CJEM JOURNAL CLUB

Ketorolac and morphine for analgesia in acute renal colic: Is this combination more effective than monotherapy?

Clinical question

For patients with a suspected diagnosis of acute renal colic, does combination intravenous (IV) ketorolac and morphine provide better analgesia than either agent alone?

Article chosen

Safdar B, Degutis LC, Landry K, et al. Intravenous morphine plus ketorolac superior to either drug alone for treatment of acute renal colic. Ann Emerg Med 2006;48:173–81.

Objective

To determine if the combination of IV ketorolac and morphine is superior to either agent alone for analgesia in acute renal colic.

Population studied

Patients were eligible if they were 18–55 years of age, had a clinical diagnosis of acute renal colic, and rated their pain as ≥ 5 out of 10 on a visual analogue scale (VAS), or as moderate or severe on a 4-category verbal pain scale (i.e., none, mild, moderate or severe). Patients were excluded if they

- had documented or suspected pregnancy;
- were breastfeeding;
- had a contraindication to nonsteroidal anti-inflammatory drugs (NSAIDS) or opioids;
- had known renal dysfunction;
- had received analgesic within 6 hours of presentation;
- had a history of bleeding diathesis;
- were currently using warfarin;
- had a history of drug dependence or were currently using methadone;
- had peritonitis or the presence of any peritoneal signs;
- did not speak English; or
- had been previously enrolled in the study.

Study design

Eligible patients who consented to be in the study were blindly randomized by a permuted-blocks randomization scheme into 1 of 3 groups. The first group received 5 mg of morphine alone, the second group received 15 mg of ketorolac alone, and the third "combination" group received 15 mg of ketorolac plus 5 mg of morphine. At 20 minutes, if the patients were still having discomfort they were given a second dose of the respective medication for each group. At 40 minutes, patients with persistent pain received 5 mg of morphine.

Outcomes measured

The primary outcome measured was a clinically significant reduction in pain intensity at 40 minutes. The secondary outcomes were the need for rescue analgesia at 40 minutes and the occurrence of adverse events.

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Potential bias

There were no indications of potential bias in the design or conduct of this trial with respect to group allocation, baseline prognostic factors, co-intervention or loss to follow-up.

Results

During the 6-month study period, 555 consecutive patients were assessed for eligibility and 130 were eventually randomized to 1 of the 3 treatment arms. There were 425 patients excluded because they either did not meet the inclusion criteria (397), were missed (4), refused to participate (22) or were unable to give consent (2). All 130 randomized patients were included in the final analysis according to intention-to-treat despite 3 protocol violations in the morphine-only group.

The mean pain score on a VAS for patients on presentation was 8.7 for those receiving morphine, 8.8 for the ketorolac group and 8.9 for the combination group. The mean pain scores at the end of 40 minutes were 3.7 cm, 4.1 cm and 2.0 cm in the morphine, ketorolac and combination groups, respectively. There was no difference in reduction of pain intensity between the morphine- and ketorolac-only groups at 40 minutes.

Primary outcome

Change in pain score

- Combination versus morphine = 1.8 cm (95% confidence interval [CI]: –3.3 to –0.1).
- Combination versus ketorolac = 2.2 cm (95% CI: –3.7 to –0.5).

A 1.3-cm change in VAS is generally considered to be clinically significant.[1,2]

Secondary outcomes

Significantly fewer patients in the combination group required rescue analgesia, compared with the morphine group (odds ratio [OR] 0.3, 95% CI 0.1–0.7). More patients required rescue analgesia in the ketorolac group than in the combination group; however, this was not statistically significant (OR 2.55, 95% CI 0.9–7.1). Of the patients in the morphine group, 21% experienced nausea and vomiting, versus 2% and 6% in the ketorlac and combination groups, respectively.

Conclusion

The authors concluded that using ketorolac and morphine together for analgesia in acute renal colic provided more pain relief and reduced the need for rescue analgesia, compared with either agent alone.

Commentary

Renal colic is a very common problem presented to the emergency department (ED). Pain can be quite significant and requires a rapid and effective medical response. Emergency physicians use a multitude of medications for analgesia in renal colic.[6] Opioids have been the traditional first-line therapy for patients suffering from acute renal colic. The 2 most common opioids studied are morphine and meperidine. A randomized controlled trial (RCT) comparing 10 mg of IV morphine with 100 mg of IV meperidine found they were equally effective.[3] However, because of meperidine's greater abuse potential and increased side-effect profile, the authors of the study recommended morphine over meperidine.

NSAIDs are reasonable alternatives to opioids. A recent Cochrane Review of RCTs comparing opioids and NSAIDs in acute renal colic found that both drugs reduced patient-reported pain scores.[4] Additionally, patients receiving NSAIDs were less likely to require rescue analgesia and had a reduced incidence of vomiting, compared with patients receiving opioids. However, the authors do admit that once patients were discharged from the hospital they had no mechanism in place to detect the uncommon but serious side effects, such as gastrointestinal bleeding and renal impairment, attributed to NSAIDs.

The paper by Safdar and colleagues is the first to compare morphine and ketorolac directly, although other studies have compared ketorolac to opioids other than morphine. An RCT comparing ketorolac and meperidine for analgesia in acute renal colic found the combination of both drugs resulted in better pain control than meperidine alone.[5] Interestingly, ketorolac alone was found to have equal efficacy as the combination group in pain relief.

Safdar and colleagues compared 2 agents, morphine and ketorolac, alone and in combination to determine which would offer the better analgesia. They found that the combination of these 2 drugs resulted in greater pain reduction than either agent alone. Patients in the morphine group were more likely to require rescue analgesia and experience vomiting than patients in the combination group.

While this RCT was well designed and well conducted, the authors admit to some limitations. First, morphine dosing was not weight-based, which may have resulted in over- or under-dosing. Second, the recommended single dose of IV ketorolac in an adult under age 65 years is

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30 mg.[6] The initial loading dose of ketorolac used in this study was only 15 mg, which may have reduced its effectiveness.

Despite these limitations, combination therapy provided greater pain relief for patients, with fewer side effects. Not only does this regimen have obvious benefits for pain management, it may also reduce ED length of stay. Emergency physicians should consider the use of this combination regimen in the treatment of renal colic pain.

Competing interests: None declared.

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