Maine Medical Center
Department of Emergency Medicine
Journal Club Summary Template

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Article Citation: Safdar B. et al. Intravenous Morphine Plus Ketorolac Is Superior to Either Drug Alone for Treatment of Acute Renal Colic. Ann Emerg Med. 2006 Aug; 48(2): 173-81.
Country(ies): United States, Yale University School of Medicine
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Purpose
Research Question(s): Does the combination of IV morphine and IV ketorolac work better to improve pain in acute renal colic than either drug alone? i.e., do they have a synergistic effect? ☐ None Stated
Hypotheses: The combination of ketorolac and morphine would better control pain than either drug alone, and they would exhibit a synergistic effect. Together, they would at least result in a 1-point reduction on a 10cm visual analog pain scale ☐ None Stated
Study Purpose: There was, prior to this study, a lack of literature comparing ketorolac with morphine for acute renal colic, and this study aimed to fill that gap.

Methods
Study Design: Prospective, double-blinded, randomized control trial
Outcome(s) ***[or Dependent Variable]:*** pain score was primary outcome. Secondary outcome was the need for, and amount of, rescue analgesia for each group. They also looked at any adverse effects of the study drugs.
Intervention ***[or Independent Variable]:*** morphine, ketorolac, or both, provided for acute renal colic pain
Ethics Review: ☐ IRB Review ☐ IACUC Review ☐ Other: Approved by the institutional Human Investigation Committee ☐ None Stated
Research Setting: Adult emergency department of a tertiary care urban hospital with 68,000 annual ED visits.

Study Subjects:

Inclusion Criteria: patients aged 18-55 with clinical diagnosis of acute renal colic pain rating greater than 5 on a 10cm visual analog scale or at least moderate on a 4 category pain scale (none, mild, moderate, severe).

Patients with flank pain were screened by triage nurse for possibility of enrollment. Physician then used objective criteria to help confirm diagnosis of renal colic. Urine was dipped in all patients to detect hematuria. Absence of hematuria in setting of classic presentation did not exclude patients from the study. All patients without previous diagnosis of renal colic had diagnosis confirmed by CT scan. For patients with previous diagnosis of renal stones and hematuria, imaging was not obtained unless other medical process was thought to be occurring. If patient had typical pain without hematuria in setting of known renal colic in the past, CT scan was obtained to confirm diagnosis. If no stone seen on CT, it was still considered a positive test if new unilateral stranding or hydronephrosis was seen on the same side as the pain. If inconclusive CT scan, patients were enrolled in the trial if the patient reported passage of a stone or if there was a stone removed during subsequent surgery.

Exclusion Criteria: history of drug dependence or current use of methadone, presence of peritonitis, if they received analgesics within 6 hours of presentation, documented or suspected pregnancy, breastfeeding, known renal dysfunction, history of peptic ulcer disease, current use of warfarin, non-English speaking, or age > 55

Study Interventions:

Study Groups: Patients were randomized into one of three groups (morphine, ketorolac, or combination) by using a randomization scheme maintained by the hospital pharmacy.

Figure 1:
Each patient received two injections: either morphine 5 mg plus placebo if in morphine only group, ketorolac 15 mg plus placebo in ketorolac only group, or both morphine 5 mg and ketorolac 15 mg in the combination group. Patients in all 3 groups were allowed to receive promethazine for nausea, although this wasn't standardized across all three groups.
Patients were then assessed for resolution of pain at time 20 minutes since initial drug administration. If pain inadequately achieved at time 20 minutes, the morphine group received an additional 5 mg of morphine, ketorolac group an additional 15 mg of ketorolac, and the combo group an additional 5 mg of morphine and 15 mg of ketorolac.
The patients requiring additional analgesia at time 20 minutes were then reassessed at time 40 minutes since initial drug administration, and the need for rescue morphine due to inadequate pain control was assessed.

130 total patients enrolled in study.
43 in morphine only group
43 in ketorolac only group

44 in combination group

Instruments/Measures Used:
Patients were asked to rate their pain on a 10cm visual analog pain scale, and pain measurements were collected at time zero (prior to drug administration), time 20 minutes and 40 minutes after drug administration. Adverse effects of medications were also reported by patients. The need for rescue analgesia at 40 minutes was also measured.

Data Collection:

Data Analysis:

***A priori* sample size calculation?** ☐ Yes ☐ No ☐ Not Described ☐ N/A
Study was appropriately powered as they estimated there would need to be a minimum of 32 patients per study group to detect a difference in pain scores of at least 10% with 80% power, and a 10% reduction in pain was thought to be clinically significant.

Statistical analyses used:
Mean self-reported pain intensity among groups were compared using analysis of variance.
Use of rescue morphine and drug adverse events were compared by calculating odds ratios using chi square tests.

Adjustment for potential confounders? ☐ Yes ☐ No ☐ Not Described ☐ N/A
If yes, list:

Results

Study participants: 555 consecutive patients presenting with flank pain were assessed for eligibility, and 130 of these patients were eventually included in the study and randomized to one of the three groups. Mean age of study participants was 38, twice as many men as women. Urine positive for blood in 118 of 130. 88 had a CT scan performed , of which 76 had confirmed stone. Four patients had both negative CT for renal stone and urine dipstick negative for blood

Brief answers to research questions *[key findings]:*
Mean pain scores at the end of the 40-minute protocol were 3.7 cm, 4.1 cm, and 2.0 cm for the morphine, ketorolac, and combination groups, respectively. Mean difference in pain score change between the combination group and morphine group was 1.8 cm, and mean difference between the combination group and ketorolac group was 2.2 cm.

Figure 1: In the morphine group, complete relief of pain was reported at time 20 minutes since initial administration of 5 mg of morphine in 7/43 patients. In the ketorolac group, at 20 minutes, complete relief of pain was reported in 5/43 patients. In the combination group, complete resolution of pain was reported in 13/44 patients.

The patients reporting inadequate pain control at 20 minutes and requiring a second dose of their study drug were then reassessed at time 40 minutes since initial administration of the drug. 18/36 patients in the morphine group required rescue morphine, 14 of the 38 patients in the ketorolac group required rescue morphine, and 7 of the 31 patients in the combo group required rescue morphine.
Patients who received combo therapy were significantly less likely to require rescue morphine, and more patients in the ketorolac group required rescue morphine compared with the combo group, however this was not statistically significant.

Adverse events, particularly nausea and vomiting, were higher in the morphine only group than the other two groups. There were no significant differences in vital sign changes amongst the three groups after medication administration.

Overall, results showed that there appears to be synergism in the analgesic effects of morphine and ketorolac combined, less adverse events, and less rescue analgesia required than either drug alone.

Additional findings:

Limitations:
Use of promethazine, as this may have confounded the pain scores reported and was not standardized across each group.
No way of recording GI bleeding or nephrotoxicity associated with the ketorolac that might occur after ED discharge.
Only studied patients between 18 and 55.
Standardized dose of 5 mg of morphine given to each patient, even though the recommended dose is 0.1 mg/kg. Doses of morphine may have been inadequate or more than adequate in certain patients.
Study enrolled patients based on clinical diagnosis of renal colic, not everyone got confirmatory testing.
Thought that 15 mg of ketorolac and 5 mg of morphine may be inadequate doses, and loading patients up front with 30 mg ketorolac and 0.1 mg/kg morphine may be studied in future.
The study defined the endpoint of needing or not needing rescue morphine as “patient reporting little or no pain, visual analog scale less than 3, or when the patient refused any more medication.” The study however, didn’t define how they reached an endpoint at 20 minutes to decide who would or would not receive a second dose of the study drug.

Clinical Implications
Applicable? Yes, as we see many patients in our ED with renal colic pain. **Feasible?** Yes, morphine and ketorolac are drugs that we give on a daily basis in the ED. **Clinically relevant?** Yes **Comments:**

Level of evidence generated from this study
☐ Ia: evidence obtained from meta-analysis of randomized controlled trials ☒ Ib: evidence obtained from at least one randomized controlled trial ☐ IIa: evidence obtained from at least one well-designed, controlled study without randomization ☐ IIb: evidence obtained from at least one other type of well-designed quasi-experimental study ☐ III: evidence obtained from a well-designed, non-experimental study ☐ IV: expert committee reports; expert opinion; case study; case report