

Intramuscular Ketorolac vs Oral Ibuprofen in Emergency Department Patients with Acute Pain

Martha L. Neighbor, MD, Kathleen A. Puntillo, RN, DNSc

■ ABSTRACT

Objective: To determine whether IM ketorolac is superior to oral ibuprofen in patients presenting to an ED in moderate to severe pain.

Methods: This prospective, randomized, double-blind study involved a convenience sample of 119 patients aged ≥ 18 years who presented to an urban teaching hospital ED with a self-assessed pain intensity score of 5, 6, 7, or 8 (on a numerical rating scale of 0–10). Patients were randomized to receive either 60 mg of IM ketorolac and a placebo capsule or 800 mg of oral ibuprofen and a saline injection. Pain scores were measured at 0, 15, 30, 45, 60, 90, and 120 minutes after dosing. Supplemental analgesics were allowed in accordance with standard medical practice.

Results: There were 18 patients excluded who did not remain in the ED for the full 2-hour study period. Of those completing the trial, 53 patients received ketorolac and 48 patients received ibuprofen. There were no significant differences in pain scores between ketorolac and ibuprofen at any time during the study. However, there was a statistically significant decrease in pain over time in both treatment groups. Yet, 40% of the patients continued to report pain intensity scores of 5–8 at 2 hours after treatment.

Conclusions: IM ketorolac and oral ibuprofen provide comparable levels of analgesia in ED patients presenting with moderate to severe pain. Unfortunately, 40% of all the patients had inadequate pain relief (pain score ≥ 5) from either ketorolac or ibuprofen.

Key words: ketorolac; ibuprofen; emergency department; acute pain.

Acad. Emerg. Med. 1998; 5:118–122.

■ Ketorolac is a widely used analgesic in the ED.¹ Ketorolac's popularity is likely due to studies demonstrating its potency to be comparable to low-dose opioids in the relief of postoperative pain,^{2–6} its availability in parenteral form, and successful marketing. However, its mechanism of action, reversible inhibition of prostaglandin synthesis at the level of cyclooxygenase,⁷ is the same as that for all other NSAIDs. Furthermore, ketorolac has been only rarely compared with other NSAIDs in the ED setting.^{8–11} We, therefore, directly compared IM ketorolac and oral ibuprofen in a double-blind, randomized manner in patients presenting to an urban teaching hospital ED experiencing moderate to severe pain from a variety of etiologies.

From San Francisco General Hospital, San Francisco, CA, Department of Emergency Services (MLN, KAP); and University of California, San Francisco, CA, School of Medicine, Department of Medicine (MLN) and School of Nursing (KAP).

Received: March 20, 1997; revision received: July 11, 1997; accepted: July 12, 1997.

Prior presentation: SAEM annual meeting, Washington, DC, May 1997.

Address for correspondence and reprints: Martha L. Neighbor, MD, Department of Emergency Services, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110. Fax: 415-206-5818; e-mail: neighbor@itsa.ucsf.edu

■ METHODS

Study Design: This was a randomized, double-blind comparison of oral ibuprofen and IM ketorolac in patients presenting between October 1995 and August 1996 with moderate to severe pain from a variety of etiologies. This study was approved by the committee on human research, and written, informed consent was obtained from each patient prior to enrollment.

Setting and Population: San Francisco General Hospital is an urban teaching hospital, with an annual adult ED census of >75,000 visits. A convenience sample of patients, aged ≥ 18 years, presenting to the ED with moderate to severe pain were eligible for enrollment. Patients were enrolled based on the availability of research assistants. Patients with any of the following were excluded from study: known allergy to NSAIDs, receiving anticoagulant therapy, pregnant or lactating, known coagulopathy or bleeding, peptic ulcer disease, renal insufficiency, migraine headache, sickle cell vaso-occlusive crisis, being treated in resuscitation rooms, NSAID use in the previous 12 hours, inability to report pain using a numeric rating scale (NRS). Patients with migraine headache and sickle-cell crisis were excluded because these patients typically receive additional medications that might confound the

results of this study. Patients in resuscitation rooms were excluded from the study because they were considered too unstable for the enrollment process. Those patients who left the ED prior to completion of the 2-hour monitoring period were excluded from the primary analysis.

Measurements: Patients rated their pain intensity using a horizontal 0–10 NRS, where 0 corresponds to “no pain” and 10 corresponds to “worst possible pain.” Construct validity of the NRS has been established through factor analysis,^{12,13} and concurrent validity has been established with visual analog scales (VASs),¹⁴ as well as pain intensity word scales and simple descriptive scales.^{12,15} While a VAS is often used in clinical research, we chose to use the NRS to measure pain intensity because of its ease of use in the clinical setting, and because of the 7% to 11% “failure rate” associated with the use of a VAS.^{16,17}

Patients were eligible for enrollment if they rated their pain on the NRS as 5–8. This level of pain is considered moderate to severe.¹⁸ Patients who rated their pain on the NRS as 9 or 10 were considered to have severe pain and were excluded from the study.

Procedures: In a randomized, double-blind fashion, patients received either 60 mg ketorolac IM and a placebo capsule, or an 800-mg ibuprofen capsule and a placebo (saline) IM injection. Blinding was ensured by identical-appearing placebo and ibuprofen capsules, and identical-appearing ketorolac and saline injections. Medication packages were prepared by the hospital pharmacy and study drugs were randomized using a computer random-number generator and stored in a locked office in the ED.

Pain intensity was measured prior to obtaining consent for enrollment, prior to treatment (baseline), and 15, 30, 45, 60, 90, and 120 minutes after treatment, using the NRS. Research nurses obtained consent from patients, administered the study medications, and collected data. Subjects pointed to a number on a card that displayed the NRS, and as a result had no written record of their previous pain ratings. Emergency physicians were allowed to provide supplemental analgesics of their choice (excluding NSAIDs) to their patients at any time, in any amounts, in accordance with standard medical practice. Side effects were elicited by the research nurses with an open-ended question.

Data Analysis: A sample size of 65 patients per group was determined a priori, based on an α -significance level of 0.05, with a power of 0.80 to detect a median effect size of 0.25 between groups. This median effect corresponds to a 10% difference in NRS scores. The demographic characteristics of the 2 treatment groups were compared using unpaired t-tests and χ^2 analyses. A repeated measures analysis of variance (ANOVA) with 1

■ **TABLE 1** Patient Characteristics*

	Ketorolac (n = 61)	Ibuprofen (n = 58)
Sex		
Female	17 (28%)	17 (28%)
Male	44 (72%)	40 (69%)
Age—mean \pm SD	34.8 \pm 9.0 yr	35.1 \pm 10.3 yr
Ethnicity		
White	29 (48%)	23 (40%)
Black	13 (21%)	15 (26%)
Hispanic	16 (26%)	14 (24%)
Native American	2 (3%)	0
Chinese	1 (2%)	3 (5%)
Other	0	3 (5%)
Living situation		
Home	44 (75%)	41 (73%)
Shelter/streets	15 (25%)	15 (27%)
Pretreatment pain score—mean \pm SD (0–10 scale)	6.8 \pm 1.2	7.0 \pm 1.2

*Differences in patient characteristics between groups were not significant.

between-subjects factor (i.e., type of drug) and 1 within-subjects factor (i.e., time) was used to analyze differences in pain over time according to type of drug received. All tests of significance were 2-sided. An interim analysis of the data was performed by an independent group after 119 patients were enrolled. The study was stopped when it was determined that this number of patients was sufficiently large to answer the study question.

■ RESULTS

A total of 119 patients met inclusion criteria and were enrolled in the study; 61 received ketorolac and 58 received ibuprofen. Comparison of the 2 drug groups showed no significant differences in age, gender, ethnicity, living situation (i.e., whether home or shelter/street), pretreatment pain scores (Table 1), or final diagnoses (Table 2). Of the 119 patients, 101 (53 ketorolac and 48 ibuprofen) remained in the ED for the 2-hour study period and were included in the primary analysis. No differences were found between the patients who stayed 2 hours and those who left prior to 2 hours in terms of their ages, baseline pain scores, and pain scores at 15, 30, 45, 60, and 90 minutes.

The repeated-measures ANOVA revealed a significant decrease in pain over time in both the ketorolac and ibuprofen treatment groups (Fig. 1). However, there was no difference over time between the 2 drug groups. In fact, pain intensity scores of patients who received ketorolac and patients who received ibuprofen did not differ significantly at any of the study times. Nine patients received

■ TABLE 2 Final Diagnoses*

	Ketorolac (n = 61)	Ibuprofen (n = 58)
Fracture	11 (18%)	12 (21%)
Headache	3 (5%)	4 (7%)
Sprain/strain	20 (33%)	22 (38%)
Contusion	8 (13%)	8 (14%)
Pneumonia/bronchitis	1 (2%)	2 (3%)
Cellulitis/abscess†	11 (18%)	3 (5%)
Abdominal/flank pain	2 (3%)	3 (5%)
Radiculopathy	2 (3%)	1 (2%)
Other	3 (5%)	3 (5%)

*Differences in final diagnoses between groups were not significant.

†Sample size may have been too small to detect a significant difference.

supplemental analgesia (average of 5 mg of morphine), 5 in the ketorolac group and 4 in the ibuprofen group. Entering the use of supplemental morphine as a covariate in the repeated-measures ANOVA model did not influence study results.

In spite of an overall significant decrease in pain intensity over time, 40 (40%) of the study patients continued to report pain intensity scores of 5–8 at 2 hours after treatment with the study medication. This frequency of inadequate analgesia after 2 hours did not vary according to the type of analgesic the patient received. Of the patients showing little response, there were 21 receiving ketorolac, with a mean pain score of 6.0 ± 1.0 , and 19 receiving ibuprofen, with a mean pain score of 6.3 ± 1.0 after 2 hours.

Possible side effects to the study medications (5 in each treatment group) were comparable and included nausea or gastrointestinal upset, dizziness or lightheadedness, sleepiness, and headache. All of our patients tolerated oral therapy without vomiting.

■ DISCUSSION

We directly compared IM ketorolac and oral ibuprofen in ED patients experiencing moderate to severe pain and found the 2 drugs to be equally effective in relief of pain. In the ibuprofen group, the mean pain score decreased from 7.0 to 3.8. In the ketorolac group the mean pain score decreased from 6.8 to 3.7. These represent a 46% reduction in pain scores. Although many factors may affect whether a change in reported pain score is clinically "meaningful" to a patient, researchers have suggested that a minimum of 13%¹⁹ to 23%²⁰ reduction in pain from baseline infers clinical significance. NRS pain scores below 4 have been shown to correspond to mild pain, while scores from 5 to 10 are considered to be moderate to severe.¹⁸ Therefore, both of our treatment groups had statistically and clinically significant reductions in pain.

However, we found no significant differences in analgesic efficacy between the 2 study drugs. In fact, the

differences between the 2 treatment groups over time were so very small that a post-hoc power analysis indicated that a minimum of 1,700 additional patients would be needed to show a statistical difference, if it existed.

Ketorolac has been only rarely compared with other NSAIDs in the ED setting, and in the few published studies, has not been found to be superior to either ibuprofen, diclofenac, or indomethacin.^{8–11} In a retrospective study of ED patients in acute pain, Wright and colleagues found a single oral dose of 800 mg of ibuprofen and a single oral dose of 60 mg of ketorolac IM produced similar degrees of pain relief.⁸ In a study looking at pain relief in ureteral colic, Stein et al. found no difference between ketorolac and the NSAID diclofenac.⁹ In the treatment of pain in acute gouty arthritis, Shrestha et al. compared IM ketorolac and oral indomethacin and found no significant difference between the 2 groups.¹⁰

Turturro et al. compared IM ketorolac and oral ibuprofen in a group of 77 patients with musculoskeletal pain and concluded that these 2 NSAIDs had comparable efficacies.¹¹

Our study differs from these previously published investigations in several important ways. First, unlike the retrospective study by Wright et al.,⁸ ours was a prospective, randomized, double-blind trial. Second, unlike those of both Wright et al.⁸ and Stein et al.,⁹ whose ketorolac groups both had higher levels of pain than did the comparison groups, our treatment groups were comparable in their pretreatment pain intensity scores. Third, the study by Shrestha et al.¹⁰ used the Wong-Baker Faces Scale, which incorporates visual manifestations of pain, and may more directly measure the emotional components of pain.²¹ We used the NRS to emphasize the intensity dimension of pain,²² but further research is warranted to evaluate the effects of analgesics on ED patients' sensory, emotional, and behavioral responses to pain. Finally, whereas other studies limited their study population to patients with only one type of pain (e.g., ureteral colic, gout, musculoskeletal pain), our patients had pain from diverse etiologies, reflecting the broader population of ED patients who currently receive ketorolac for pain relief.

Despite the published literature, ketorolac continues to enjoy widespread use in the ED for an ever-increasing number of pain etiologies. One rationale for its use is its availability in parenteral form. However, our study failed to reveal any difference in efficacy between IM ketorolac and oral ibuprofen, even at early time points when peak analgesic effect would be expected from the IM route of delivery.

In our study, 40% of the patients continued to experience moderate to severe pain (NRS scores of 5–8) at 2 hours after treatment. While the frequencies of inadequate analgesia were similar in both the ibuprofen and ketorolac groups, few patients in either group received supplemental analgesics. We did not enroll patients who reported ex-

treme pain, that is, NRS scores of 9 or 10. Yet, even in patients with moderate to severe pain, NSAIDs do not generally appear to provide adequate analgesia. Furthermore, the underuse of supplemental analgesia suggests that inadequate treatment of pain remains an important issue for ED staff.

In postoperative patients, ketorolac has been found to be comparable to low- to moderate-dose opioids. This has, in part, created the impression that ketorolac is an unusually potent analgesic. As noted above, and as demonstrated in this study, however, ketorolac is not superior to ibuprofen in treating a variety of kinds of pain commonly encountered in the ED setting. Furthermore, ketorolac is much more expensive than ibuprofen. At our institution, a single dose of ketorolac, 60 mg IM, costs \$6.80, compared with ibuprofen, 800 mg orally, which is \$0.03, and morphine, 8 mg IV, which is \$0.48. We conclude that the widespread use of ketorolac for treating patients with moderate pain in the ED does not appear justified.

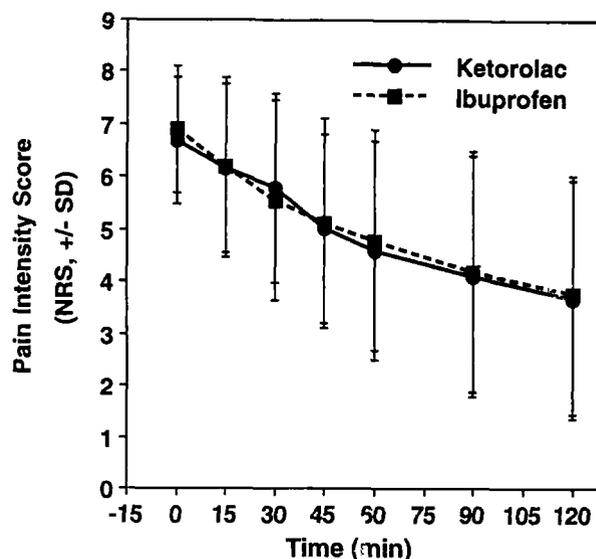
LIMITATIONS AND FUTURE QUESTIONS

There were several limitations to our study. First, a selection bias may exist because we used a convenience sample of patients. Analysis of the treatment groups however, shows that randomization was successful. A selection bias may also exist because we did not include patients with extreme pain or patients being treated in resuscitation rooms. Furthermore, we excluded patients with migraine headaches and sickle cell vaso-occlusive disease, because these patients typically are managed with antiemetics, opioid analgesics, or other medications that might confound the results.

Second, our patients were a heterogeneous group with different etiologies for their pain, some of which (e.g., radiculopathy) may not be responsive to NSAIDs. This may, in part, explain the large number of patients in our study who continued to experience moderate to severe pain at 2 hours after treatment. The majority of our patients had musculoskeletal etiologies for their pain. It is possible that any advantage of one drug over the other in the treatment of nonmusculoskeletal disorders was "swamped" by the evenness of response in the musculoskeletal group.

Our study was also limited in that we did not control for patients' undergoing other procedures (e.g., cast application, joint manipulation, immobilization) for their medical conditions that could have influenced their pain. However, a post-hoc analysis showed that there were almost equal numbers of patients in the 2 drug groups (17 in the ketorolac and 13 in the ibuprofen group) who received these types of treatments.

Ethical considerations precluded our study's having a group who received a placebo. As a result, we cannot assess whether the improvement in pain over time reflects



■ FIGURE 1. Intramuscular ketorolac vs oral ibuprofen. Mean (\pm SD) pain scores over time. NRS = numeric rating scale.

efficacy of both ibuprofen and ketorolac or was a placebo response. Additionally, we did not have a positive control group, for example, patients who received morphine. A more positive response in a morphine group would have demonstrated that our study design was sufficiently sensitive to detect differences in pain relief among groups, had they existed.²²

Future studies should address these limitations. Specifically, the impact of underlying etiology for the pain as a determinant of response to NSAID therapy, the influence of concurrent procedures on the perception of pain by the patient, and the relative impact of NSAID to opioid therapy for these conditions should be addressed.

CONCLUSIONS

This study directly compared IM ketorolac and oral ibuprofen in the treatment of ED patients experiencing moderate to severe pain from a variety of etiologies and found no significant difference. While ketorolac may be useful when a parenteral NSAID is required, because of its far greater cost, it should not routinely be used in place of other similarly effective but much less expensive oral NSAIDs when used with proper dosing.

The authors are indebted to the research nurses: Nel O'Neil, Linda Couts, Katherine Ley, and Deborah Frederick for their assistance in subject enrollment and data collection. They also thank the UCSF Research Center for Symptom Management for their assistance in statistical analysis of the data. The authors also acknowledge the nursing staff of the Emergency Department, San Francisco General Hospital, and thank Robert Brody, MD, Rhonda Nichols, RN, MS, Ed Lor, PharmD, Yong Liu, PharmD, and John Fazio, RN MS, for their assistance. Supported in part by grants from the Emergency Medicine Foundation and the Emergency Nursing Foundation and from the Academic Senate University of California, San Francisco.

■ REFERENCES

1. Bartfield JM, Kern AM, Raccio-Robak N, Snyder HS, Baevisky RH. Ketorolac tromethamine use in a university-based emergency department. *Acad Emerg Med.* 1994; 1:532-8.
2. Powell H, Smallman JM, Morgan M. Comparison of intramuscular ketorolac and morphine in pain control after laparotomy. *Anaesthesia.* 1990; 45:538-42.
3. Power I, Noble DW, Douglas E, Spence AA. Comparison of IM ketorolac trometanol and morphine sulphate for pain relief after cholecystectomy. *Br J Anaesth.* 1990; 65:448-55.
4. 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.* 1990; 10(suppl):40S-44S.
5. Spindler JS, Mehlich D, Brown CR. Intramuscular ketorolac and morphine in the treatment of moderate to severe pain after major surgery. *Pharmacotherapy* 1990; 10(suppl):51S-57S.
6. Stouten EM, Armbruster S, Houmes RJ, Prakash O, Erdmann W, Lachmann B. Comparison of ketorolac and morphine for postoperative pain after major surgery. *Acta Anaesthesiol Scand.* 1992; 36:716-21.
7. Buckley MM, Brogden RN. Ketorolac: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs.* 1990; 39:86-109.
8. Wright JM, Price SD, Watson WA. NSAID use and efficacy in the emergency department: single doses of oral ibuprofen versus intramuscular ketorolac. *Ann Pharmacother.* 1994; 28:309-12.
9. Stein A, Ben Dov D, Finkel B, Mecz Y, Kitzes R, Lurie A. Single-dose intramuscular ketorolac versus diclofenac for pain management in renal colic. *Am J Emerg Med.* 1996; 14:385-7.
10. Shrestha M, Morgan DL, Moreden JM, Singh R, Nelson M, Hayes JE. Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. *Ann Emerg Med.* 1995; 26:682-6.
11. Turturro MA, Paris PM, Seaberg DC. Intramuscular ketorolac versus oral ibuprofen in acute musculoskeletal pain. *Ann Emerg Med.* 1995; 26:117-20.
12. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. *Ann Rheum Dis.* 1978; 37:378-81.
13. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain.* 1986; 27:117-26.
14. Puntillo K, Weiss SJ. Pain: its mediators and associated morbidity in critically ill cardiovascular surgical patients. *Nurs Res.* 1994; 43:31-6.
15. Reading AE. A comparison of pain rating scales. *J Psychosom Res.* 1980; 24:119-24.
16. Huskisson EC. Measurement of pain. *Lancet.* 1974; 2:1127-31.
17. Kremer E, Atkinson JH, Ignelzi RJ. Measurement of pain: patient preference does not confound pain measurement. *Pain.* 1981; 10:241-8.
18. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate, severe? Grading pain severity by its interference with function. *Pain.* 1995; 61:277-84.
19. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Ann Emerg Med.* 1996; 27:485-9.
20. Todd KH. Clinical versus statistical significance in the assessment of pain relief. *Ann Emerg Med.* 1996; 27:439-41.
21. Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Pediatr Nurs.* 1988; 14:9-17.
22. Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD (eds). *Issues in pain measurement.* New York, NY: Raven Press, 1989, pp 391-403.