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Evaluation of Intravenous Ketorolac Administered by Bolus or Infusion for Treatment of Postoperative Pain

A Double-blind, Placebo-controlled, Multicenter Study

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Background: **Ketorolac is a nonsteroidal analgesic that may provide postoperative analgesia without opioid-related side effects. This double-blind, randomized, multicenter study evaluated the analgesic efficacy and safety of intravenous ketorolac in 207 patients during the first 24 h after major surgery.**

Methods: **Subjects were assigned to receive one of three analgesic regimens: a ketorolac infusion, ketorolac boluses, or placebo. All subjects had access to intravenous morphine *via* patient-controlled analgesia (PCA). Evaluations included PCA morphine used, pain assessment (categorical pain intensity scores and visual analogue pain scores), pain relief (categorical pain relief scores), sedation, presence of adverse events, and overall rating of regimens by study observers and patients.**

Results: **Patients in the ketorolac infusion group (but not the ketorolac bolus group) used less morphine (average 33 mg) than did the placebo group (44 mg) ($P = 0.009$). Significant differences favoring both ketorolac groups were seen in the pain intensity and the categorical pain relief scores at various time points during the study. At the termination of the study, compared with the placebo group, categorical pain intensity scores were lower in the ketorolac bolus group; visual analogue pain scores were lower in both ketorolac groups; and pain relief scores were higher in the ketorolac bolus group. The incidence of vomiting was significantly greater in the placebo group (27%) than in the ketorolac infusion group (12%) or bolus group (9%) ($P = 0.032$ and $P = 0.005$, respectively). The incidence of postoperative fever was 10% in the ketorolac bolus group and 25% in the placebo group ($P = 0.013$). Study observers noted less nursing difficulty while caring for patients in the ketorolac infusion group ($P = 0.015$). Study observers and patients in both ketorolac groups reported statistically significant overall drug superiority compared with placebo.**

Conclusions: **It is concluded that intravenous boluses or infusions of ketorolac in conjunction with PCA morphine provide effective, safe analgesia after major surgery and improve on the response to PCA morphine alone. (Key words: Analgesia, patient-controlled: morphine. Analgesic techniques, intravenous: bolus; infusion. Analgesics, nonsteroidal antiinflammatory drugs: ketorolac. Morbidity: fever; vomiting. Pain: postoperative.)**

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ALTHOUGH parenteral opioids have historically been the primary form of therapy for patients experiencing severe acute and postoperative pain, in a number of studies this approach has been found to lack efficacy.[1–8] Attempts to improve analgesia have included the addition of a second agent such as a phenothiazine derivative or hydroxyzine, but frequently the addition has resulted in unwanted sedation and other side effects, with little improvement in comfort. The concept of combining an opioid with a nonsedating, nonopioid analgesic agent is appealing and has been used to advantage for many years in drug combinations available for administration by the oral route (*e.g.*, codeine or oxycodone plus acetaminophen). After major surgery, many patients initially are not able to take oral medications, and until recently, effective nonopioid anal-

Table 1. Study Groups

Group	Patient-controlled Analgesia Drug	Initial Intravenous Bolus	Intravenous Infusion	Intravenous Bolus Every 3 h
Infusion	Morphine	30 mg ketorolac	5 mg/h ketorolac	Placebo
Bolus	Morphine	30 mg ketorolac	Placebo	15 mg ketorolac
Placebo	Morphine	Placebo	Placebo	Placebo

gesics have not been available for parenteral administration.

Ketorolac tromethamine is a nonsteroidal antiinflammatory drug (NSAID) used primarily as an analgesic. It acts principally through inhibition of prostaglandin synthesis. The parenteral formulation is now widely administered by the intramuscular route, but approval for marketing in the United States for intravenous use is still pending. Available evidence suggests that ketorolac can be safely administered intravenously. Basic toxicology studies show no evidence of gross or microscopic vessel changes after injection of ketorolac 10 mg/ml into the marginal ear vein of rabbits.†† Case reports[9] and studies[10,11] describing clinical use of intravenous ketorolac have not documented problems unique to that route of administration.

The current study was undertaken to evaluate the efficacy and safety of ketorolac administered by intravenous infusion and by intravenous boluses in an adult population with postoperative pain during the first 24 h after major surgery.

Materials and Methods

This study was conducted using a double-blind, randomized, stratified, parallel, and multidose design. Patients from three sites undergoing major orthopedic, gynecologic, or general surgery were enrolled. Human Subjects Board approval was obtained at each site, and every patient gave signed, informed consent.

Study Population

Entry criteria included ability to speak English, weight of at least 40 kg, legal age, ability to receive intravenous medications and to operate a patient-controlled analgesia (PCA) device, entry into the study within 18 h after completion of surgery, baseline pain intensity of "moderate" or greater on a categorical scale, and no use of PCA in the postoperative period before entry into the study.

Exclusion criteria included known allergy, sensitivity, or contraindications to any opioid or nonopioid analgesic agent including aspirin or other NSAIDs; ASA physical status 3 or more at the time of surgery; a history of active peptic ulcer within the preceding 6 months; a history of bleeding problems or anticoagulant use within the preceding 4 weeks; patients who were pregnant or breast-feeding; a history of known or suspected alcohol or drug abuse; or a medical or psychiatric condition that might compromise ability to give informed consent or complete the study. Patients in the study received anesthetics as judged appropriate by their anesthesiologists.

Postoperatively, when patients first reported moderate or greater than moderate pain, they were stratified by type of surgery and randomly assigned, by a computer program, to begin therapy in one of three treatment groups: ketorolac infusion, ketorolac boluses, or placebo (table 1). Because drug bioavailability is similar, the total 24-h intravenous doses used were similar to those approved for marketing by the Food and Drug Administration for intramuscular administration. The intravenous bolus doses were given at intervals that are commonly used clinically. To preserve the double-blind study design, all patients received coded boluses and infusions on identical time schedules.

Patient-controlled Analgesia

When patients first reported moderate or greater than moderate pain after surgery, in addition to receiving their study drug, a PCA pump containing morphine was connected to the intravenous infusion. Initial PCA settings were as follows: incremental dose of 1 mg; lockout interval of 6 min; and 4-h limit of 30 mg for Abbott (North Chicago, IL) pumps and 1-h limit of 10 mg for Bard (North Reading, MA) pumps. The incremental dose was increased to 1.5 mg if analgesia was inadequate after 1 h. For continuing inadequate analgesia after an additional 1 h, the incremental dose was further increased to 2.0 mg. For initial loading and

†† Unpublished data, Syntex Laboratories Inc.

subsequent breakthrough pain, supplemental intravenous morphine could be given from the PCA pump by the patient's nurse in 2.0-mg increments every 5 min to a maximum of 10 mg during the 24-h study period. If analgesia remained inadequate, the patient was provided with additional analgesia and removed from the study.

Measures of Pain

Pain assessments were made just before entry into the study and at 2, 4, 6, and 24 h. Observations included assessment of pain intensity on both a categorical scale (0 = none; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe) and on a 100-mm visual analogue scale (by placement of a slash mark) anchored at 0 mm with the words "no pain" and at 100 mm with the words "worst possible pain." Two hours after entry into the study and again at 4, 6, and 24 h, patients were also asked to rate their pain relief on a categorical scale (0 = none; 1 = a little; 2 = some; 3 = a lot; and 4 = complete).

Adverse Events

Sedation was rated by study observers at 2, 4, and 6 h and at termination on a categorical scale (1 = completely awake; 2 = awake but drowsy; 3 = asleep but responsive to verbal command; 4 = asleep but responsive to tactile stimulus; and 5 = asleep and not responsive to any stimulus). Adverse events occurring during the study were documented and graded by observers as mild, moderate, or severe. Side effects expected to occur commonly in the postoperative period were treated as follows: metoclopramide 10 mg intravenously every 3 h for nausea or vomiting; diphenhydramine 12.5 mg intravenously every 3 h for severe itching; "in-and-out" bladder catheterization as needed for urinary retention; and naloxone intravenously by titration for respiratory depression.

Poststudy Evaluations

The following questions were answered by study observers:

1. "How would you rate the overall drug tolerability that you feel the patient experienced?" (0 = poor; 1 = fair; 2 = good; 3 = very good; and 4 = excellent)
2. "How would you rate this medication overall?" (0 = poor; 1 = fair; 2 = good; 3 = very good; and 4 = excellent)
3. "How would you rate the overall difficulty in providing nursing care for this patient during the study period, independent of study medication administration and compared to other patients with similar diagnoses?" (0 = very difficult; 1 = more than average; 2 = average; 3 = less than average; and 4 = minimal). A global impression for each subject was based on discussion with the primary ward nurse and review of the chart.

The following questions were answered by patients:

1. "How much relief of pain did you have overall from the study medication?" (0 = none; 1 = a little; 2 = some; 3 = a lot; and 4 = complete)
2. "How would you rate this medication overall?" (0 = poor; 1 = fair; 2 = good; 3 = very good; and 4 = excellent)

Statistical Methods

The amount of morphine used during the study and time using PCA pumps were analyzed by a nonparametric procedure, the partial Kruskal-Wallis statistic, adjusted for the number of patients for each site and surgery type. The categorical data were analyzed by a chi-squared procedure (the Cochran-Mantel-Haenszel statistic[12]). This test produced a statistic adjusted for the number of patients in each site and surgery type. The measurements of pain made on the 100-mm visual analogue scale were analyzed by a three-way analysis of variance with factors of treatment; site; surgery type; and interactions of treatment with site, treatment with surgery type, and site with surgery type. The interactions between treatment and site, treatment and surgery, and site and surgery were assessed by analysis of variance for visual analogue scale data and a linear model for categorical data.[13] For visual analogue scale data, the pooled results were presented when the interactions were not significant at the 0.10 level. For the categorical data, because the Cochran-Mantel-Haenszel test does not require the assumption of no interactions, the results based on that test were pooled. Only data from patients remaining in the study for the entire 24 h were analyzed for poststudy pain scores, pain relief scores, and morphine use. Data from all patients receiving the study drug were analyzed for adverse events, regardless of the length of time in the study. All test hypotheses were two-sided. *P* values less than or equal to 0.05 were considered significant in treatment comparisons.

Table 2. Reasons for Early Withdrawal

	Infusion [n (%)]	Bolus [n (%)]	Placebo [n (%)]	Total [n (%)]
Adverse events	8 (12)	7 (10)	11 (15)	26 (13)
Study administration problems	3 (5)	4 (6)	9 (13)	16 (8)
Inadequate analgesia	2 (3)	1 (1)	5 (7)	8 (4)
Intercurrent illness	0 (0)	3 (4)	0 (0)	3 (1)
Other	6 (9)	4 (6)	2 (3)	12 (6)
Total	19 (29)	19 (27)	27 (38)	65 (32)

Results

Study Population

A total of 207 patients entered the study. Of these, 142 (69%) completed the 24-h study period. The remaining 65 (31%) were withdrawn before completion of the study for the reasons shown in table 2. Safety data from all patients receiving the study drug and collected before termination were included in the analysis. Data from 6 of the 207 patients were excluded from efficacy analysis because of protocol violations: 1 after discovery of an alcohol abuse history, 3 for invalid surgical procedures, 1 for a broken randomized code, and 1 for an interrupted infusion. Decisions to include or exclude data were made before the study code was broken. Patients in the bolus group entered the study an average of 2.6 h after surgery, compared with 1.9 h for patients in the infusion and placebo groups ($P = 0.026$). Because there were no significant differences among the three treatment groups with regard to demographics and baseline variables across study sites and types of surgery (table 3), the data were pooled before the baseline analysis. Mean times that patients were enrolled in the study (± SD) were: infusion group 21.3 (± 5.7) h, bolus group 20.9 (± 6.7) h, and placebo group 21.1 (± 5.6) h. These times are not significantly different.

Patients in this study received anesthetics as judged appropriate by their anesthesiologists. These included 203 general anesthetics (9 of which were combined with a regional anesthetic technique, *i.e.*, epidural or spinal) and 4 spinal anesthetics. The nine patients receiving combined general–regional anesthetic techniques were distributed as follows: bolus group, one; infusion group, two; and placebo group, six. Of the four patients who received spinal anesthetics, three were in the bolus group and one was in the placebo group. No epidural or intrathecal opioids were administered.

Patient-controlled Analgesia

PCA morphine use among patients completing the study in the three treatment groups and significance of the differences are shown in table 4. Compared with the placebo group, morphine use during 24 h was 25% less in the ketorolac infusion group ($P = 0.009$).

Measures of Pain

Levels of pain intensity and pain relief at the 24-h observation point for patients who completed the study are listed in table 5. On the basis of categorical pain intensity scores, analgesia was superior in the ketorolac infusion group compared with that in the placebo

Table 3. Demographics and Baseline Variables

	Infusion	Bolus	Placebo	*P*
Total patients (n)	65	68	68	
General surgery patients (n)	15	12	16	
Gynecologic surgery patients (n)	30	32	32	
Orthopedic surgery patients (n)	20	24	20	
Age (hr) [mean (SD)]	43.9 (11.8)	44.3 (14.2)	46.1 (14.5)	NS
Weight (kg) [mean (SD)]	73.0 (12.8)	74.0 (16.3)	75.0 (18.8)	NS
% women	64	74	78	NS
Duration surgery to entering study [h; mean (SD)]	1.9 (1.1)	2.6 (2.7)	1.9 (1.3)	Bolus *vs.* placebo, 0.035 Bolus *vs.* infusion, 0.013
VAS baseline pain score (mm)				
Mean (SD)	69 (15)	71 (18)	72 (19)	NS
Median (IQ)	69 (81, 57)	69 (86.5, 56)	76 (88.5, 55)	

NS = no statistically significant differences; IQ = interquartile range, 75%, 25%.

Table 4. Patient-controlled Morphine Use among Patients Completing the Study

Actual Patient-controlled Morphine Use (mg)	Infusion (n = 46)	Bolus (n = 50)	Placebo (n = 45)	*P*
Mean (SD)	33 (28)	31 (18)	44 (26)	Infusion *vs.* placebo, 0.009
Median (IQ)	25 (44, 15)	31 (45, 17)	42 (56, 23)	Bolus *vs.* placebo, NS

NS = no statistically significant differences; IQ = interquartile range, 75%, 25%.

group. On the basis of the visual analogue pain scores, analgesia was superior in the ketorolac infusion and bolus groups compared with that in the placebo group. Categorical pain relief scores were higher in the ketorolac bolus group compared with the that in the placebo group.

In the overall evaluations by patients, pain relief scores in the ketorolac infusion group and in the ketorolac bolus group both were significantly greater than those in the placebo group ($P = 0.002$ and 0.023, respectively) (table 6). Pain and pain relief levels at various observation times throughout the study and significance of the differences are shown in figures 1–3.

Adverse Events

There were no statistically significant differences either in sedation among the treatment groups at any time point or in the overall sedation scores. All adverse events in patients receiving the study drug were recorded, whether or not they were thought to be associated with the study. A total of 445 adverse events (mild, moderate, and severe) were observed in 182 patients (infusion group, 54 patients with 133 events; bolus group, 64 patients with 145 events; and placebo group, 64 patients with 167 events). Adverse events that might be expected to be of clinical significance postoperatively are listed in table 7. Compared with the placebo group, the incidence of fever was lower in the ketorolac bolus group, and vomiting was significantly less frequent in both ketorolac groups. The incidence of other adverse events did not differ significantly between groups.

Adverse events caused premature withdrawal from the study of 26 patients (8 in the infusion group, 7 in the bolus group, and 11 in the placebo group). The predominant reason for termination was nausea either alone or accompanied by vomiting (10 patients: 3 in the infusion group, 2 in the bolus group, and 5 in the placebo group). Four patients withdrew because of hypotension (2 in the infusion group, 1 in the bolus group, and 1 in the placebo group). Two patients had decreased urine output (1 in the infusion group and 1 in the placebo group). Seven patients (4 in the bolus group and 3 in the placebo group) had skin complaints (itching, rash, facial erythema, or hot flashes). Seven patients (3 in the infusion group, 1 in the bolus group, and 3 in the placebo group) reported nervous system events (anxiety, sleepiness, vagueness, disorientation, numbness and tingling, or dysphoria). Three patients withdrew because of concurrent illness (back pain in 2 and hypotension secondary to intraabdominal bleeding in 1 patient in the bolus group).

Poststudy Evaluations

Study observers' overall evaluation showed less nursing difficulty in the ketorolac infusion group. Observers' and patients' overall rating of the study drug was significantly greater in the ketorolac infusion and bolus groups compared with that in the placebo group (table 6).

Discussion

This study showed that patients receiving PCA morphine after major surgery used less of the opioid if they also received intravenous infusions of ketorolac. In addition, these patients reported lower levels of pain if they received either intravenous infusions or bolus doses of ketorolac. The rationale for including boluses and infusions of ketorolac was to study both commonly used intravenous methods of administration of analgesic agents after major surgery.

The systemic opioid-sparing effects of ketorolac have been shown previously. After major orthopedic surgery, compared with placebo, a 66% reduction in morphine use was noted when intramuscular ketorolac was administered.[14] Epidural PCA fentanyl use after radical prostatectomy was reduced by 40% in patients given intramuscular ketorolac.[15] In the current study, an opioid-sparing effect of about 25% was seen with intravenous ketorolac infusions. Similar reduction in

Table 5. Pain Measures at 24 h among Patients Who Completed the Study

	Infusion (n = 45)	Bolus (n = 49)	Placebo (n = 43)	*P*
Categorical pain intensity scores: 5-point scale* [median (IQ)]	1 (1, 1)	1 (1, 0)	1 (1, 1)	Infusion *vs.* placebo, NS Bolus *vs.* placebo, 0.003
Visual analog pain scale: 100-mm line [mean (SD)]	13 (12)	13 (16)	22 (21)	Infusion *vs.* placebo, 0.011 Bolus *vs.* placebo, 0.008
Categorical pain relief scores: 5-point scale† [median (IQ)]	3 (3, 3)	3 (4,3)	3 (3, 2)	Infusion *vs.* placebo, NS Bolus *vs.* placebo, 0.001

NS = no statistically significant differences; IQ = interquartile range, 75%, 25%.

* Categorical pain intensity scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

† Categorical pain relief scale: 0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete.

opioid use in the ketorolac bolus group did not reach statistical significance.

As a result of the rigorous protocol design, numerous adverse events were identified in this study (table 7). Many were of little or no clinical significance, and most appeared with comparable frequency in the treatment groups. It should be noted that observers recorded all such events, even when it seemed unlikely that they were study-related. Overall, sedation was not marked and did not differ among the study groups. The magnitude of the reduction in morphine requirements of the patients receiving ketorolac may not have been sufficient to result in less sedation. It is also possible that a sedating effect of ketorolac itself offset any potential advantage associated with less morphine use.[16] No clinically apparent respiratory depression was seen with PCA morphine alone or in combination with ketorolac.

Significantly less vomiting was seen in both groups receiving ketorolac, perhaps because of the reduced doses of PCA morphine used. Alternatively, because pain is one of the causes of perioperative vomiting, it is possible that the lower levels of pain in the ketorolac groups contributed to the lower incidence of this event.[17] A similar finding was reported when ketorolac was used as an adjuvant to general anesthesia for pediatric surgery.[10]

Significantly fewer patients with fever were seen in the ketorolac bolus group. Because there was also a trend toward fewer fevers in the ketorolac infusion group, the observation could have been the result of the drug's antipyretic effect. It is also possible that with

Table 6. Observer and Patient Overall Evaluations among Subjects Who Completed the Study

Assessment	Infusion	Bolus	Placebo	*P*
Observer evaluations				
Nursing difficulty* [median (IQ)]	3 (4, 3) n = 46	3 (4, 2) n = 49	3 (3, 2) n = 44	Infusion *vs.* placebo, 0.011
Drug tolerability† [median (IQ)]	3 (4, 3) n = 47	3 (4, 2) n = 51	3 (3, 2) n = 45	Infusion *vs.* placebo, 0.005
Overall study drug evaluation† [median (IQ)]	3 (4, 3) n = 46	3 (4, 3) n = 49	3 (3, 2) n = 44	Infusion *vs.* placebo, 0.001 Bolus *vs.* placebo, 0.003
Patient evaluations				
Overall categorical pain relief scores: 5-point scale‡ [median (IQ)]	3 (3, 3) n = 45	3 (3, 3) n = 47	3 (3, 2) n = 43	Infusion *vs.* placebo, 0.004 Bolus *vs.* placebo, 0.016
Overall study drug evaluation† [median (IQ)]	3 (4, 3) n = 45	3 (4, 2) n = 47	3 (3, 2) n = 43	Infusion *vs.* placebo, 0.035 Bolus *vs.* placebo, 0.018

NS = no statistically significant differences; IQ = interquartile range, 75%, 25%.

* Responses rated: 0 = very difficult, 1 = above average, 2 = average, 3 = below average, 4 = minimal.

† Responses rated: 0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent.

‡ Responses rated: 0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete.

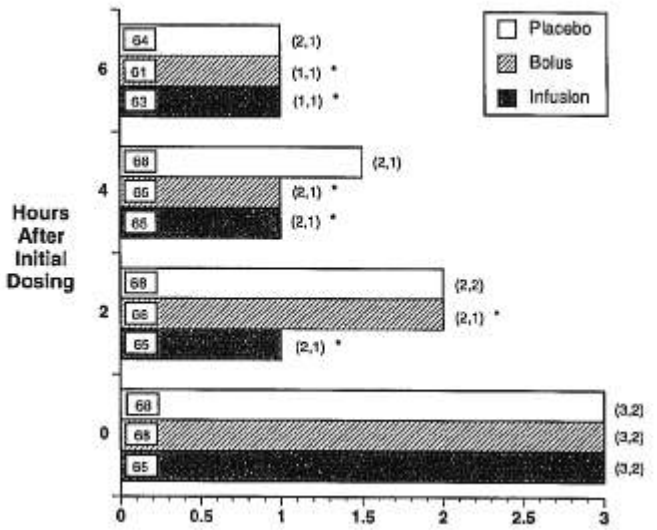

Fig. 1. Median categorical pain intensity scores (0 = none; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe). The number within each bar represents the number of patients in a treatment group at that time point; numbers in brackets to the right of each bar indicate the 75–25% interquartile range. *Statistically significant difference from the placebo group by pairwise Cochran-Mantel-Haenszel tests.

less pain, patients receiving ketorolac were able to breathe and cough more effectively thereby reducing their risk for postoperative atelectasis. Others have also reported lower maximum temperatures after surgery in patients receiving ketorolac.[15]

There were more patients with oliguria and urinary retention in the ketorolac infusion group than in the other two groups. Although it is well known that renal insufficiency is a rare but serious complication of NSAID use, the oliguria was corrected with fluid administration. This suggests it may not have been related to the study drug. Furthermore, if the oliguria was caused by ketorolac, it should have occurred with similar frequency in both the infusion and the bolus groups.

Urinary retention is a common side effect of opioids. It is unclear why its incidence was not highest in the placebo group, in which more morphine was used. Because the number of cases of urinary retention was small, it is difficult to draw any conclusions about etiologic factors.

One patient randomized to the ketorolac bolus group in this study developed postoperative intraabdominal bleeding. This 38-yr-old woman underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for the treatment of endometriosis and dysmenorrhea. Two hours after entering the study (*i.e.*, 2 h after receiving a single 30-mg intravenous bolus of ketorolac), nausea and hypotension developed. She was taken back to the operating room for abdominal exploration and control of bleeding. The problem was resolved, and subsequent recovery was uneventful. Ketorolac inhibits platelet aggregation and may prolong bleeding time. It does not appear to affect platelet count, prothrombin time, or partial thromboplastin time. There is no way to determine whether the single dose of ketorolac administered to this patient played a role in her postoperative bleeding.

Study observers noted significantly less nursing difficulty in the ketorolac infusion group compared with the placebo group. We speculate that this could be a consequence of fewer nurse calls to patients' rooms as a result of superior analgesia and a lower incidence of vomiting when ketorolac was administered.

Intramuscular opioids have been the principal method of providing postoperative pain control in the past, but in recent years alternatives have become popular. Important among these have been epidural or intrathecal opioid administration and self-administration of opioids intravenously by PCA pumps. More recently,

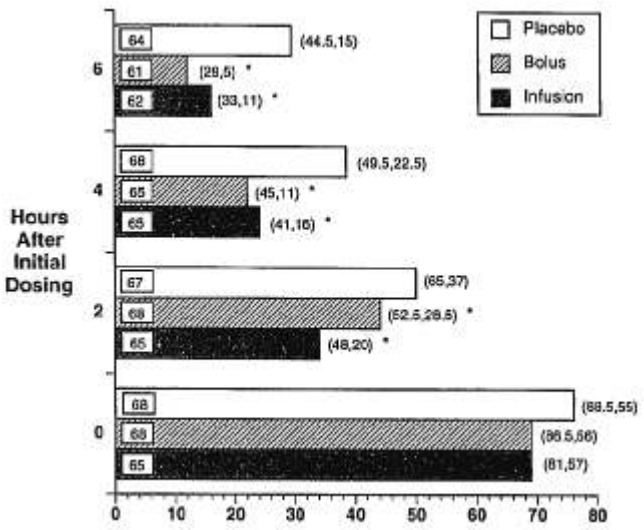

Fig. 2. Median pain scores on a 100-mm visual analogue scale (0 = no pain; 100 = worst possible pain). The number within each bar represents the number of patients in a treatment group at that time point; numbers in brackets to the right of each bar indicate the 75–25% interquartile range. *Statistically significant differences from the placebo group by the least-significant-difference multiple-comparison procedure.

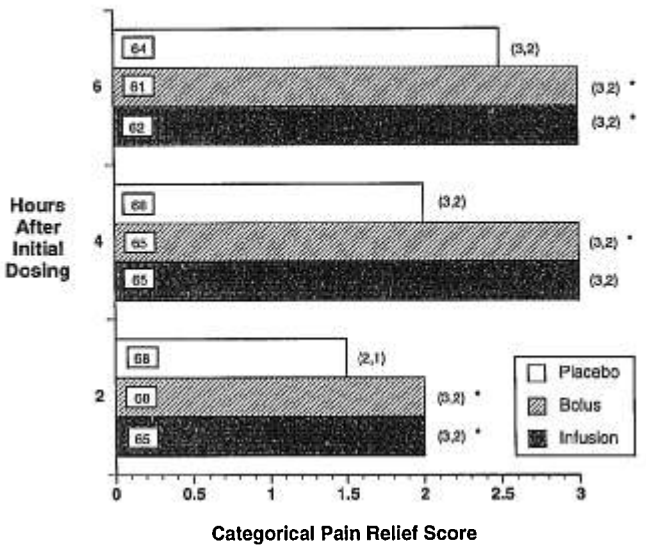

Fig. 3. Median categorical pain relief scores (0 = none; 1 = a little; 2 = some; 3 = a lot; and 4 = complete). The number within each bar represents the number of patients in a treatment group at that time point; numbers in brackets to the right of each bar indicate the 75–25% interquartile range. *Statistically significant differences from the placebo group by pairwise Cochran-Mantel-Haenszel tests.

the role of NSAIDs has gained prominence. Advantages over opioids include a reduction in opioid-related side effects, especially respiratory depression, absence of tolerance or addiction potential, and less sedation. Significant interest has been generated after the introduction of ketorolac, the first NSAID for analgesic use in the United States approved for marketing for parenteral administration.

Most evaluations of NSAIDs for postoperative pain relief have involved comparison with opioids in "either/or" protocols. With improved understanding of postoperative pain and its consequences, there is growing emphasis on the advantages of combined pharmacologic approaches to therapy.[18,19] Concurrent use of systemic opioids with centrally mediated actions and NSAIDs with peripheral sites of action appears to have advantages over use of either class of drug alone. It is unlikely that NSAIDs can completely replace opioids in most patients suffering moderate or severe postoperative pain shortly after surgery. In our study, patients receiving ketorolac used about 75% as much morphine as those receiving a placebo. This finding suggests that in the treatment of patients with moderate or severe surgical pain, NSAIDs may best be considered as adjuncts to opioid therapy.

Though statistically significant, it was not determined in this study whether the 25% morphine-sparing effect of ketorolac is clinically important. The addition of ketorolac as an analgesic after surgery is more expensive than the use of opioids alone. This study did not establish whether the increased cost of ketorolac was offset by savings resulting from the reduced incidence of vomiting (in both ketorolac groups) and fever (in the ketorolac bolus group) and the reduced nursing difficulty (in the ketorolac infusion group). In some institutions, the costs of infusion pumps and pharmacy charges associated with preparing infusions might make a ketorolac intravenous bolus technique a more economical choice.

There is evidence that later in the postoperative period as pain begins to subside, NSAIDs alone can provide adequate analgesia. In a comparison between single-dose intramuscular ketorolac and morphine postoperatively, it was found that both 10 and 30 mg ketorolac were equal in analgesic effect to 12 mg morphine on postoperative day 1 or 2.[20] In a comparison of intramuscular ketorolac 30 mg and morphine 10 mg for pain relief after cholecystectomy, the authors concluded that ketorolac alone provided poor pain relief in the immediate postoperative period compared with the relief provided by morphine, but the next day the effect of the two drugs was similar.[21] The current study did not evaluate the possible role of ketorolac as a postoperative analgesic beyond 24 h.

To date, most clinical experience with ketorolac is with the intramuscular route of administration. An intramuscular infusion of ketorolac compared with an intramuscular placebo infusion postoperatively resulted in lower pain scores and reduced PCA morphine requirements.[22] In a similar study, compared with a placebo group, patients receiving intramuscular ketorolac by infusion had reduced overall PCA morphine requirements, whereas a group receiving intramuscular boluses of ketorolac did not.[23]

The intravenous route of administration for drugs in postoperative patients is an appealing alternative to intramuscular injection. Advantages include patient comfort and elimination of the risk of tissue hematoma, infection, or nerve damage. The analgesic effects of intravenous ketorolac and morphine immediately after major surgery have been compared. In one study, although neither drug produced adequate analgesia in the doses used (ketorolac 10 or 30 mg and morphine 2 or 4 mg), no adverse effects associated with intravenous administration were reported.[24] In another

Table 7. Percent of Adverse Events among All Patients Receiving Study Drug

Adverse Events* (P)	Infusion (%, n = 66)	Bolus (%, n = 70)	Placebo (%, n = 71)
Nervous system			
Somnolence	35	44	41
Dizziness	8	4	13
Headache	5	3	1
Confusion	2	0	0
Insomnia	3	0	1
Gastrointestinal			
Nausea	44	51	59
Vomiting†	12	9	27
Infusion *vs.* placebo, $P = 0.032$			
Bolus *vs.* placebo, $P = 0.005$			
Cardiovascular			
Hypotension	8	7	4
Tachycardia	2	0	1
Respiratory			
Hypoventilation	2	3	1
Asthma	2	0	0
Urogenital			
Urinary retention	9	4	0
Oliguria	8	1	3
Skin			
Pruritus	9	19	13
Rash	2	3	4
Urticaria	2	0	0
Other			
Injection site skin reaction	5	0	0
Injection site pain	3	3	1
Fever†	14	10	25
Bolus *vs.* placebo, $P = 0.013$			

* Adverse events (mild, moderate, and severe) seen in all patients receiving any study drug regardless whether they completed the 24-h study.

† Differences in the incidence of adverse events among the three treatment groups are statistically significant as indicated.

study, intravenous ketorolac at doses of 10 or 90 mg produced no change in cardiac or hemodynamic parameters in patients undergoing major vascular surgery.[25] The current study confirms no cardiac complications or other adverse events specifically associated with the intravenous route.

In summary, intravenous boluses or infusions of ketorolac in conjunction with PCA morphine provided effective, safe analgesia after major surgery. Patients receiving ketorolac infusions self-administered less PCA morphine. Patients receiving either ketorolac intravenous boluses or infusions reported less pain and experienced less postoperative vomiting (in both ketorolac groups) and fewer fevers (in the ketorolac bolus group) than did patients receiving PCA morphine alone.

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