Intravenous Morphine Plus Ketorolac Is Superior to Either Drug Alone for Treatment of Acute Renal Colic

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Study objective: To study the efficacy of intravenous ketorolac, morphine, and both drugs in combination in reducing pain in acute renal colic.

Methods: We conducted a prospective, double-blinded, randomized controlled trial in an urban, teaching emergency department. Patients aged 18 to 55 years and with a clinical diagnosis of acute renal colic and a pain rating greater than 5 on a 10-cm visual analogue scale or at least "moderate pain" on a 4-category verbal pain scale were eligible for inclusion. Exclusion criteria were contraindication to nonsteroidal anti-inflammatory drugs or opiates, a history of drug dependence, presence of peritonitis, or analgesics within 6 hours of presentation. Patients received either morphine 5 mg at time zero and 5 mg at 20 minutes, ketorolac 15 mg at time zero and 15 mg at 20 minutes, or a combination of both. Primary outcomes were pain reduction and the need for rescue analgesia at 40 minutes.

Results: Of the 555 consecutive patients screened, 158 patients met inclusion criteria and 130 patients were randomized during 6 months. Mean difference in change in pain score (visual analog scale 40 minutes minus visual analog scale 0 minutes) between combination group and morphine group was 1.8 cm (95% confidence interval [CI] −3.3 to −0.1) and, compared to the ketorolac group, was 2.2 cm (95% CI −3.7 to −0.5); $P<.003$. Patients with combination therapy were less likely to require rescue morphine compared to the morphine group (odds ratio 0.2; 95% CI 0.1 to 0.7; $P=.007$).

Conclusion: A combination of morphine and ketorolac offered pain relief superior to either drug alone and was associated with a decreased requirement for rescue analgesia. [Ann Emerg Med. 2006;48: 173-181.]

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INTRODUCTION

Background

Renal colic often presents as an excruciating malady that afflicts 5% to 12% of individuals in industrialized nations at least once during their lifetime[1,2] and recurs in up to 50%. Family members have a 3-fold increased risk for urolithiasis.[3] Despite the dramatic presentation, the majority of stones pass spontaneously without requiring intervention.[4] Prompt and effective pain control is a critical priority in treating these patients. However, the most effective analgesic regimen has yet to be determined.[5]

Both nonsteroidal anti-inflammatory drugs and opioids provide pain relief in acute renal colic.[6–8] The preferred route of administration is intravenous (IV).[9–14] Opioids are cheap, effective, and titratable, but physicians have become wary of using them because of associated nausea,[15] vomiting, sedation, dizziness, respiratory depression, and hypotension.[16] Several authors recommend nonsteroidal anti-inflammatory drugs, particularly ketorolac (the only parenteral nonsteroidal anti-inflammatory drug available in the United States) as the first-line analgesic in renal colic.[5,6,9,11,14,17–23] Although rare, gastrointestinal bleeding and acute renal failure have been associated with ketorolac. However, recent reviews indicate that in short-term use and in typical doses, ketorolac poses little risk of renal failure[24] and does not increase the risk of surgical bleeding.[25,26] In a systematic review of 20 randomized controlled trials involving 1,613 patients, nonsteroidal anti-

Editor's Capsule Summary

What is already known on this topic

The ideal pain management strategy for renal colic is unknown. The relative value of opioids and nonsteroidal anti-inflammatory agents alone or in combination has not been fully characterized, particularly for morphine.

What question this study addressed

This randomized controlled trial of 130 patients with presumed renal colic compared intravenous morphine, intravenous ketorolac, and a combination of both agents to determine which strategy provided the most pain control with the fewest adverse effects.

What this study adds to our knowledge

Although morphine and ketorolac resulted in similar analgesia, the combination of both agents provided superior pain relief and resulted in less use of rescue analgesia compared with either agent alone. In comparison with morphine, combined therapy caused less nausea and vomiting.

How this might change clinical practice

Emergency physicians should consider the use of combined analgesia, using opioids and nonsteroidal anti-inflammatory agents in the initial approach to patients presenting with renal colic.

inflammatory drugs achieved greater reduction in pain scores and had fewer adverse effects when compared to opioids for renal colic.[27] These trials had limitations in dosage,[28] route,[14,22] or the choice of opioid (meperidine).[14,28,29] In addition, the concept of "balanced analgesia," ie, combining different groups of drugs to achieve sufficient analgesia through additive or synergistic effect with concomitant reduction in adverse effects, has been proposed in previous studies but was not found to be significant.[28]

IMPORTANCE

Gaps exist in the renal colic literature: ketorolac has yet to be compared with morphine, the preferred opioid for acute renal colic.[17] Morphine is 10 times more potent than meperidine [17,30,31] and is a standard for treating severe pain in emergencies.[19,32] Although the synergistic role of opioids and nonsteroidal anti-inflammatory drugs has been postulated in several other clinical settings,[33,34] it has not been demonstrated in acute renal colic. We designed a double-blinded randomized controlled trial to address these questions.

Goals of This Investigation

Our primary hypothesis was that combination of morphine and ketorolac would result in at least a 1-point reduction in a 10-cm visual analogue pain scale compared with the successive means. Our secondary objectives were to compare the need for and amount of rescue analgesia in each treatment group and the incidence and type of adverse effects of the study drugs.

MATERIALS AND METHODS

Study Design

We conducted a prospective, randomized, controlled, double-blinded, clinical trial comparing ketorolac, morphine, and a combination of both drugs for the treatment of acute renal colic.

Setting

The study was performed in the adult emergency department (ED) of a tertiary-care urban hospital with 68,000 annual ED visits during July 1, 2003, to January 15, 2004. Approval was obtained from the institutional Human Investigation Committee.

Selection of Participants

Consecutive patients presenting with flank pain to the ED were screened for inclusion. Those who met all the following criteria were eligible for inclusion: age between 18 and 55 years, clinical diagnosis of acute renal colic, and patient pain rating of 5 or more on 10-cm visual analogue scale or at least "moderate" pain on a 4-category verbal pain scale (none, mild/little/some, moderate, severe).

Acute renal colic was defined as abrupt onset of severe paroxysmal unilateral flank pain. Pain location could be anywhere from the flank down to the ipsilateral groin.

Patients were excluded from the study if they met any of the following criteria: (1) documented or suspected pregnancy, (2) breastfeeding, (3) contraindication to nonsteroidal anti-inflammatory drugs or opiates, (4) known renal dysfunction, (5) received analgesics within 6 hours before presentation, (6) history of bleeding diathesis, (7) confirmed history of peptic ulcer disease, (8) current use of warfarin, (9) history of drug dependence or current use of methadone, (10) peritonitis or presence of any peritoneal sign, (11) non–English speaking, or (12) previously enrolled in the study.

Patients older than 55 years were excluded because renal colic is less likely in this age group, and more worrisome differential diagnoses such as expanding abdominal aortic aneurysm need to be considered and definitively ruled out.[35]

Consent involved a 2-step process. The study was explained to the eligible patients, and informed consent was obtained by the treating physician. Patients were then asked to initial a 1-page bulleted information sheet. The information sheet highlighted only the salient features of the study in bold: (1) participation was voluntary; (2) the study involved 2 drugs, morphine and ketorolac; (3) potential adverse effects of each drug were listed; (4) both drugs worked well; and (5) the patient would be assigned to 1 of the 3 treatment groups. Once pain was relieved, written consent was obtained.

Patients with flank pain were screened by the triage nurse, and a clinical diagnosis of acute renal colic was made by the

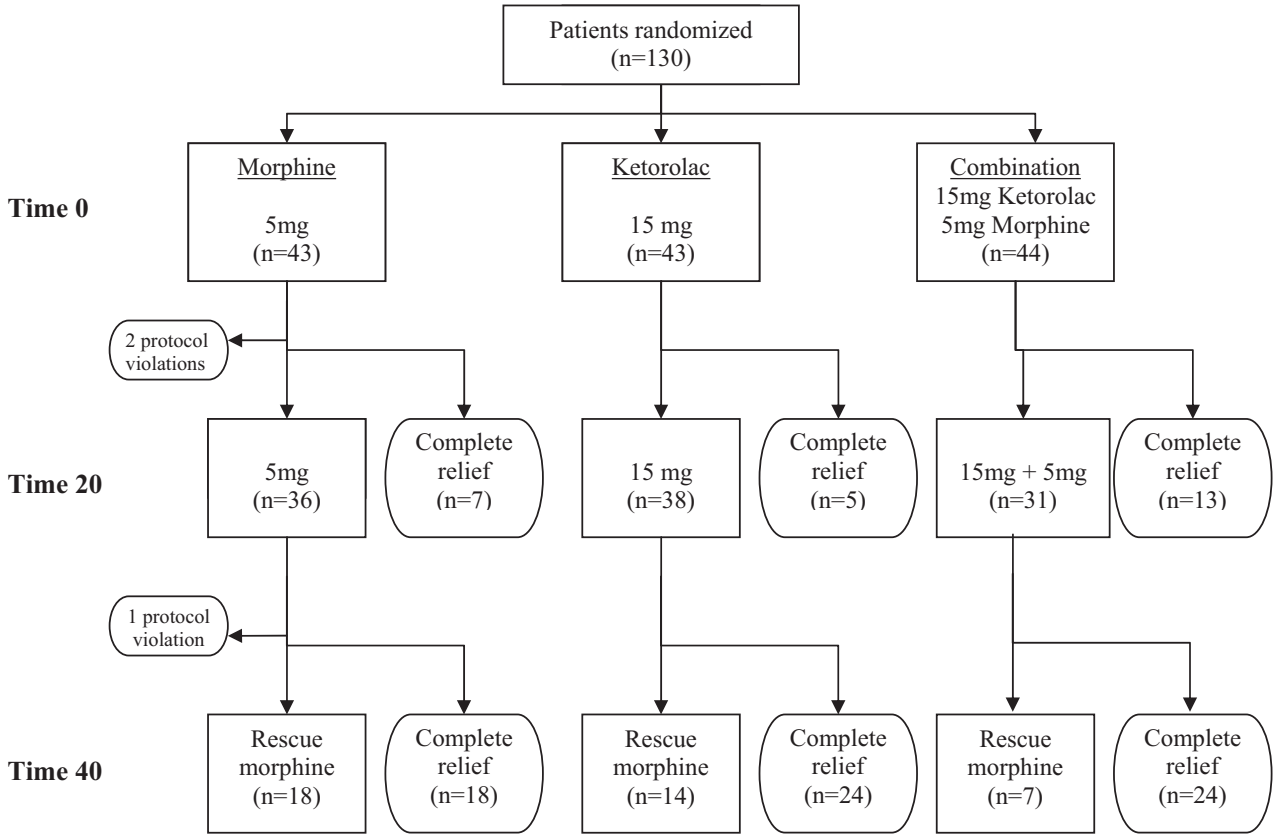

Figure 1. Dosages and administration of study drugs.

treating physician. Enrollment was carried out for consecutive patients 24 hours a day, 7 days a week during the study period. Objective criteria were sought to confirm the diagnosis. Urine was dipped in all patients to detect hematuria. Absence of hematuria in the presence of classic presentation, however, did not exclude a patient from the study.[36]

Patients were randomized into one of the 3 groups by using a permuted-blocks randomization scheme maintained by the hospital pharmacy (Figure 1). The premixed medications were prepared by the pharmacy and were kept in the Pyxis (a locked medication container) in the ED. All syringes were identical, and each patient received 2 injections (either a medication with placebo or the 2 medications combined) according to the time scheme outlined in Figure 1. Rescue analgesia, defined as 5 mg of IV morphine, was administered for persistent pain at 40 minutes and was titrated at the discretion of the ED attending physician. For our secondary outcome (use of rescue morphine), a satisfactory endpoint was little or no pain, as reported by the patient, visual analog scale less than 3, or when patient refused any more medication. Promethazine was used to treat nausea.

Computed tomography (CT) scan was considered the confirmatory study per standard practice at our institution. All patients without previous diagnosis of renal colic had the diagnosis of renal colic confirmed by CT scan. Patients with confirmed history of renal stones by documented CT scans or recovered stone and who presented with an identical episode of renal colic and hematuria did not receive imaging unless there was a suspicion of a different disease process. However, if such a patient had typical pain without hematuria or had intractable pain, a CT scan was obtained to confirm the diagnosis and location of the calculus. The CT scan was defined as positive if a stone was seen in the urinary collecting system. In the absence of stones, CT scan was considered positive if new unilateral stranding or hydronephrosis was read by the radiologist. All these findings were considered relevant only if present on the same side as the pain. For cases in which CT scan findings were inconclusive, the diagnosis was made if the patient reported passage of a stone or if a stone was recovered during subsequent surgery.

All patients, health care practitioners, and research associates were blinded to the study drug given or the allocation sequence. Pharmacists who were aware of the study medication played no role in enrollment. The code of the allocation sequence was revealed to the researchers only once recruitment, data collection, and data entry were complete.

Methods of Measurements

The treating physician prospectively collected information such as visual analogue pain scale scores, adverse effects, vital

signs, and results of urine dip, urine analysis, urine human chorionic gonadotropin, and CT scan (if done) by using a standard instrument developed for the study. Pain was measured on a 10-cm visual analogue scale administered at time 0 and 20 min and 40 min from administration of study drugs. Patients were blinded to their original scores. Patients were observed and asked about adverse events after administration of study medications, and responses were categorized as nausea/vomiting, sedation, respiratory depression, and dizziness. Any additional response was noted as "other" and explained.

The research assistant (S.R.V.) collected baseline demographic information such as age, sex, time of ED arrival, time of symptom onset, etc by using a retrospective medical record review. She reviewed the ED log sheet daily during the enrollment period. In cases in which patients were deemed eligible and were not enrolled, reasons for exclusion were identified from the record or the treating physician and recorded.

Outcome Measures

Our primary outcome was pain reduction as documented by changes in pain intensity scores at the end of 40 minutes. Secondary outcome measures were need for rescue analgesia at 40 minutes and the occurrence of adverse events.

With a minimum of 32 patients per group (total of 96), the study had the power to detect a difference in pain scores as small as 1 point between successive means, with 80% power and a 2-sided level of significance of 5%. The SD used for this calculation was 2.5 (approximated from the range of scores [10−1=9/4]. A minimum of 10% difference was thought to be clinically significant. A 10% reduction on visual analog scale translated to a 1-point difference. There is evidence in the literature that minimum clinically significant difference in pain scores on visual analogue scale is 13 mm (1.3 cm), or 13%.[37,38] Given our supposition, our sample size should identify clinically relevant differences in pain scores between the 3 groups.

Primary Data Analysis

An intent-to-treat analysis was performed using SPSS software (version 12.0; SPSS, Inc., Chicago, IL). Continuous variables were compared using analysis of variance and differences in proportions of discrete variables using χ^2 tests. The primary analysis involved a test for differences in mean self-reported pain intensity among groups using analysis of variance. Use of rescue morphine and presence of adverse events was considered a binomial variable, and adjusted odds ratios were calculated using χ^2 tests. Two-sided tests of significance were used throughout. Baseline characteristics were measured with descriptive frequencies.

RESULTS

During the 6-month study period, 555 consecutive patients presenting with flank pain were assessed for eligibility for enrollment in the study, and 130 patients were randomized to one of the 3 treatment arms. Four hundred twenty-five patients were excluded (Figure 2).

There were 3 protocol violations: 2 patients received rescue morphine *instead* of a second dose of study drug, and 1 patient received rescue morphine *in addition* to the second dose of study drug before the protocol ended. All 3 patients were in the morphine group.

Characteristics of Study Subjects

All 3 treatment groups were well matched for baseline characteristics (Table 1). Mean age of patients was 38 years (SD±10.6). Twice as many men as women were enrolled, which is consistent with natural patterns of the disease. Overall initial mean pain score on the visual analog scale was 8.8 cm (SD±1.5). Urine dipstick test was positive in 118 of 130 (91%) patients. Eighty-eight of 130 (68%) patients had a CT scan performed, of which 76 (86%) were positive for a stone. One patient with a negative CT scan result passed the stone in the ED. The diagnosis of acute renal colic was not confirmed in 4 of 130 (3%) patients who had both negative CT scans and negative urine dipstick test results (2 in the ketorolac group and 2 in the combination group). Three of 130 (2%) patients were admitted to the hospital for surgical intervention (2 in the ketorolac group and 1 in the combination group).

Main Results

Pain reduction was measured by change in pain intensity scores at the end of 40 minutes. Mean pain scores at the end of the protocol were 3.7 cm, 4.1 cm, and 2.0 cm in morphine, ketorolac, and combinations groups, respectively. There was no difference in reduction in mean pain scores between the morphine and ketorolac groups (mean 0.4; 95% confidence interval [CI] −1.1 to 2.0). Mean difference in change in pain score (visual analog scale 40 to visual analog scale 0 minutes) between the combination group and morphine group was 1.8 cm (CI −3.3 to −0.1) and, compared to ketorolac group, was 2.2 cm (CI −3.7 to −0.5); $P<.003$ (Figure 3).

Age, sex, initial pain score, and use of promethazine had no impact on pain reduction.

Thirty-nine of 130 patients (30%) required rescue morphine for adequate pain relief at completion of the protocol: 18 of 43 (42%) in the morphine group, 14 of 43 (33%) in the ketorolac group, and 7 of 44 (16%) in the combination group. Patients who received combination therapy were significantly less likely to require rescue morphine compared with the morphine group (odds ratio [OR] 0.3; 95% CI 0.1 to 0.7). More patients in the ketorolac group required rescue morphine compared with the combination group; however, this was not found statistically significant (OR 2.55; 95% CI 0.9 to 7.1). In addition, no statistically significant difference was found when need for rescue analgesia was compared between morphine and ketorolac (OR 0.7; 95% CI 0.2 to 1.6). The median dose of rescue morphine used was 0 mg, with interquartile ratio 5 mg, 5 mg, and 0 mg in morphine, ketorolac, and combination groups, respectively.

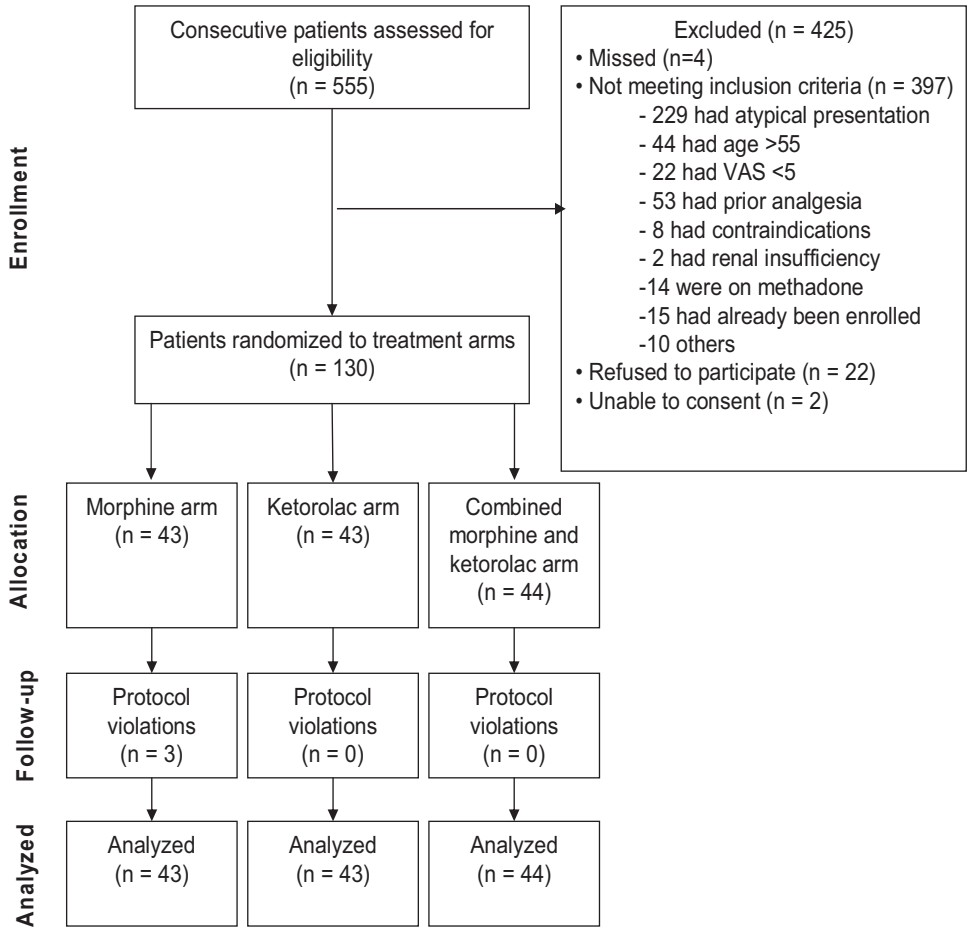

Figure 2. Progress of patients through randomized trial. *VAS*, Visual analog scale.

Table 1. Baseline patient characteristics of the 3 treatment groups (n=130).

Variable	Morphine, N=43	Ketorolac, N=43	Combination, N=44
Age, y			
Mean (±SD)	37.3 (±10)	39.3 (±9.9)	37.8 (±12)
Range, y	18–53	19–55	18–55
Sex			
Male, No. (%)	29 (67)	29 (67)	30 (68)
Female, No. (%)	14 (33)	14 (33)	14 (32)
Initial pain score			
Mean VAS (± SD)	8.7 (±1.6)	8.8 (±1.6)	8.9 (±1.4)
Urine analysis			
Positive blood, No. (%)	25/30 (83)	24/29 (83)	27/29 (93)
CT scans			
Positive, No. (%)	25/30 (83)	25/29 (86)	26/29 (89)

We noted that 13 of 44 (30%) patients who received combination therapy had their pain relieved without receiving the second dose of study drug. They got half the total recommended dose of study drugs (15 mg ketorolac and 5 mg of morphine). This was in contrast to 7 of 43 (16%) patients in the morphine group and 5 of 43 (11%) patients in the ketorolac group who had their pain relieved after the first dose of the study drug. The total dose per drug given during 20 minutes was less in the combination group compared with the other 2 groups suggestive of synergy. The combination group required less medication compared to the ketorolac group (OR 0.3; 95% CI 0.1 to 0.9).

The proportion of patients experiencing any adverse event was greater in the morphine group than either of the other groups (Table 2). Nausea or vomiting that developed after administration of study drug and before administration of the rescue morphine was recorded as an adverse effect. Use of promethazine did not differ among the 3 treatment groups (P=.3) or show any relation to the pain scores.

There were no significant differences between the groups with regard to changes in blood pressure, pulse rate, respiratory rate, or oxygen saturation. Of note, for 1 patient in the morphine group, saturation decreased to 92%, and he required oxygen. He was monitored until his oxygen saturation normalized and was discharged shortly thereafter. This patient had received 10 mg morphine and an additional 20 mg of

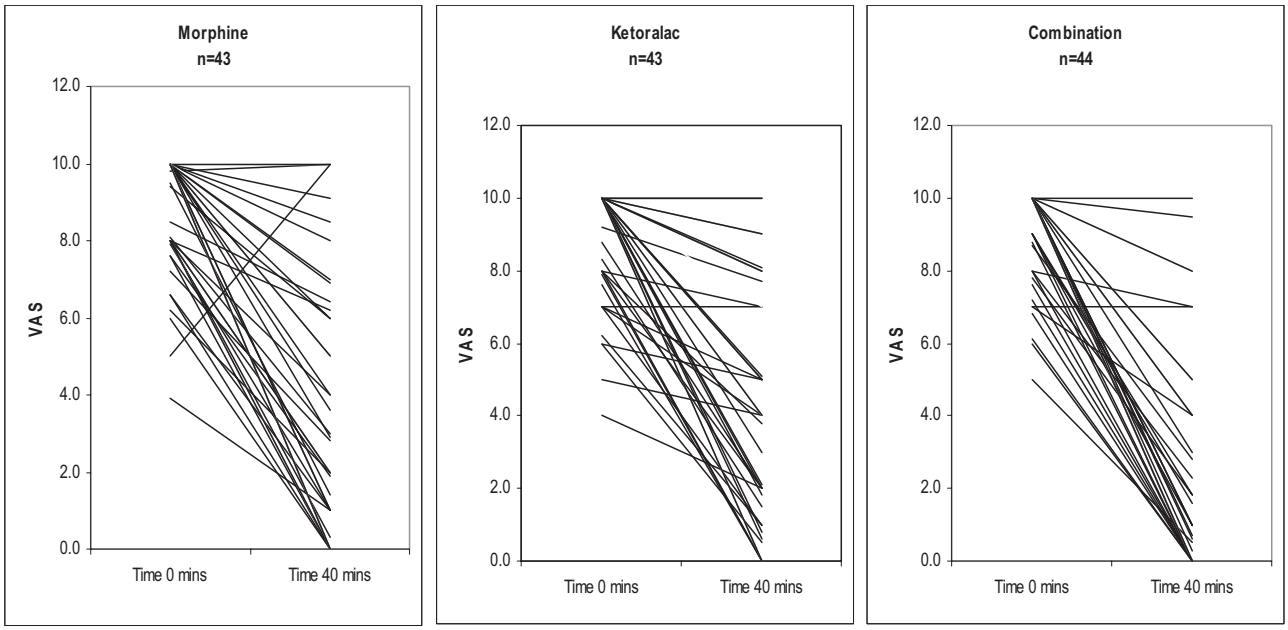

Figure 3. Before-and-after plots showing changes in pain scores in each group. Each plot consists of 2 1-way plots depicting by-subject pretreatment and posttreatment visual analog scale, with each subject's values linked by a line.

Table 2. Adverse outcomes in treatment groups.

Adverse Effect	Morphine, N=43	Ketorolac, N=43	Combination, N=44	Total, N=130
Nausea	7 (16%)	1 (2%)	2 (4%)	10 (13%)
Vomiting	2 (5%)	0	1 (2%)	3 (4%)
Itching	1 (2%)	0	0	1 (1%)
Rash	0	0	0	0
Dizziness	4 (9%)	0	1 (2%)	5 (6%)
Other	2 (5%)*	1 (2%)†	4 (9%)‡	7 (9%)

*One patient's O_2 saturation decreased to 92% after receiving 30 mg of morphine in 1 hour (protocol deviation). Another patient complained of rapid pulse rate.
†One patient complained of chills.
‡One patient complained of drowsiness, 1 complained of flushing in head and neck without any rash, 1 felt burning as medication was administered, and 1 patient's systolic blood pressure decreased by 30 points without changes in pulse rate.

rescue morphine because of intolerable pain within a 1-hour period (protocol deviation).

LIMITATIONS

The study contained several limitations. First, the use of promethazine for treating nausea may have confounded the pain scores reported by patients receiving this drug. It is difficult to determine whether relief from nausea may affect a patient's perception of pain or the overall level of discomfort. This concern arises because of a report on 40 patients that raised the possibility that metoclopramide, an antiemetic, may by itself relieve pain when used in renal colic patients.[39] However, this effect has never been validated in subsequent studies or been reported for promethazine. Second, even though adverse events were recorded according to a set of a priori defined events, they were recorded by the treating physician or nurses, introducing potential for bias. Also, we had no mechanism to record rare adverse events such as gastrointestinal hemorrhage and nephrotoxicity associated with ketorolac that might occur after discharge from the ED. Our recommendation to use combination therapy is therefore limited to previously healthy individuals younger than 55 years. Third, the dose of morphine used in this study was based on 0.1 mg/kg for an average weight patient. It was not recalculated for individual patient weight. The dose may therefore have been inadequate or more than adequate for certain patients. Finally, we enrolled patients on the basis of clinical diagnosis of renal colic. Although an ideal research methodology would call for a confirmatory study in every patient, our protocol reflected ED practice in the real-world setting in which treatment is often based on clinical diagnosis. We reanalyzed our data for only patients who had CT-proven kidney stones and found the same result.

DISCUSSION

Our study is the first to compare IV ketorolac with IV morphine for the treatment of acute renal colic using a randomized, controlled, double-blinded design. We found that 30 mg of IV ketorolac or 10 mg of IV morphine when used alone for treating renal colic was similar with respect to pain relief. Morphine has a clear advantage over ketorolac because it does not have a ceiling for analgesic effect that the latter does. On the other hand, morphine was associated with more adverse effects such as nausea and vomiting. We found that combining 30 mg IV ketorolac and 10 mg IV morphine provided more

effective pain relief, reduced the need for rescue analgesia, and was associated with fewer adverse effects.

These results are in contrast to the findings of previously published trials,[14,22,28,29] all of which made comparisons with meperidine. Sandhu et al[29] compared 30-mg intramuscular (IM) ketorolac with 100 mg of IM meperidine in a double-blinded study of 76 patients. They found the ketorolac group to have better pain relief, fewer adverse effects, and fewer requirements for rescue analgesia compared with the meperidine group. In 1996, Cordell et al[28] reported that 60 mg of ketorolac is superior either alone or in combination (ketorolac with meperidine) compared with 50 mg IV meperidine alone. However, higher-than-recommended doses of ketorolac and lower-than-minimum weight-based dose for meperidine were used in the study. This, combined with the fact that it was a pharmaceutical company–sponsored trial, made some view the results with skepticism.[7] In 1999, Larkin et al[14] attempted to resolve some of these issues by comparing 60 mg of IM ketorolac with a weight-adjusted dose of IM meperidine. They concluded that ketorolac was more efficacious than meperidine in the treatment of renal colic. They also found that patients in the ketorolac group went home earlier than those in the meperidine group, reducing overall cost of treatment.

Unlike the findings published in the above trials, ours showed no difference in pain relief or use of rescue morphine between morphine and ketorolac when used alone. In our protocol, we controlled for factors that we identified as possible confounders in the previous trials. Patients were enrolled consecutively instead of by convenience.[14,28,29] Only 4 eligible patients were missed.

Second, we chose to compare ketorolac with morphine, a standard opioid for severe pain. Morphine is about 10 to 15 times more potent than meperidine. In addition, it has a less troublesome adverse effect profile than meperidine.[17] Although one may argue that both medications can be titrated to achieve the desired analgesic effect, more meperidine is required compared with morphine to obtain a given analgesic endpoint. The higher dose causes more adverse effects for the same analgesic effect achieved by morphine. Also, meperidine is more lipid soluble, leading to rapid concentration in the central nervous system and therefore has more abuse potential. For these reasons, morphine is a preferred opioid for treating severe pain in most EDs.

Finally, we used comparable US Food and Drug Administration–approved doses of each drug. The US Food and Drug Administration–approved dose for ketorolac is 15 to 30 mg IV or 30 to 60 mg IM per dose.[40] Our study patients received 30 mg ketorolac during 20 minutes. The recommended dose of IV morphine for moderate to severe pain in adults is 0.05 to 0.1 mg/kg every 3 to 4 hours, which, for an average patient of 70 kg, is 5 to 7 mg. Repeated smaller doses are preferred to an initial large bolus dose.[41] Our protocol allowed patients to receive 2 doses of 5 mg, for a total of 10 mg of morphine within 20 minutes.

Our clinical observation is in line with the synergism between nonsteroidal anti-inflammatory drugs and opioids that has been demonstrated in animals.[42–44] The clinical utility of this synergism has been demonstrated in postoperative settings.[33,34,45,46] The role of nonsteroidal anti-inflammatory drugs in renal colic was elucidated when prostaglandins were found to play an important role in pathogenesis of ureteral pain. Ureteral obstruction stimulates the release of prostaglandin E_2 in the renal medulla. Prostaglandin E_2 causes ureteral contractility, increases renal blood flow, and increases pressure in the renal pelvis, thus exacerbating pain.[47] Nonsteroidal anti-inflammatory drugs interrupt this vicious cycle by inhibiting prostaglandin synthesis, resulting in reduced ureteral pressures, decreased contractility and inflammation, and, thereby, less pain.[48] The mechanism for synergy with opioids is not yet clear. Maves et al[49] hypothesized that ketorolac may have a central modulatory effect on opioid pharmacology, and the synergistic effect may be separate from its peripheral anti-inflammatory properties.

In Retrospect

We could have used 30 mg of ketorolac as the loading dose, followed by a placebo dose, which is more comparable to usual practice in which a full 30-mg dose of ketorolac is used more often than a 15-mg dose. One may argue that by splitting the dose, the best analgesic effect of ketorolac was not achieved during the study period that the patient was observed. However, the dosage we used is consistent with PDR recommendations. At the time, we had decided to split the 30-mg dose because we considered it unethical to give a placebo dose to a patient who we assumed had severe pain, and we thought that comparing a full 30-mg dose of ketorolac with a 5-mg dose of morphine would not be a fair comparison.

We would have liked to use weight-based dosages of morphine. Because only 11% of patients in the morphine group compared with only 16% in the ketorolac group achieved pain relief at time 20, we believe that 5 mg of morphine and 15 mg ketorolac are inadequate initial doses for these drugs. Comparing 0.1 mg/kg morphine and 30 mg ketorolac as initial doses versus a combination of both drugs will yield a better comparison.

In summary, acute renal colic is a common presenting patient complaint in the ED. Our results demonstrate that patients who are treated with a combination of ketorolac and morphine experience greater pain relief and fewer adverse effects and require less rescue analgesia than patients treated with either agent alone, which may affect their overall stay in the ED (additional charts comparing pain scores at 0 minutes, 20 minutes, and 40 minutes as well as change in pain scores for patients with CT-proven kidney stones, are shown in Figures E1-E4, available online at www.annemergmed.com).

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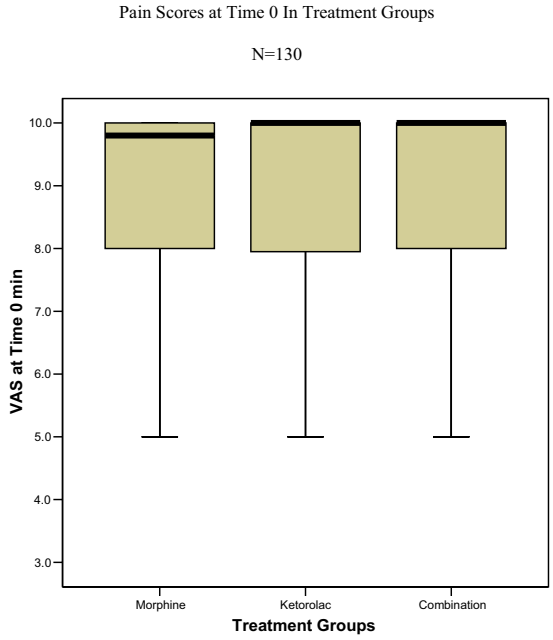

Figure E1. Pain scores at time 0 in treatment groups.

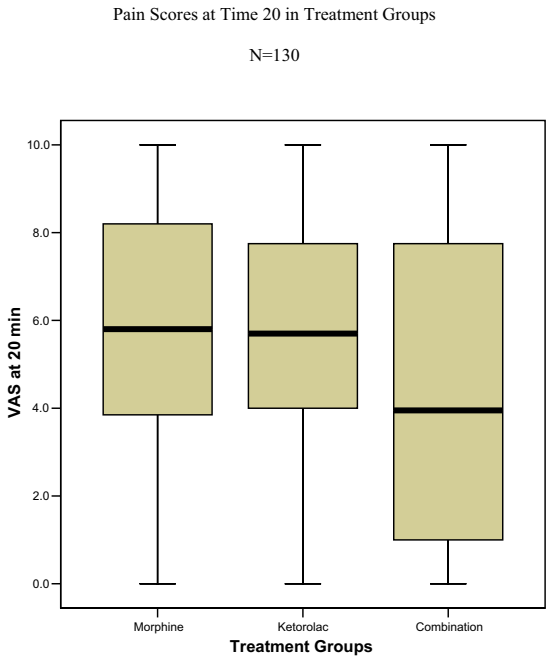

Figure E2. Pain scores at time 20 in treatment groups.

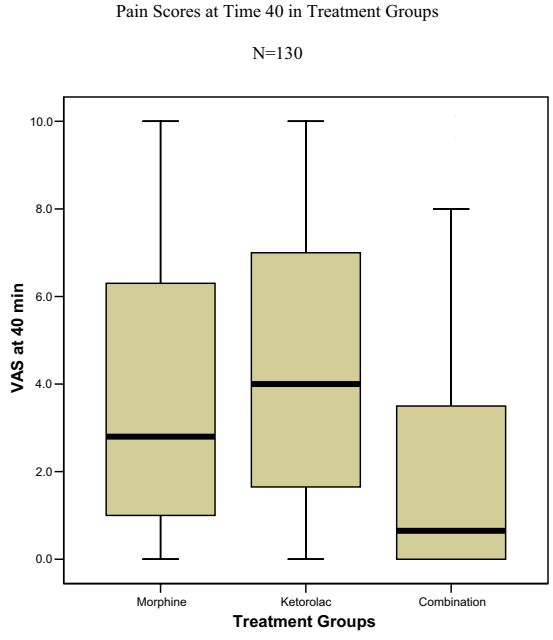

Figure E3. Pain scores at time 40 in treatment groups.

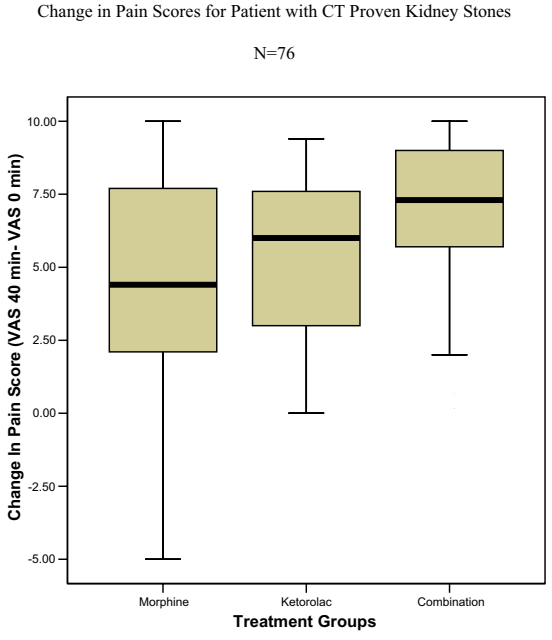

Figure E4. Change in pain scores for patient with CT-proven kidney stones.