Atomized Intranasal Ketorolac Versus Intravenous Ketorolac for the Treatment of Severe Renal Colic in the Emergency Department: A Double-Blind, Randomized Controlled Trial

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Study objective: Atomized intranasal (IN) drug administration offers an alternative to the intravenous (IV) route. We aimed to evaluate the analgesic efficacy of IN versus IV ketorolac in emergency department patients with acute renal colic.

Methods: We conducted a double-blind, randomized controlled trial on adult patients (aged 18 to 64 years) with severe renal colic and numerical rating scale pain ratings $\geq$7.0. They were randomly assigned (1:1) to receive single doses of either IN or IV ketorolac. Our main outcomes were differences in numerical rating scale reduction at 30 and 60 minutes. A 95% confidence interval (CI) was calculated for each mean difference, with a minimum clinically important difference set at 1.3 points. Secondary outcomes included treatment response, adverse events, rescue medications, and emergency department revisits. We analyzed using intention-to-treat.

Results: A total of 86 and 85 patients with similar baseline characteristics were allocated to the IV and IN groups, respectively. Mean numerical rating scale scores were 8.52 and 8.65 at baseline, 3.85 and 4.67 at 30 minutes, and 2.80 and 3.04 at 90 minutes, respectively. The mean numerical rating scale reduction differences between the IV and IN groups were 0.69 (95% CI -0.08 to 1.48) at 30 minutes and 0.10 (95% CI -0.85 to 1.04) at 60 minutes. There were no differences in secondary outcomes.

Conclusion: Neither IN or IV ketorolac was superior to the other for the treatment of acute renal colic, and both provided clinically meaningful reductions in pain scores at 30 to 60 minutes. [Ann Emerg Med. 2024;83:217-224.]

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INTRODUCTION

Background

Renal colic is believed to be one of the worst types of pain an individual can suffer. The drug of choice for initial analgesia is determined by many factors, including availability, safety, efficacy, and cost, alongside the preferences of the affected patient and treating clinician.[1] According to international guidelines, nonsteroidal anti-inflammatory drugs (NSAIDs) represent first-line analgesics for this indication; compared to opioids, NSAIDs achieve better pain reduction, have a preferable side effect profile, and decrease the requirement for rescue analgesia.[2-5]

Ketorolac tromethamine is an NSAID recommended for short-term treatment of moderately severe acute pain requiring opioid analgesia.[2] In 1989, the intranasal (IN) administration of ketorolac was approved by the United States Food and Drug Administration (FDA) for the temporary management ($\leq$5 days) of moderate to moderately severe pain.[6] In terms of pharmacokinetics, IN ketorolac shows a rapid increase in plasma concentration and provides analgesic efficacy similar to other methods of parenteral administration.[7] In clinical practice, many postoperative studies have demonstrated that IN ketorolac is well tolerated and efficient in relieving moderate-to-severe postoperative pain.[8-15]

The efficacy of ketorolac in the treatment of renal colic has been studied in multiple randomized controlled trials. Motov et al[16] found that a combination of intravenous (IV) lidocaine and ketorolac resulted in better analgesia in comparison to lidocaine alone, but not ketorolac alone. In

Editor's Capsule Summary

What is already known on this topic

Many analgesics can be administered via the intranasal route.

What question this study addressed

For emergency department (ED) patients with severe renal colic, which administration route provides superior pain reduction for ketorolac 30 mg: intranasal or IV?

What this study adds to our knowledge

In this randomized, double-blind trial of 171 subjects, both routes were associated with large and similar reductions in pain scores at 30- and 60-minute patient assessments. Based on confidence intervals, the possibility of a clinically important advantage to the IV route at 30 minutes cannot be excluded.

How this is relevant to clinical practice

For ED patients with severe renal colic, these findings report substantial analgesic efficacy using intranasal ketorolac.

contrast, Drapkin et al[17] reported that the combination of IV lidocaine and IV ketorolac was superior to either drug alone for the treatment of renal colic.[17] In another clinical trial, the use of IV ketorolac either alone or in combination with meperidine was superior to IV meperidine alone.[18] Another trial found that intramuscular (IM) ketorolac was more efficacious than IM meperidine as a single agent, allowing for early patient discharge.[19]

Cohen et al[20] reported that ketorolac demonstrated similar effectiveness to other NSAIDs in the treatment of renal colic, resulting in lowered pain severity, a decrease in the number of patients who needed rescue medication, and the severity of side effects.[20] In another double-blind study, Martín Carrasco et al[21] demonstrated that the analgesic efficacy of IV ketorolac trometamol was similar to that of IV dipyrone combined with a spasmolytic agent, although the former resulted in fewer side effects.[21] Similarly, a double-blind clinical trial indicated that the addition of magnesium sulfate to IV ketorolac did not increase analgesic efficacy compared with IV ketorolac alone.[22] Finally, Motov et al[23] conducted a randomized, double-blind trial showing that 3 single-dose regimens of IV ketorolac (at 10, 15, or 30 mg) demonstrated similar analgesic efficacy without an increase in adverse effects.[23] According to a recent meta-analysis of randomized controlled trials, the administration of ketorolac for the treatment of renal colic was associated with significantly lower pain scores and lowered requirements for rescue medications; however, there was no significant effect on the frequency of side effects, such as nausea, vomiting, and dizziness.[24]

Importance

To the best of our knowledge, IN ketorolac has not been adequately studied in renal colic, and the few existing studies on this topic are not conclusive. However, a prior clinical trial did reveal that IN ketorolac combined with fentanyl was equivalent in terms of analgesic effect, safety profile, and the need for rescue treatment in comparison to IV ketorolac and fentanyl in the treatment of emergency department (ED) patients with acute renal colic.[25] Compared with IV ketorolac, IN analgesics are quick, needle-free, and easy to administer, potentially reducing waiting time, the need for cannulation, and unnecessary blood tests for patients with characteristic presentations of acute renal colic. Moreover, IV ketorolac could reduce opioid use in the ED given concerns about their potential side effects.

Goals of This Investigation

The aim of this double-blind, randomized controlled trial was to compare the efficacy of IN ketorolac in comparison with IV ketorolac with regards to reducing pain intensity as assessed by a numerical rating scale among adults with severe acute renal colic. Secondary outcomes included the requirement for rescue pain medication, treatment response (defined as a numerical rating scale score of $\leq$3 at 60 minutes), recurring ED visits within 24 hours, and the occurrence of any adverse events.

MATERIALS AND METHODS

Study Design and Setting

This prospective, double-blind, randomized, parallel, 1:1 clinical trial was conducted in the ED affiliated with the Sultan Qaboos University Hospital, a tertiary academic hospital in Muscat, Oman. Patient screening and enrollment started in December 2020 and ended in February 2022.

The study protocol was approved by the Medical Research and Ethics Committee at Sultan Qaboos University (MREC #2195), with all patients providing written informed consent prior to their participation. The trial was registered under ClinicalTrials.gov identifier NCT04441762.

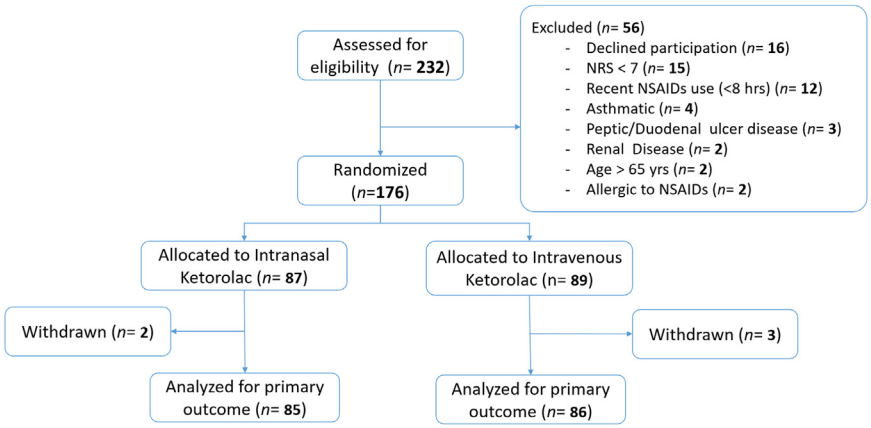

Figure 1. Enrollment flow diagram showing the allocation of adult patients presenting with severe renal colic to the emergency department of the Sultan Qaboos University Hospital, Muscat, Oman (N=171). *NRS*, numerical rating scale; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

Selection of Participants

We enrolled adult patients aged 18 to 65 years presenting to the ED with severe flank pain (defined as a numerical rating scale score of $\geq$7) and a clinical diagnosis of acute renal colic. All diagnoses were made per the treating emergency physician's gestalt, based on medical history and physical examination. We excluded patients with any contraindication to ketorolac, including acute gastrointestinal bleeding, active peptic ulcer disease, a background of asthma, urticaria, or other hypersensitivity after taking NSAIDs; pregnant or breastfeeding mothers; patients with renal disease, a history of renal transplant, and hemodynamic instability (systolic blood pressure of <90 mmHg); and those who had already received NSAIDs in the preceding 8 hours.

Interventions

We randomized patients using a computer-generated sequence based on 1:1 allocation in blocks of 6. The participants received a unique code consisting of one number and 2 letters to minimize recognition of the sequence. The code and its relevant interventions were sealed in a nontransparent envelope. Every 6 envelopes were placed in a box, and the next block was placed in that box once all previous envelopes had been used. Patients were randomly assigned to receive either 30 mg of IV ketorolac in a 10-mL syringe in combination with 1 mL of normal saline solution 0.9% using an IN device (0.5 mL in each nostril) or 30 mg of IN ketorolac (0.5 mL in each nostril) in combination with 10 mL of IV normal saline solution 0.9%.

We asked each patient to self-report his/her initial baseline pain according to the numerical rating scale. The scale was displayed as a 10-cm horizontal line on which the patient's pain intensity was indicated by a point between the extremes of "no pain at all" (0) and "worst pain ever" (10). Subsequently, a nurse not involved in the patient assessment process was asked to open the envelope and follow the instructions to prepare the study medications and discard all labels. All enrolled patients received 10 mL of unlabeled IV syringes over 10 minutes and an 0.5-ml unlabeled IN preparation administered into each nostril using an IN mucosal atomization device (Teleflex Medical Inc). Thus, the patient, the treating physician, and the attending nurse were not aware of the assigned intervention.

Measurements and Outcomes

The main outcome of the trial was changes in numerical rating scale scores between the 2 different administration routes 30 and 60 minutes after administration. Our secondary outcomes included treatment success as defined by a numerical rating scale score of $\leq$3 at 60 minutes, the occurrence of any adverse events (eg, nausea, vomiting, allergic reactions), the need for rescue medications, and revisits to the ED within a 24-hour period. Per the definition of the FDA, serious adverse events were defined as any potentially life-threatening events, including events resulting in death or significant disability/incapacity, and those requiring inpatient hospitalization or the prolongation of hospitalization.[26]

Analysis

Our sample size was determined based on an anticipated Cohen's d effect size of 0.50 (medium effect size), alpha error of 5%, power of 90% and allocation ratio of 1:1. The calculated sample size was 172 (86 in each arm) using G*Power version 3.1.9.2 software. We assumed a

Table 1. Baseline characteristics.

Characteristic	Group Allocation, n (%)	
	IV Ketorolac (n=86)	IN Ketorolac (n=85)
Age (y)*	35.4 (8.4)	35.9 (8.5)
Sex		
Man	72 (83.7)	71 (83.5)
Woman	14 (16.3)	14 (16.5)
Confirmed calculi	60 (69.8)	57 (67.1)
Calculi location		
Renal	20 (35.1)†	17 (30.4)‡
Proximal ureter	7 (12.3)†	11 (19.6)‡
Mid-ureter	5 (8.8)†	4 (7.1)‡
Distal ureter	25 (43.9)†	24 (42.9)‡
Obstructive stone	27 (47.4)†	30 (53.6)‡
Stone size (mm)*	5.3 (2.5)	5.0 (1.8)
Pain medication prior to ED presentation	12 (14.0)	6 (7.1)
Vitals at presentation		
Systolic BP (mmHg)*	137 (20)	136 (17)
Diastolic BP (mmHg)*	82 (15)	82 (13)
Pulse rate (beats/minute)*	85 (15)	86 (13)
Respiratory rate (breaths/minute)*	19 (2)	20 (3)
Temperature (°C)*	36.7 (0.3)	36.8 (0.3)

BP, blood pressure; *ED*, emergency department; *IN*, intranasal; *IV*, intravenous; *SD*, standard deviation.
*Presented as mean (SD).
†Percentages for this variable were calculated out of the total number of patients for whom this information was available (n=57).
‡Percentages for this variable were calculated out of the total number of patients for whom this information was available (n=56).

minimum clinically significant difference in pain scores as a change of 1.3 in the numerical rating scale.[27]

We used a student's *t* test to compare our main outcomes using Statistical Package for the Social Sciences (SPSS) for Windows program, Version 25.0 (IBM Corp). We analyzed our results using intention-to-treat.

We also performed a post-hoc Bayesian evaluation using Bayes factors using R software version 4.0.2 (Appendix E1, available at http://www.annemergmed.com).

RESULTS

Characteristics of Study Subjects

We assessed 232 patients for eligibility in this trial, of which 56 were excluded for reasons detailed in Figure 1. The remaining 176 were then randomized. Five patients withdrew from the study after randomization because they rescinded their consent for participation in the study, left the ED before 30 minutes had elapsed, or were found to not meet the inclusion criteria. These patients were not included in the final analysis. The baseline characteristics of the remaining 85 patients in the IN group and 86 in the IV group were similar (Table 1).

Main Results

Numerical rating scale scores in both groups significantly improved compared with baseline. The average difference in numerical rating scale score reduction between the 2 groups was 0.69 (95% confidence interval [CI] of -0.08 to 1.48) at 30 minutes and 0.10 (95% CI -0.85 to 1.04) at 60 minutes (Table 2). Figure 2 shows the degree of change in pain intensity for each patient.

Treating physicians administered rescue analgesia to 11.6% of IV ketorolac patients and 10.6% of IN ketorolac patients, a difference of 1% (95% CI -8.8% to 10.8%). The treatment response was 69.8% for the IV group and 67.1% for the IN group, representing a 2.7% difference (95% CI -11.1% to 16.4%). Within 48 hours, 18.6% of IV patients and 17.6% of IN patients revisited the ED, a difference of 1% (95% CI -10% to 12%) (Table 3). There were no reports of any significant adverse effects. Nausea and vomiting were the most frequently recorded side-effects (Table 4).

Table 2. Main outcomes measures.

Pain Outcome Measures	IV Ketorolac	IN Ketorolac	Mean Difference Between Groups
NRS score, mean (95% CI)			
Baseline	8.52 (8.30 to 8.75)	8.65 (8.42 to 8.87)	0.12 (-0.20 to 0.44)
30 min	3.85 (3.35 to 4.44)	4.67 (4.08 to 5.27)	0.82 (-0.02 to 1.66)
60 min	2.80 (2.12 to 3.50)	3.04 (2.35 to 3.73)	0.22 (-0.75 to 1.20)
NRS change from baseline, mean (95% CI)			
30 min	4.67 (4.15 to 5.29)	3.98 (3.44 to 4.56)	0.69 (-0.08 to 1.48)
60 min	5.71 (4.98 to 6.38)	5.61 (4.84 to 6.33)	0.10 (-0.85 to 1.04)

CI, confidence interval; *NRS*, numerical rating scale.

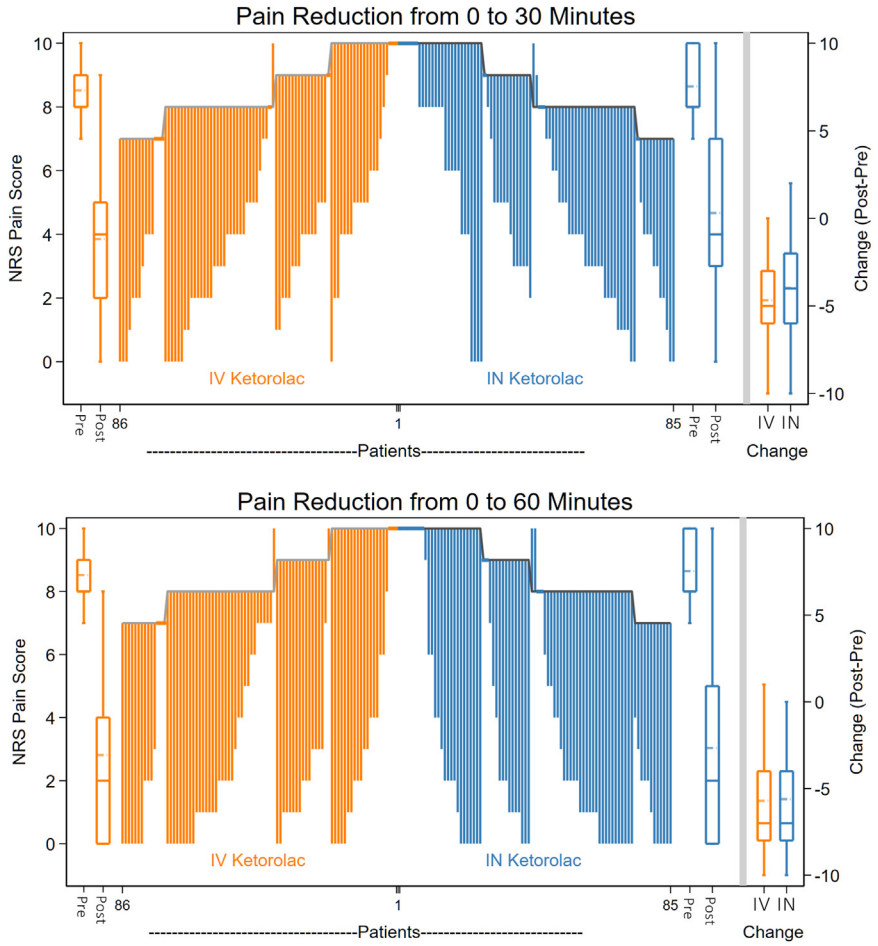

Figure 2. Numerical scale rating pain reduction associated with intranasal ketorolac and intravenous ketorolac at 30 minutes and 60 minutes after medication administration. The length of the lines in the waterfall plots indicates the degree of change in pain intensity for each patient. The boxplots adjacent to the waterfall plots show the pain scores pre- and postintervention. The median is represented by the middle line, the interquartile range is represented by the box, the range is represented by the whiskers, and the mean is represented by the dot. The box plots on the far right show the difference in pain score between baseline and post treatment. *NRS*, numerical rating scale.

Our post-hoc Bayesian analysis corroborates our main findings.

LIMITATIONS

First, our study is limited by the fact that it was conducted in a single center, which hinders generalization of the findings. However, the center covers a wide demographic area, and the patients can be considered representative of the local population. Moreover, we did not examine the time needed to reach a meaningful pain response; however, per our goals, we intended solely to study the reduction rate in numerical rating scale score at 30 and 60 minutes. Finally, the use of rescue medications (ie, opioids, such as morphine, fentanyl, tramadol, etc) was

Table 3. Secondary outcome measures.

Outcome	IV Ketorolac (N= 86)	IN Ketorolac (N=85)	Difference (95% CI)
Need for rescue analgesia			
	10 (11.6%)	9 (10.6%)	1% (-8.8% to 10.8%)
Responded to treatment			
	60 (69.8%)	57 (67.1%)	2.7% (-11.1% to 16.4%)
Responders with confirmed renal stones			
	66.7% (40/60)	63.2% (36/57)	3.5% (-13.4% to 20.3%)
Responders without confirmed renal stones			
	76.9% (20/26)	75.0% (21/28)	1.9% (-20.7% to 23.9%)
ED revisit within 48 h			
	16 (18.6%)	15 (17.6%)	1% (-10% to 12%)

CI, confidence interval; *ED*, emergency department; *IN*, intranasal; *IV*, intravenous.

Table 4. Adverse events.

Side Effect	Group Allocation, n (%)	
	IV Ketorolac (n=86)	IN Ketorolac (n=85)
Nausea/vomiting	2 (2.3)	2 (2.4)
Asthma-like symptoms	0 (0)	2 (2.4)
Dizziness	0 (0)	1 (1.2)

guided by physician gestalt and patient request and was not standardized.

DISCUSSION

We found that both routes for ketorolac were associated with significantly improved pain scores when treating severe renal colic and that neither IN or IV administration was superior at 30 and 60 minutes. The confidence intervals for these latter calculations exclude clinically important differences (ie, numerical rating scale score of $\geq$1.3) at 60 minutes but cannot exclude a possible advantage for the IV route at 30 minutes (Table 2). The frequency of rescue analgesia in our study groups was considerably lower than rates reported by other studies.[28,29]

The efficacy of ketorolac has been compared with other NSAIDs and narcotics. In some studies, IV and IM routes have been found to be more effective in the treatment of renal colic and superior to opioids.[19,20,29,30] Ketorolac can be administered through the IN route, which does not require a needle brick or IV access for administration. The IN route uses the highly vascularized nasal cavity for systemic absorption that aids in transporting medications directly to the brain through the olfactory neuroepithelium and trigeminal nerve system.[31] Although little is known regarding the analgesic mechanism of IN ketorolac in renal colic, this medication has been shown to be beneficial in treating migraine in children, acute postoperative pain, and pain as a result of dental surgery.[10,12,32]

To the best of our knowledge, this study is the first randomized, double-blind clinical trial to compare IN ketorolac to IV ketorolac in adult ED patients with renal colic. Our findings therefore add additional supportive evidence to indicate that noninvasive IN ketorolac is a feasible alternative to the traditional IV route in the ED. Our findings are comparable with those published in a previous randomized clinical study comparing ketorolac with diclofenac for the treatment of adult renal colic.[20,29]

We also found that no serious adverse events were observed in either group, and the most frequently reported adverse side effect of treatment was nausea and vomiting, a finding consistent with previous research.[19,32] In previous studies wherein IN ketorolac has been compared with an IN placebo, researchers have indicated significant nasal irritation in the IN ketorolac arm; however, we can conclude that this side effect was mild, transient, and not clinically significant given that no patient withdrawals occurred as a result.[8,10] Therefore, to maintain the blinding of patients and physicians in our trial, we did not assess specifically for this side effect.

In summary, our findings indicate that neither IN or IV ketorolac was superior to the other for the treatment of acute renal colic, and both were associated with clinically meaningful reductions in pain scores at 30 to 60 minutes. Furthermore, the IN route of administration showed similarity to the IV route in terms of secondary outcomes, including the need for rescue medications, the frequency of ED revisits within a 48-hour interval, and side effect profile.

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Author contributions: The primary investigator, USSAK, together with AKSAA, was responsible for the initial conception and subsequent design of the research trial. Funding was procured by USSAK and MAJ, whereas supervision of the trial's conduct and data collection was overseen by USSAK and AKSAA. MSRAA and FBAR were delegated the task of patient follow-up. Statistical consultation on both the study design and analysis was provided by AAR and RV, with RV taking specific charge of the Bayesian analysis. The statistical analyses were jointly executed by USSAK, IAZ, and RV, with RV additionally engaged in the critical review of the analytical portion. The drafting of the manuscript was undertaken by USSAK, and substantial revisions were

collaboratively made by all authors, including RV. The responsibility for the integrity of the entire paper is held by AKSAA as the corresponding author.

Data sharing statement: We comply with the journal's data sharing policy by providing access to the deidentified participant data used in our randomized controlled trial upon request. To obtain the dataset, a comprehensive data dictionary, and the analytic code used for data analysis, please contact Al-khalasi, MD, via email at u.alkhalasi@gmail.com.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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