Received: 12 August 2020 | Revised: 7 December 2020 | Accepted: 14 December 2020

DOI: 10.1111/acem.14202

ORIGINAL CONTRIBUTION

Comparison of intravenous ketorolac at three doses for treating renal colic in the emergency department: A noninferiority randomized controlled trial

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Funding information
Supported by Tehran University of Medical Sciences.

Supervising Editor: James Miner

ABSTRACT

Background: Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that is extensively used for the management of renal colic in the emergency department (ED). It has been proposed that ketorolac is used at doses above its analgesic ceiling with no more advantages and increased risk of adverse effects. In this study, we compared the analgesic effects of three doses of intravenous ketorolac in patients with renal colic.

Methods: This noninferiority, randomized, double-blind clinical trial evaluated the analgesic efficacy of three doses of intravenous ketorolac (10, 20, and 30 mg) in adult patients presenting to the ED with renal colic. Exclusion criteria consisted of age > 65 years, active peptic ulcer disease, acute gastrointestinal hemorrhage, renal or hepatic insufficiency, NSAID hypersensitivity, pregnancy or breastfeeding, unstable vital signs, and patients who had received analgesics in the past 24 hours. Pain was recorded every 15 minutes from baseline up to 60 minutes, and the primary outcome was pain reduction at 30 minutes. If patients still required additional pain medications at 30 minutes, they would receive 0.1 mg/kg intravenous morphine sulfate as a rescue analgesic.

Results: A total of 165 subjects enrolled in this study, 55 in each group. The median visual analog scale score in 30 minutes was improved from 90 at baseline to 40 among subjects who were randomized to 30-mg group. This improvement was 40 and 50 mm in 20- and 10-mg ketorolac treatment arms, respectively, with no significant difference between the three doses ($p < 0.05$). Secondary outcomes showed similar rescue analgesic administration and adverse effects. There was no serious adverse event.

Conclusion: Ketorolac at 10-, 20-, and 30-mg doses can produce similar analgesic efficacy in renal colic.

INTRODUCTION

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) with no tolerance or physical dependence in comparison to opioids.[1] It has been used successfully as a single agent or in combination with other medications for pain relief and is now widely used in emergency departments (EDs).[2,3] The most common adverse effects of ketorolac are nausea, vomiting, dyspepsia, inhibition of platelet aggregation, gastrointestinal (GI) bleeding, allergic reactions, lightheadedness, and drowsiness, similar to the other

NSAIDs.[1,4] These adverse effects are usually dose dependent and the risk will be increased with higher doses especially in case of GI bleeding.[5]

Renal colic is one of the most common complaints in EDs for which ketorolac has long been used with an acceptable efficacy for pain relief.[6,7] Based on previous studies, ketorolac was as effective as opioids and other analgesics for the pain management of renal colic.[6,8-12]

The current Food and Drug Administration–recommended dose for intravenous ketorolac is 30 mg intravenously for emergency pain control.[13] However, some evidence showed that lower doses could have similar effects with fewer adverse reactions. In a study by Motov et al.,[2] a single intravenous dose of 10 mg ketorolac was as effective as 15- and 30-mg doses in acute pain management of all causes. Furthermore, another study showed that a dose of 15 mg of ketorolac is as efficacious as the 30-mg dose in postoperative pain management.[14]

In the present noninferiority clinical trial, we compared the efficacy and adverse effects of three doses of ketorolac in patients with renal colic to explain whether the 10- and 20-mg intravenous dose could be as effective as 30 mg for pain management with fewer adverse effects in renal colic.

METHODS

Study design and setting

This is a prospective, double-blind, randomized clinical trial for noninferiority testing of 10 and 20 mg ketorolac in renal colic compared with 30 mg. Our University of Medical Sciences institutional review board has approved the trial protocol that was then registered in ClinicalTrials.gov (registration No. NCT03665753).

The study was conducted in three academic hospitals affiliated with our university (Imam, Shariati, and Sina Hospitals with 70,000, 40,000, and 50,000 annual ED visits, respectively). Patient screening and enrollment were performed by three investigators (L.E., M.Y., M.B.). Of note, the pain management protocol for renal colic in adult patients in our EDs consists of the administration of 30 mg of ketorolac intravenously.

Selection of participants

Adult patients with acute severe flank 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 costovertebral angle tenderness) and/or laboratory studies such as microhematuria. Exclusion criteria consisted of age > 65 years, active peptic ulcer disease, acute GI bleeding, renal or hepatic insufficiency, history of NSAID hypersensitivity, pregnancy or breastfeeding, and unstable vital signs (systolic blood pressure < 90 or > 180 mm Hg, pulse rate < 50 or > 150 beats/min) and patients who had already received analgesics in the past 24 hours.

Patients were enrolled between November 2018 and September 2019 and all the participants provided written informed consent. Consecutive patients presenting to the EDs on the investigators' shifts (L.E., M.Y., M.B.) were screened for eligibility. The clinical shifts assignment for three investigators were random during the study period.

Intervention

The 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. The process was supervised by H.M.

After inclusion, a thorough medical history was obtained from patients and vital signs including heart rate, respiratory rate, blood pressure, and O_2 saturation at the time of admission were examined and documented. At the same time, baseline pain was assessed using visual analog scale (VAS), a 100-mm horizontally positioned line with two points of "no pain" and "the worst possible pain" at either end. 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 dilute 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. After announcing the code, the medication was administered intravenously over 1 to 2 minutes. The rest of patient management (intravenous fluid administration and monitoring) was performed as per routine clinical practice but no other medications were given to the patients during the 1-hour study period. The patients would not receive analgesics other than rescue treatment (0.1 mg/kg intravenous morphine sulfate) if pain persisted 30 minutes after ketorolac administration.

Vital signs, VAS scores, and the development of adverse effects were recorded at baseline and after15, 30, 45, and 60 minutes of intravenous ketorolac injection. The need for rescue treatment in 30 minute was also assessed. In the case of morphine sulfate administration, the pain and occurrence of adverse effects were not assessed after the 30-minute time point.

Outcome measures

The primary study endpoint was the alleviation of pain defined by VAS, 30 minutes after ketorolac administration. The secondary endpoints were pain reduction at 15, 45, and 60 minutes following the intervention, the development of adverse effects, and the need for rescue analgesia after 30 minutes. Adverse effects were recorded including headache, dizziness, nausea, vomiting, dyspepsia, and

pruritus. The patients who received rescue treatment were not assessed further in regard to adverse effects and pain intensity.

Data analysis

For sample size calculation, using data of the renal colic subgroup in the study by Motov et al.,[2] we performed a power analysis by noninferiority margin of 1.51 significant increase in pain score, a standard deviation (SD) of 2.7, both measured by numerical rating scale (NRS) on a scale of 0 to 10, power of 80%, and a two-sided 95% confidence interval (CI). This analysis resulted in a sample size of 55 patients per group (165 patients in total). Quantitative variables were described as mean ± SD, whereas categorical variables were expressed as frequency (percentage). VAS 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). We calculated a two-sided 95% CI for the mean score of VAS (measured on a scale of 0 to 100 mm) in each group. Studies have proposed different minimum clinically important differences (ranging from 8 to 40 mm) in VASs.[15] In this context, we used a 15-mm difference, suggested by some studies.[16,17] If the upper limits of CI for the 10- and 20-mg groups were higher than the noninferiority limit, equal to 15 mm more than the mean pain score in the 30-mg group, the noninferiority hypothesis would be rejected. All tests were performed using SPSS 21.0 software (IBM Corp.).

RESULTS

In this trial, 194 patients who met the inclusion criteria were enrolled. Twenty-nine patients were excluded due to the age > 65 years old, recent analgesic consumption, renal insufficiency, history of peptic ulcer disease, or inability to consent. We randomized 165 patients with renal colic into three equal 55-patient groups (1:1:1 ratio; Figure 1) who were nearly similar in baseline characteristics (Table 1). In addition, there was no significant difference in terms of recorded vital signs among the groups (Figure 2). The median VAS score in 30 minutes was improved from 90 at baseline to 40 among subjects who were randomized to the 30-mg group. This improvement was 40 mm (from 80 to 40 mm) and 50 mm (from 90 to 40 mm) in 20- and 10-mg ketorolac treatment arms, respectively. All the groups had significant response to ketorolac, compared to the baseline pain scores ($p < 0.001$; Figure 3). The trends of VAS scores were not statistically different among the groups. In addition, subjects showed pain reductions at all time points (15 to 60 minutes), compared to the baseline pain, which reductions were similar among treatment groups (Table 2). In the noninferiority analysis, the 10- and 20-mg doses of ketorolac were not inferior to the 30-mg dose (Figure 4). The groups were also similar in terms of the need for rescue analgesia (16 [29.1%], 19 [34.6%], and 16 [29.1%] for the 10-, 20-, and 30-mg groups, respectively). The

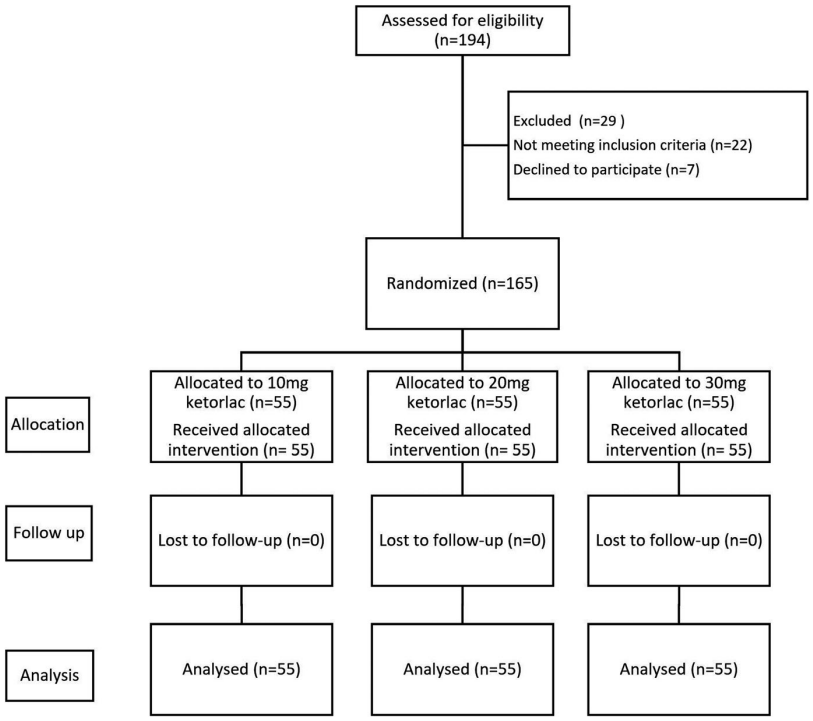

FIGURE 1 Study flow diagram

TABLE 1 Comparison of the baseline variables among the study groups

Characteristic	Group A(10 mg)	Group B(20 mg)	Group C(30 mg)	Total
No. of subjects	55	55	55	165
Age (years)	40.38 ± 10.82	39.18 ± 9.17	41.64 ± 9.82	40.40 ± 9.95
Male	41 (74.5)	44 (80.0)	38 (69.1)	123 (74.5)
Heart rate (beats/min)	77.45 ± 6.43	75.75 ± 5.88	76.11 ± 7.42	76.44 ± 6.61
O_2 saturation (%)	98.53 ± 1.07	98.64 ± .99	98.13 ± .92	94.43 ± 1.01
Systolic blood pressure (mm Hg)	122.75 ± 13.02	123.45 ± 13.44	124.05 ± 13.38	123.42 ± 13.21
Diastolic blood pressure (mm Hg)	77.44 ± 8.48	78.82 ± 8.88	78.10 ± 9.21	78.12 ± 8.82
Respiratory rate (breaths/min)	14.48 ± 2.46	14.35 ± 1.42	14.67 ± 1.91	14.50 ± 1.97
Duration of pain at presentation (h)	4.04 ± 2.24	3.75 ± 1.70	3.60 ± 1.40	3.79 ± 1.81
VAS score (mm)	90 (85–92)	80 (73–90)	90 (80–90)	90 (83–90)

Note: Data are reported as mean ± SD, *n* (%), or median (95% CI).
Abbreviation: VAS, visual analog scale.

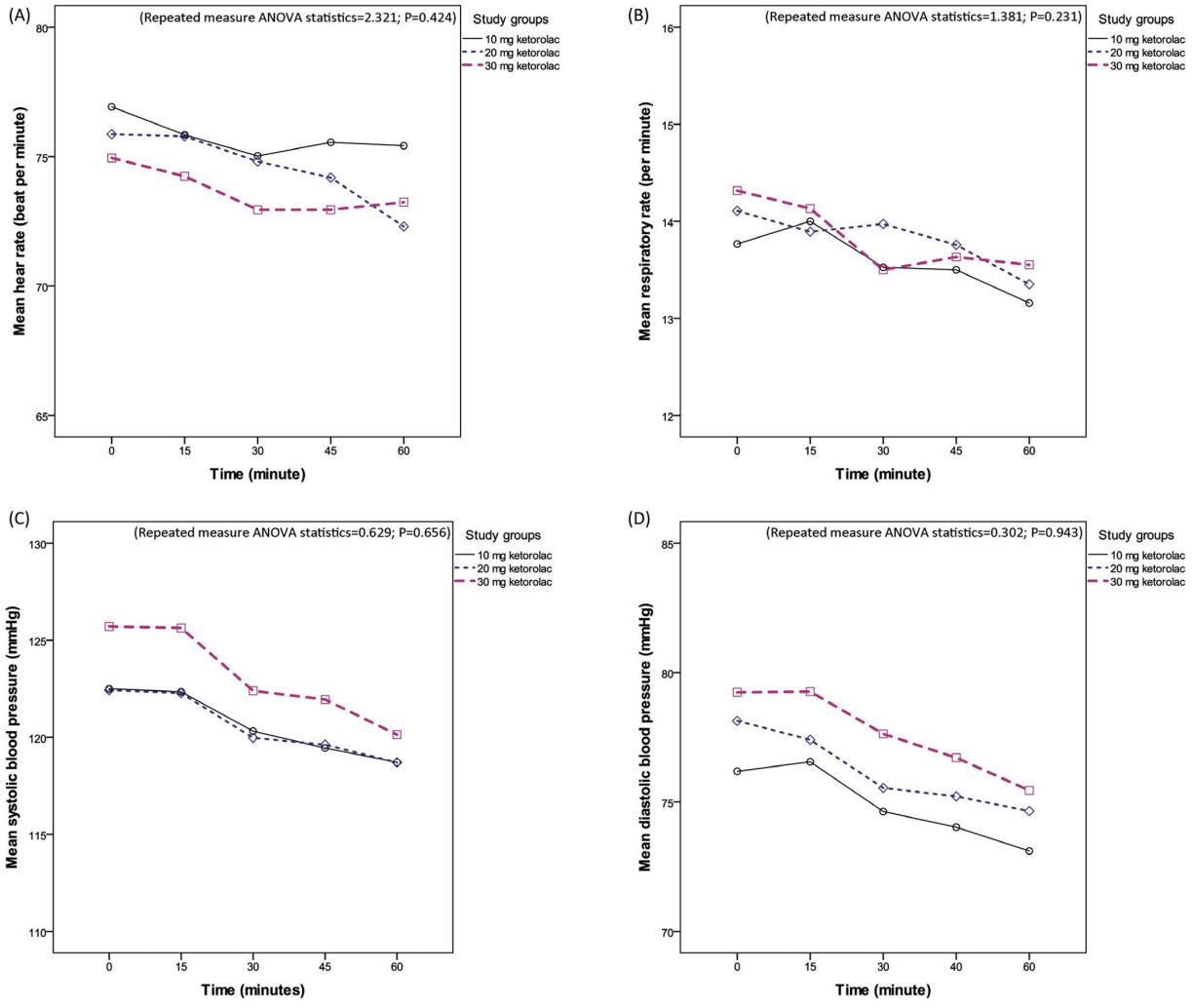

FIGURE 2 Vital signs for the 10-, 15-, and 30-mg ketorolac groups over time: (A) Mean heart rate; (B) mean respiratory rate; (C) mean systolic blood pressure; and (D) mean diastolic blood pressure

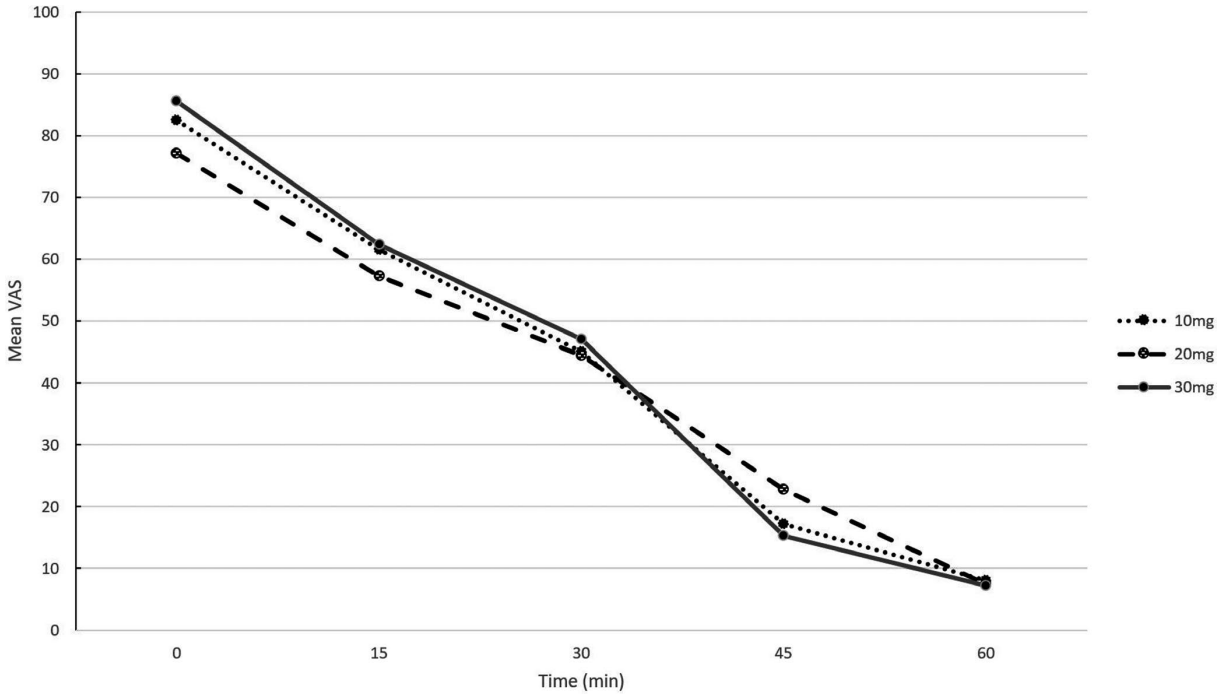

FIGURE 3 Mean pain scores for the 10-, 15-, and 30-mg ketorolac groups over time

TABLE 2 Comparison of the pain intensity as defined by VAS between the study groups within the first 60 minutes after the intervention

VAS score	Group A (10 mg)	Group B (20 mg)	Group C (30 mg)
Baseline	90 (85–92)	80 (73–90)	90 (83–90)
After 15 min	61 (58–70)	60 (50–68)	60 (60–70)
After 30 min	40 (35–50)	40 (40–49)	40 (34–50)
After 45 min	15 (10 –20)	20 (13–25)	13 (10–18)
After 60 min	5 (0–10)	5 (0–10)	5 (0–10)

Note: Data are reported as median (95% CI).
Abbreviation: VAS, visual analog scale.

most common adverse effects were nausea and vomiting with similar frequencies among all groups. Headache (the second most frequent adverse effect) and dyspnea were more frequently observed in the 30-mg group. Although the overall rate of adverse effects was lower in the 10-mg group the difference was not statistically significant. Table 3 provides an overview of adverse effects and the need for rescue analgesia in the study groups.

DISCUSSION

This noninferiority trial showed that the administration of 10 mg intravenous ketorolac was comparable to higher doses of 20 and 30 mg in renal stone pain management in terms of efficiency. Renal colic is prevalent in the general population and comprises 1% of the total ED visits and 1% of hospital admissions.[18] The pain mechanism in this condition is multifactorial. Beside local irritation by the stone, obstruction in urinary flow with subsequent pressure increase and prostaglandin-mediated ureteral spasm causes renal colic.[19] Although new treatment options have been proposed (e.g., desmopressin and lidocaine),[20,21]

NSAIDs and opioids are still the mainstays of treatment. NSAIDs act directly on prostaglandin production and are superior in treatment of renal colic in comparison to opioids with regard to their greater analgesia and fewer side effects.[22]

As an NSAID, ketorolac is widely used for adult pain control in the EDs. Intravenous ketorolac is associated with improved or equal pain relief with less adverse effects in renal colic compared to intravenous opioids,[23,24] and many researchers have recommended this medication for pain management in renal colic.[25] Considering the intravenous dosage, ketorolac is routinely prescribed in the ED at doses of 30 and 60 mg.[26] Since it has been proven that patients who received higher doses are at increased risk for adverse effects such as GI bleeding and thrombotic events,[5,27] several studies tried to define the optimal dose of ketorolac. Studies on postoperative care after spinal and other major surgeries showed that smaller doses of ketorolac (as low as 7.5 mg in one study) had similar analgesic and morphine-sparing effects in comparison to higher doses (as high as 30 mg).[28-30] For cancer pain relief, studies yielded similar results. Researchers showed that intramuscular ketorolac at the dose of 10 mg was as effective as higher doses (30 and 90 mg).[31,32] Motov et al.[2] conducted a single-center study on patients with renal colic,

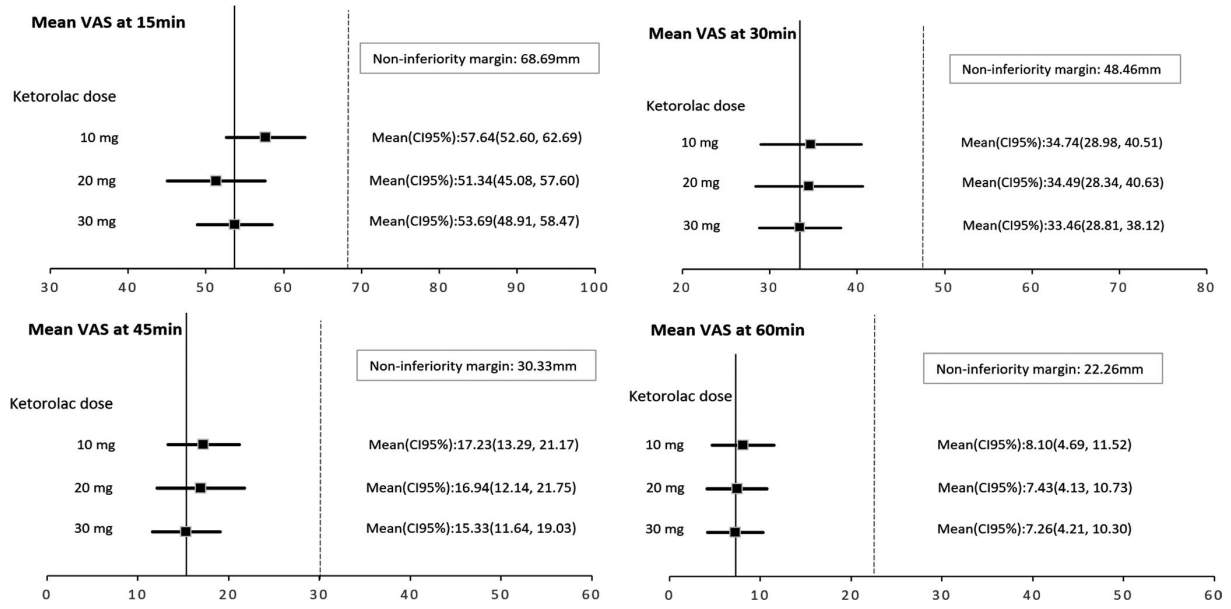

FIGURE 4 Mean pain (VAS) in the treatment groups in comparison to the 30-mg group over time. *Dashed line* is noninferiority limit (15 mm higher than mean). The noninferiority hypothesis would be rejected if CI for 10-mg and 20-mg groups crosses this line. VAS, visual analog scale

TABLE 3 Frequency of adverse effects and need for morphine and their comparisons among the study groups

Characteristic	Group A (10 mg)	Group B (20 mg)	Group C (30 mg)	p-value[a]
Need for morphine	16 (29.1)	19 (34.6)	16 (29.1)	0.775
Dizziness	2 (3.6)	4 (7.3)	8 (14.5)	0.112
Nausea/vomiting	17 (30.9)	16 (29.1)	12 (21.8)	0.526
Headache	5 (9.1)	8 (14.5)	10 (18.2)	0.383
Dyspepsia	0 (0)	0 (0)	2 (3.6)	0.132
Any adverse effect	20 (36.4)	24 (43.6)	25 (45.5)	0.335

Note: Data are reported as *n* (%).

[a]$p < 0.05$ was considered as statistically significant.

musculoskeletal pain, abdominal pain, or headache with a pain score of at least 5 of 10. The authors found no significant difference in the extent of pain relief by 10-, 15-, and 30-mg intravenous ketorolac doses and concluded that the 10-mg dose is the effective ceiling dose for ketorolac. Similar to our study, they also reported a gradual but equal decrease in pain in different doses and proposed that ketorolac at 10 mg has similar efficacy to higher doses.

Although there was no significant difference among the study groups regarding the occurrence of adverse effects, the frequency of adverse effects in patients who received 10 mg ketorolac was lower than in the other groups. This should be interpreted considering that the power was not assessed for secondary outcomes. This finding was similar to the findings of Motov et al.[2] and Duttchen et al.[29] that no difference was noted in the rate of adverse effects among intravenous ketorolac treatment arms. In contrast to the study of Motov et al. in which more patients experienced dizziness, our patients showed a higher rate of nausea and vomiting. This can be attributed to the nausea and vomiting caused by renal colic rather than the adverse effect of medications. This can also explain the slightly higher rate of adverse effects in our study (36% to 45%) in comparison to the that in the study by Motov et al. study (30% to 38.75%). Finally, while some studies used NRS, we used VAS. Although NRS is considered reliable, according to some other studies, VAS is slightly superior to the other scales.[33]

LIMITATIONS

We recruited consecutive patients during the three investigators' random shifts (nights and days) rather than consecutive patients presenting to the ED of three academic hospitals. Although there is a risk of selection bias, because the shifts were random, we believe that this risk is low. The patients were included with the primary diagnosis of renal colic according to the emergency physicians' gestalt. Although none of patients discharged with other final diagnoses, some of them did not undergo computed tomography scan to confirm urolithiasis as the cause of pain. Moreover, although the maximum plasma concentration of ketorolac is reached about 1 minute after IV administration[13] and it has linear pharmacokinetics, our study was limited to pain relief properties of this medication in the ED and did not evaluate the treatment effects beyond 1 hour. This is also true regarding the adverse effect after 60 minutes. In addition, the power for secondary outcomes (e.g., adverse effects) was not calculated in this study. Finally, nausea/vomiting can be attributed to renal colic, morphine

sulfate, or ketorolac. While our study design offsets the effect of morphine sulfate by not assessing adverse effects after rescue treatment, it is difficult to distinguish between the other two.

CONCLUSION

In this study, ketorolac showed a similar analgesic profile in doses of 10, 20, and 30 mg in pain management of renal colic. Our results were consistent with the previous studies that proposed a lower dose of 10 mg would be sufficient for pain control.

ACKNOWLEDGMENTS

The authors thank Dr. Sergey Motov and Amin Doosti-Irani for assistance in sample size calculation. We also thank Dr. Ahmad Mirfazaelian for his editorial comments.

CONFLICT OF INTEREST

The authors have no potential conflicts to disclose.

AUTHOR CONTRIBUTIONS

Hadi Mirfazaelian gave the idea and conceived the study. Lily Eidinejad, Maryam Bahreini, and Mahtab Yazdchi involved in sampling and drafting. Ayat Ahmadi provided statistical advice on study design and analyzed. Venkatesh Thiruganasambandamoorthy helped in drafting the manuscript and provided critical comments. Hadi Mirfazaelian takes responsibility for the paper as a whole.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Eidinejad L, Bahreini M, Ahmadi A, Yazdchi M, Thiruganasambandamoorthy V, Mirfazaelian H. Comparison of intravenous ketorolac at three doses for treating renal colic in the emergency department: A noninferiority randomized controlled trial. *Acad Emerg Med*. 2021;28:768–775. https://doi.org/10.1111/acem.14202