			
Mild	12 (16%)	19 (25%)	13 (18%)
Moderate	4 (5%)	7 (9%)	3 (4%)
Severe	1 (1%)	0	1 (1%)
Headache			
Mild	4 (5%)	0	1 (1%)
Moderate	5 (7%)	5 (7%)	4 (6%)
Severe	1 (1%)	1 (1%)	3 (4%)
Dizziness			
Mild	5 (7%)	5 (7%)	0
Moderate	0	2 (3%)	4 (6%)
Severe	0	0	1 (1%)
Nausea			
Mild	14 (19%)	6 (8%)	14 (19%)
Moderate	7 (10%)	15 (20%)	6 (8%)
Severe	3 (4%)	3 (4%)	2 (3%)
Vomiting			
Mild	0	2 (3%)	1 (1%)
Moderate	4 (5%)	9 (12%)	2 (3%)
Severe	0	1 (1%)	1 (1%)
No. of patients given antiemetics	14 (19%)	25 (33%)	9 (12%)
Nausea–vomiting as reason to withdraw from study	2	3	1
Oral phase			
Number			
N	49	55	46
Gastrointestinal			
Nausea*	4 (8%)	21 (38%)	15 (33%)
Vomiting	3 (6%)	10 (18%)	6 (6%)
Constipation	1 (2%)	2 (4%)	3 (7%)
Abdominal pain	0	3 (5%)	1 (2%)
Central nervous system			
Headache	9 (18%)	9 (16%)	7 (15%)
Somnolence†	3 (6%)	8 (15%)	14 (30%)
Dizziness	2 (4%)	8 (15%)	6 (13%)

* Significant difference between groups K30 and F10 + F50 combined, $P = .0009$.

† Significant difference between groups K30 and F10 + F50 combined, $P = .0261$.

Oral Phase

During the oral phase, the daily pain relief, overall evaluation of pain relief, overall evaluation of medication, and drug tolerability were similar for the three groups when data from both study sites were pooled. However, at one site the overall evaluation of medication was lower in group K30 than in the other two groups (treatment-by-site effect, $P = .019$). Return of bowel function (first bowel movement) occurred earlier in group K30 than in the other two groups (32 *vs.* 52 h, $P = .001$).

Adverse effects reported during this phase also are tabulated in table 6. These were predominantly related to the central nervous system or the gastrointestinal tract. Nausea and somnolence were reported more frequently by patients taking 60 mg codeine plus 600 mg acetaminophen (C + A) than by patients taking ketorolac ($P = .0009$ and .0261, respectively). Vomiting and dizziness also were reported numerically more often by patients taking C + A, although the difference did not reach statistical significance. Although most patients experienced "some" problems with different aspects of daily life, the daily quality of life assessment was not different among the three treatment groups. Similarly, the end of study psychologic general well-being index (range 0–105) was 75 ± 12, 77 ± 15, and 77 ± 14 for groups K30, F10, and F50, respectively, and subsets of the index also failed to distinguish between the three treatment groups.

Discussion

Given the increasing number of surgical procedures performed on an ambulatory basis, there are obvious advantages to using a drug such as ketorolac that provides effective pain relief with decreased or zero frequency of typical opioid side effects such as respiratory depression, sedation, constipation, and urinary retention. Availability in both oral and parenteral forms makes ketorolac unique among the nonsteroidal antiinflammatory drugs and heightens interest in the potential roles it may play in the perioperative period.

In this study, iv fentanyl and oral C + A were chosen as the comparative opioid analgesics because they commonly are used in the ambulatory setting. Two different iv fentanyl doses were used; the lower, subtherapeutic dose (10 μg) was expected to have a placebo-like effect. The poor response to 10-μg doses of fentanyl compared with the other two treatments (lowest analgesic score, shortest interval between doses, and numerically highest withdrawal rate) indicates that the pain model chosen for this study was sufficient and appropriate. Patients with a variety of surgical procedures, including gynecologic procedures, were included in this study to represent the spectrum of surgical procedures commonly performed on an outpatient basis.

During the IV phase, 50 μg fentanyl provided better analgesia during the earliest period, as evidenced by higher PID and PAR scores at 15 min. However, during the remainder of the 4-h study period, 30 mg ketorolac was virtually undistinguishable from 50 μg fentanyl in analgesic effects, as measured by SPID and TOTPAR. Peak analgesic effect from each drug also occurred at the same time.

Several studies found that the onset of action of intramuscular ketorolac is comparable to that of intramuscular morphine.[5,16] However, the onset of action and time to peak effect of iv ketorolac have not been specifically defined. In a single-dose study of 10 or 30 mg iv ketorolac *versus* 2 or 4 mg iv morphine given after gynecologic surgery,[7] 70–80% of patients in all four treatment groups withdrew from the study within 1 h because of inadequate analgesia, suggesting that the time profile of action of iv ketorolac is similar to that of iv morphine. Therefore, by inference, the onset of action of iv ketorolac is probably slower than that of iv fentanyl, which can attain a peak effect site concentration within 5 min.[17] Our results are consistent with this deduction. This initial delay in onset of analgesia probably reflects the mode of analgesic action of ketorolac, the inhibition of algesic compounds (presumably prostaglandins) production peripherally. It also could explain the more frequent requests for medication in group K30. In the overall evaluation, the more favorable observer rating of 50 μg fentanyl also could be related to the longer time interval between requested doses in group F50.

The slow onset of analgesic action of iv ketorolac can be a disadvantage when treating patients in acute pain. Ketorolac still would be preferred if it were associated with fewer adverse effects of importance to the patient's recovery. However, this was not demonstrated in our study. The incidence of adverse side effects during the IV phase was not different among the three groups. Several previous reports[9,15,18] comparing intramuscular ketorolac to opioid analgesics in the immediate postoperative period noted the similar lack of discrimination between drugs. This could be due to a major limitation of these studies, including the current one, *i.e.*,

the inability to discriminate between the residual effects of general anesthesia and the adverse effects of the study drugs in the immediate postanesthesia period. In our study particularly, iv fentanyl was permitted as part of the anesthetic technique to mimic common clinical practice. Because most of the operations were of relatively short duration, residual effects from the intraoperatively administered fentanyl could cloud any distinction between ketorolac and fentanyl given in the recovery period. Although only patients who experienced at least moderate pain after surgery were entered in the study, thereby excluding those who might be more sensitive to the effects of fentanyl, the residual influence of intraoperative fentanyl still can be underscored by comparing the withdrawal rate of patients in group K30 with the much higher rate encountered by Peirce *et al.*[7] In that study, no opioid analgesic was allowed for 3 h preceding the administration of ketorolac, and patients did not have the benefits of residual opioid effect when ketorolac was given. The same confounding factor could mask any difference in the time taken by patients to reach certain recovery milestones before discharge from the hospital. Interestingly, the only milestone that occurred beyond the immediate recovery period, return of bowel function, was the only one clearly favored ketorolac therapy over opioid therapy. Thus, although iv ketorolac is generally efficacious in the postoperative period, a controlled trial designed to avoid opioids entirely and to administer ketorolac early is needed to define the overall advantage of ketorolac over the opioids. Pending such a definitive study, one solution to the delayed onset of action of iv ketorolac, should one choose to use it, would be to assume that all patients will have pain (an unproven assumption) and administer ketorolac before pain is felt by the patient, so that its maximum analgesic effect occurs by the time the patient is alert enough to feel significant pain. However, restraint should be exercised when administering ketorolac pre- or intraoperatively, since the risk of increased bleeding secondary to ketorolac's platelet inhibiting effects has not been clearly defined. Another possible solution would be to administer a small dose of an opioid concurrently with the initial dose of ketorolac to control the patient's pain until ketorolac could exert its maximum effect.

The oral phase was a comparison between ketorolac and C + A. In terms of pain relief, the daily rating and overall rating for the whole study period showed 10 mg ketorolac to be comparable, but not superior, to C + A. The number of drug doses taken, approximately one dose every 8 h, was similar between the two oral medications. The predominant difference between the treatments was a lower incidence of nausea and somnolence in the ketorolac group. Our results are similar to those of Forbes *et al.*[12] but different from those of Vangen *et al.*[13] Forbes *et al.* found that 10 mg ketorolac provided better analgesia than did C + A after oral surgery on the first day of a multidose study, with a fourfold lower incidence of adverse side effects.[12] On the other hand, in patients after gynecologic surgery, Vangen *et al.* found that oral ketorolac and C + A provided similar analgesia with a similar incidence of adverse effects.[13] The difference in these two studies could be related to the different types of surgery.

Although the lower incidence of somnolence and nausea seen in the ketorolac group would seem to be advantageous in the outpatient setting, it should be noted that in this study the difference in the incidence of side effects did not translate into measurable difference in the patient's quality of life, general psychologic well-being, or global evaluation and tolerance of the medication. In other words, if we assume that the most important goals (or outcome) of analgesic therapy to be control of pain and restoration of the patient to premorbid level of function, then in this study there was no difference in "outcome" between ketorolac and the opioids. This lack of global "outcome difference" between ketorolac and opioids needs to be weighed against the actual difference in some side effects (nausea and somnolence) as well as the current cost difference between ketorolac and the opioids.

In summary, except for the first 15 min after dosing, ketorolac given intravenously followed by orally was as efficacious as iv fentanyl followed by oral C + A in providing pain relief for ambulatory surgical patients. The incidence of adverse side effects in the immediate postoperative period and the recovery milestones were not different between the two treatments. During the oral therapy period, ketorolac was associated with less nausea and somnolence and earlier return of bowel function. However, both treatments were well tolerated and there was no difference in patients' perception of quality of life and well-being. Therefore, ketorolac given intravenously and orally is a safe and effective analgesic in the ambulatory surgical setting and may offer some advantages over opioids once the patients leave the health care facility, although a difference in outcome is uncertain. To resolve the issues of delayed onset of action, the possible reduction of adverse effects during the early recovery period, and the socioeco-

nomic impact of using a more costly medication, further studies using ketorolac intraoperatively, possibly in place of opioids, are needed.

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References

1. Bravo LJ, Mattie H, Spierdijk J, Bovill JG, Burm AG: The effects on ventilation of ketorolac in comparison with morphine. Eur J Clin Pharmacol 35:491–494, 1988

2. Camu F, Van Overberge L, Bullingham R, Lloyd J: Hemodynamic effects of two intravenous doses of ketorolac tromethamine compared with morphine. Pharmacotherapy 10:122S–126S, 1990

3. Murray AW, Brockway MS, Kenny GN: Comparison of the cardiorespiratory effects of ketorolac and alfentanil during propofol anaesthesia. Br J Anaesth 63:601–603, 1989

4. MacDonald FC, Gough KJ, Nicoll RA, Dow RJ: Psychomotor effects of ketorolac in comparison with buprenorphine and diclofenac. Br J Clin Pharmacol 28:453–459, 1989

5. Rice AS, Lloyd J, Miller CG, Bullingham RE, O'Sullivan GM: A double-blind study of the speed of onset of analgesia following intramuscular administration of ketorolac tromethamine in comparison to intramuscular morphine and placebo. Anaesthesia 46:541–544, 1991

6. Brown CR, Moodie JE, Dickie G, Wild VM, Smith BA, Clarke PJ, Evans SA, Bynum LJ: Analgesic efficacy and safety of single-dose oral and intramuscular ketorolac tromethamine for postoperative pain. Pharmacotherapy 10:59S–70S, 1990

7. Peirce RJ, Fragen RJ, Pemberton DM: Intravenous ketorolac tromethamine versus morphine sulfate in the treatment of immediate postoperative pain. Pharmacotherapy 10:111S–115S, 1990

8. Power I, Noble DW, Douglas E, Spence AA: Comparison of i.m. ketorolac tromethamol and morphine sulphate for pain relief after cholecystectomy. Br J Anaesth 65:448–455, 1990

9. Powell H, Smallman JM, Morgan M: Comparison of intramuscular ketorolac and morphine in pain control after laparotomy. Anaesthesia 45:538–542, 1990

10. McQuay HJ, Poppleton P, Carroll D, Summerfield RJ, Bullingham RE, Moore RA: Ketorolac and acetaminophen for orthopedic postoperative pain. Clin Pharmacol Ther 39:89–93, 1986

11. 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

12. Forbes JA, Butterworth GA, Burchfield WH, Beaver WT: Evaluation of ketorolac, aspirin, and an acetaminophen-codeine combination in postoperative oral surgery pain. Pharmacotherapy 10:77S–93S, 1990

13. Vangen O, Doessland S, Lindback E: Comparative study of ketorolac and paracetamol/codeine in alleviating pain following gynaecological surgery. J Int Med Res 16:443–451, 1988

14. Dupy HJ: The Psychological General Well-Being (PGWB) Index in Assessments of Quality of Life in Clinical Trials of Cardiovascular Therapies. Edited by Wenger NK, Mattson ME, Furberg CD. New York, Le Jacq, 1984, pp 170–183

15. Bellville JW, Forrest WH Jr, Brown BW Jr: Clinical and statistical methodology for cooperative clinical assays of analgesics. Clin Pharmacol Ther 9:290–302, 1968

16. Brown CR, Moodie JE, Wild VM, Bynum LJ: Comparison of intravenous ketorolac tromethamine and morphine sulfate in the treatment of postoperative pain. Pharmacotherapy 10:116S–121S, 1990

17. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics and rational opioid selection. ANESTHESIOLOGY 74:53–63, 1991

18. Stanski DR, Cherry C, Bradley R, Sarnquist FH, Yee JP: Efficacy and safety of single doses of intramuscular ketorolac tromethamine compared with meperidine for postoperative pain. Pharmacotherapy 10:40S–44S, 1990