Maine Medical Center
Department of Emergency Medicine
Journal Club Summary Template

Date: 4/22/2021	**Presenter Name: Jennifer Zacharia**

Article Citation:
Eidinejad L. et al. Comparison of intravenous ketorolac at three doses for treating renal colic in the emergency department: A noninferiority randomized controlled trial. Acad Emerg Med. 2020 Dec 28.

Country(ies): Iran, Canada

Funding Source(s): Tehran University of Medical Sciences

☐ None Stated

Purpose

Research Question(s):

1. Are lower doses of IV ketorolac (10 mg or 20 mg) as effective in acute pain management for renal colic compared to a 30 mg dose?
2. Do lower doses of IV ketorolac (10 mg or 20 mg) have fewer adverse effects compared to a 30 mg dose?

☐ None Stated

Hypotheses:
Noninferiority hypothesis: 10 mg and 20 mg doses of ketorolac are noninferior to a 30 mg dose of ketorolac in acute pain management for renal colic.

☐ None Stated

Study Purpose:
To compare the analgesic efficacy and adverse effects of three doses of IV ketorolac in patients with renal colic to determine whether the 10 mg and 20 mg doses are as effective as the 30 mg dose for pain management with fewer adverse effects.

Methods

Study Design: Prospective, double-blind, randomized clinical trial

Outcome(s) *[or Dependent Variable]:*

1. Primary outcome:
   - Pain reduction at 30 minutes after ketorolac administration
2. Secondary outcomes:
   - Pain reduction at 15, 45, and 60 minutes after ketorolac administration
   - The need for rescue analgesia at 30 minutes
   - The development of adverse effects (headache, dizziness, nausea, vomiting, dyspepsia, pruritus)

Intervention *[or Independent Variable]:*
Three doses of IV ketorolac (10 mg, 20 mg, or 30 mg)

Ethics Review: ☒ IRB Review ☐ IACUC Review ☐ Other: ☐ None Stated

Research Setting:
The study was conducted in three academic hospitals affiliated with Tehran University of Medical Sciences (Imam, Shariati, and Sina Hospitals with 70,000, 40,000, and 50,000 annual ED visits, respectively).

Study Subjects:
Adult patients presenting to the ED with renal colic

Inclusion Criteria:
Adult patients with acute severe flank pain or abdominal pain were included if it was considered to be due to renal colic according to the emergency physician's gestalt. The pain could be with or without other signs and symptoms (e.g. frequency, dribbling, and CVA tenderness) and/or laboratory studies such as microhematuria.

Exclusion Criteria:
Age > 65 years, active peptic ulcer disease, acute GI bleeding, renal or hepatic insufficiency, history of NSAID hypersensitivity, pregnancy or breastfeeding, unstable vital signs (SBP < 90 or > 180 mmHg, HR < 50 or > 150 bpm), and patients who had already received analgesics in the past 24 hours.

Study Interventions:
Three doses of IV ketorolac (10 mg, 20 mg, or 30 mg) were given to adult patients presenting to the ED with renal colic

Study Groups:
Three equal 55-patient groups receiving either 10 mg, 20 mg, or 30 mg of IV ketorolac

Instruments/Measures Used:
Pain was assessed using a visual analog scale (VAS), a 100-mm horizontally positioned line with two points of ‘‘no pain’’ and ‘‘the worst possible pain’’ at either end.

Data Collection:
- A 10 mg, 20 mg, or 30 mg dose of IV ketorolac was administered to the patient in a method that blinded the patient, treating physician, and nurse administering the medication.
- No other medications were given to the patients during the 1-hour study period.
- Vital signs, VAS scores, and adverse effects were recorded at baseline and after 15, 30, 45, and 60 minutes of IV ketorolac injection.
- The need for rescue treatment at 30 minutes was also assessed. If patients still required additional pain medications at 30 minutes, they would receive 0.1 mg/kg IV morphine sulfate as a rescue analgesic. The patients who received morphine rescue treatment were not assessed further in regard to pain intensity and adverse effects.

Data Analysis:

***A priori* sample size calculation?** ☒ Yes ☐ No ☐ Not Described ☐ N/A

For sample size calculation, they performed a power analysis by noninferiority margin of 1.51 significant increase in pain score, a standard deviation of 2.7, both measured by numerical rating scale on a scale of 0 to 10, power of 80%, and a two-sided 95% confidence interval. This analysis resulted in a sample size of 55 patients per group (165 patients in total).

Statistical analyses used:

- Visual analog scale measures at different times were compared using Freidman k–related samples.
- Categorical data were analyzed using chi-square test.
- A p-value of <0.05 was considered statistically significant.
- Noninferiority analysis was performed for the primary study outcome for all randomized patients (intention to treat). They calculated a two-sided 95% CI for the mean VAS score (measured on a scale of 0-100 mm) in each group. A 15 mm difference in VAS score was considered the minimum clinically important difference. If the upper limits of CI for the 10 mg and 20 mg groups were higher than the noninferiority limit (> 15 mm above the mean VAS score in the 30 mg group) the noninferiority hypothesis would be rejected.

Adjustment for potential confounders? ☒ Yes ☐ No ☐ Not Described ☐ N/A

If yes, list:

- Randomization: Randomization was performed based on a sequence generated by Web-based software (www.sealedenvelope.com) with a 1:1:1 allocation and a block size of 6. Every single code and its relevant ketorolac dose (10, 20, and 30 mg) were written on a piece of paper that was placed in an opaque envelope. The envelopes were numbered consecutively indicating the order in which they must be opened.
- Double-blinding: A research nurse who was not aware of the study protocol and instructed not to reveal the ketorolac dose opened the sealed envelopes and prepared the ketorolac dose according to the instructions. This was performed by adding normal saline solution to ketorolac and diluting it to 10 ml in identical syringes and handing it in to in-duty nurse for administration. By this method, neither the patient nor the treating physician and in-duty nurse was aware of the assigned group.
- No other medications were given to the patients during the 1-hour study period.
- The patients who received morphine as rescue treatment at 30 minutes were not assessed further in regard to pain and adverse effects.

Results

Study participants:

165 subjects; 55 subjects in each group (receiving 10 mg, 20 mg, or 30 mg IV ketorolac) **(Figure 1)**
Mean age 40.40, 74.5% male **(Table 1)**

Brief answers to research questions *[key findings]:*

1. Ketorolac at 10 mg, 20 mg, and 30 mg doses produce similar analgesic efficacy in renal colic
   - All groups had significant response to ketorolac compared to baseline pain scores (p<0.001) **(Figure 3)**
   - There was no statistically significant difference in the trends of VAS scores between the three groups (p<0.05) **(Table 2)**
     - Median VAS score from baseline to 30 minutes:

10 mg group: 90 → 40
20 mg group: 80 → 40
30 mg group: 90 → 40

- The 10 mg and 20 mg doses of ketorolac are not inferior to the 30 mg dose **(Figure 4)**

2. There was no statistically significant difference in the need for rescue analgesia between the groups (p=0.775) **(Table 3)**
   - 10 mg group: 29.1%
   - 20 mg group: 34.6%
   - 30 mg group: 29.1%
3. There was no statistically significant difference in rate of adverse effects between the groups (p=0.335) **(Table 3)**
   - The rate of adverse effects was lowest in the 10 mg group (36.4%) and highest in the 30 mg group (45.5%), but this was not statistically significant (p=0.335)
   - Adverse effects included nausea/vomiting (most common), headache, dizziness, and dyspepsia

Limitations:

- Risk of selection bias since patients were recruited during the three investigators' shifts rather than consecutive patients presenting to the ED, but the risk is low since the shifts were random
- The inclusion of patients with the diagnosis of renal colic was based on the emergency physicians' gestalt. Not all patients underwent CT scan to confirm urolithiasis as the cause of pain.
- The study did not evaluate the analgesic or adverse effects of ketorolac beyond 1 hour.
- The power for secondary outcomes (e.g. adverse effects) was not calculated in this study.
- The most common adverse effect of nausea/vomiting may be attributed to renal colic in addition to ketorolac.

Clinical Implications

Applicable? Yes
Feasible? Yes
Clinically relevant? Yes

Comments: Ketorolac is routinely prescribed in the ED at a 30 mg dose, but this article demonstrates that lower doses can achieve similar analgesic efficacy while minimizing risk of adverse effects (e.g. GI bleeding). This study suggests that 10 mg is sufficient for pain control and may be the analgesic ceiling for ketorolac.

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

Additional Comments/Discussion/Notes