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Comparison the clinical efficacy of intravenous fentanyl and ketorolac in relieving renal colic pain; a controlled randomized clinical trial

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ABSTRACT

Introduction: Renal colic pain is due to increased pressure on the wall of the urinary tract and is caused by the passage of a stone through the urinary tract. Although most kidney stones are eliminated spontaneously, rapid relief of the patient's pain is an important issue in the acute phase.

Objectives: This study aimed to compare the effect of intravenous ketorolac and intravenous fentanyl in relieving pain in patients with renal colic.

Patients and Methods: In a randomized controlled clinical trial, 110 patients who were referred to the emergency department for renal colic were randomly divided into two groups using the randomized block method. One group received intravenous fentanyl at a dose of 0.1 mg, and the other group received intravenous ketorolac at a dose of 30 mg. Vital signs and pain level of the patients were recorded using the Visual Analogue Scale (VAS) before drug injection and at 20, 40, and 60 minutes after injection. The results were compared between the two groups.

Results: No significant difference was found in initial pain intensity between the two groups. Furthermore, pain intensity after the intervention did not significantly differ between the groups at 20, 40, and 60 minutes. Additionally, there was no significant difference in the reduction of pain intensity between the two study groups (P=0.959). Both interventions effectively reduced patients' pain with a similar pattern over time. There was no significant difference in pulse rate and respiratory rate between the two groups after the intervention. The incidence of blood pressure reduction was significantly lower in the group that received fentanyl (P<0.001), however the frequency of other complications was not significantly different between the two groups.

Conclusion: Both intravenous ketorolac and fentanyl were equally effective in relieving pain in patients with renal colic, showing similar pain reduction patterns over 60 minutes. While both interventions had comparable effects on pulse and respiratory rates, fentanyl was associated with a significantly lower incidence of blood pressure reduction. Our findings suggest that both drugs are effective for acute renal colic pain, with fentanyl potentially offering a more favorable cardiovascular profile.

Trial Registration: The trial protocol was approved in the Iranian registry of clinical trial (identifier: IRCT20150902023855N3; https://irct.behdasht.gov.ir/trial/31789, ethical code; IR.SEMUMS.REC.1399.067).

Clinical Trial

Introduction

Renal colic due to urinary stones is a common urological complication with an annual incidence of approximately 16 per 10 000, and an incidence rate of 2-5% (1). Medications used to relieve the pain of renal colic include nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, calcium channel blockers, alpha-1 receptor blockers, and corticosteroids; however, NSAIDs and narcotics are the most commonly used (2). Each of these two, NSAIDs and narcotics, has their own effects and side effects, and depending on the condition, NSAIDs and narcotics are sometimes used as the first-line treatment.

Narcotics have a rapid onset of action, but do not directly affect the prostaglandin production, which is the main cause of renal colic pain, and have side effects such as nausea, vomiting, constipation, urinary retention, hypotension, respiratory depression, excessive sedation, and the risk of dependence, which require more careful

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Implication for health policy/practice/research/medical education:
This randomized clinical trial study provides valuable evidence for management of acute renal colic pain. Clinically, the findings support the use of either intravenous ketorolac or intravenous fentanyl as effective first-line agents, demonstrating comparable efficacy and speed of pain relief, thus offering flexibility based on availability or patient-specific factors. This evidence can be conducted to endorse guidelines that include both options for emergency departments. However, the significantly lower incidence of hypotension observed with fentanyl compared to ketorolac is a crucial consideration for clinical practice and medical education, guiding drug selection particularly in patients at risk for hemodynamic instability. Medical education curricula should emphasize the equivalent analgesic efficacy while highlighting this difference in side effect profiles. Further research could explore cost-effectiveness, patient satisfaction, the need for rescue analgesia with each agent, and their comparative efficacy and safety in specific patient subpopulations (e.g., elderly, patients with comorbidities)..

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care and patient monitoring (2). NSAIDs directly affect the release of prostaglandins and reduce renal blood flow and urine production. This subsequently reduces pressure in the collecting system and pelvis (2). Studies show that patients receiving NSAIDs experience greater pain relief than those receiving narcotics (1). Therefore, NSAIDs are currently considered the first-line treatment, and narcotics are the second-line treatment for pain relief in patients with renal colic who present to the emergency department (2).

Side effects of NSAIDs include bleeding—mostly gastrointestinal bleeding, especially in patients with a history of gastritis or peptic ulcer—interaction with aspirin (resulting in incomplete platelet inhibition), and a reduced glomerular filtration rate in the kidneys (3). The use of NSAIDs is restricted during pregnancy, and in some patients their use is limited (4). Therefore, finding a treatment strategy for patients who have restrictions on NSAID use is a very important issue.

Fentanyl has been suggested for the relief of renal colic pain in some studies (5). As an opioid, fentanyl has a faster onset of action and is 90 times more potent as an analgesic than morphine. It is administered in various forms, such as intravenous, intranasal, and intrathecal, and has fewer side effects like hypotension, bradypnea, bradycardia, and apnea compared to other opioids (6,7).

Fentanyl has an analgesic mechanism similar to morphine and reduces neuronal excitability (8).

Although some studies have proposed fentanyl as the first choice for pain relief in renal colic (5), it remains essential to determine how effective intravenous fentanyl is compared with intravenous NSAIDs in relieving this pain. If intravenous fentanyl proves to be at least as effective as intravenous NSAIDs, it could be proposed as an alternative drug. Otherwise, another treatment strategy should be considered for cases where NSAID use is contraindicated or limited.

Objectives

This study investigated and compared the effects of intravenous fentanyl and intravenous ketorolac in relieving pain in patients with renal colic presenting to the emergency department.

Patients and Methods

Study design and participants

This randomized controlled clinical trial included 110 patients with acute unilateral flank or abdominal colic pain, aged 18 to 55 years who presented to the emergency department of Kosar Hospital in Semnan from July 2021 to May 2022. Urinary stones were confirmed by ultrasound, CT (computerized tomography) scan, or intravenous pyelography.

Inclusion and exclusion criteria

Inclusion criteria

Patients aged 18 to 55 years presenting to the emergency department with acute unilateral flank or abdominal colic pain, with urinary stones confirmed by ultrasound, CT scan, or intravenous pyelography.

Non-inclusion criteria

Patients were excluded from the study if they met any of the following criteria:

- Pain score of less than 3 on the Visual Analogue Scale (VAS) at the time of admission (9).
- History of peptic ulcer.
- History of asthma.
- Use of anticoagulants.
- Liver dysfunction.
- Kidney dysfunction.
- Sensitivity to aspirin, fentanyl, or other NSAIDs.
- Pregnancy or lactation.
- Use of sedatives, hypnotics, antipsychotics, monoamine oxidase inhibitors or analgesics within 6 hours before admission.
- Presence of fever at the time of admission.

Exclusion criteria (during the study)

The patient was excluded from the study if their condition worsened and required emergency treatment not outlined in the study protocol, or if they no longer consented to participate.

Sample size

To calculate the sample size, the formula for comparing the means of two independent groups was employed, considering the nature of the pain intensity variable (Visual Analogue Scale - VAS) and the objective to detect a difference in mean pain intensity at 60 minutes post-intervention between the two groups.

A significance level (α) of 0.05 and a study power of 80% were chosen. Based on the findings which compared the effectiveness of nebulized fentanyl and intravenous ketorolac in renal colic, the common standard deviation (σ) of pain intensity at 60 minutes was estimated to be 1.91 mm (converted from the Numerical Pain Rating Scale - NPRS to the VAS scale). Furthermore, aiming to detect a minimum clinically significant difference (d) of 10 mm in the VAS score between the two groups, a sample size of 55 participants per group was calculated.

Accounting for an approximately 10% anticipated dropout rate during the study, the final sample size was set at 60 patients per group, totaling 120 patients (Figure 1).

Randomization/Allocation

After obtaining a medical history and demographic information, eligible patients underwent a physical examination. They were then randomly divided into two groups using a permuted balanced block randomization method with replacement. The randomization list was generated using block stratified randomization software.

Blinding

This was a double-blinded study. To ensure blinding, the study medications (fentanyl and ketorolac) were prepared by a pharmacist in identical syringes or infusions, making them indistinguishable in appearance. Patients, treating physicians, and researchers involved in data collection and outcome assessment were unaware of the assigned treatment group.

Intervention

One group received intravenous fentanyl at a dose of 0.1 mg (Darupakhsh Company product), and the other group received intravenous ketorolac at a dose of 30 mg (Alborz Daru Company product). Both medications were administered via intravenous infusion. Specifically, fentanyl was infused in 100 mL of normal saline over 10 minutes, while ketorolac was administered as a rapid intravenous infusion over 15 seconds. The drug dosages were determined based on similar studies and expected treatment response. If, after 60 minutes, the pain level based on the VAS increased to more than 50% of the initial level, patients received 5 mg of intramuscular morphine as a rescue analgesia.

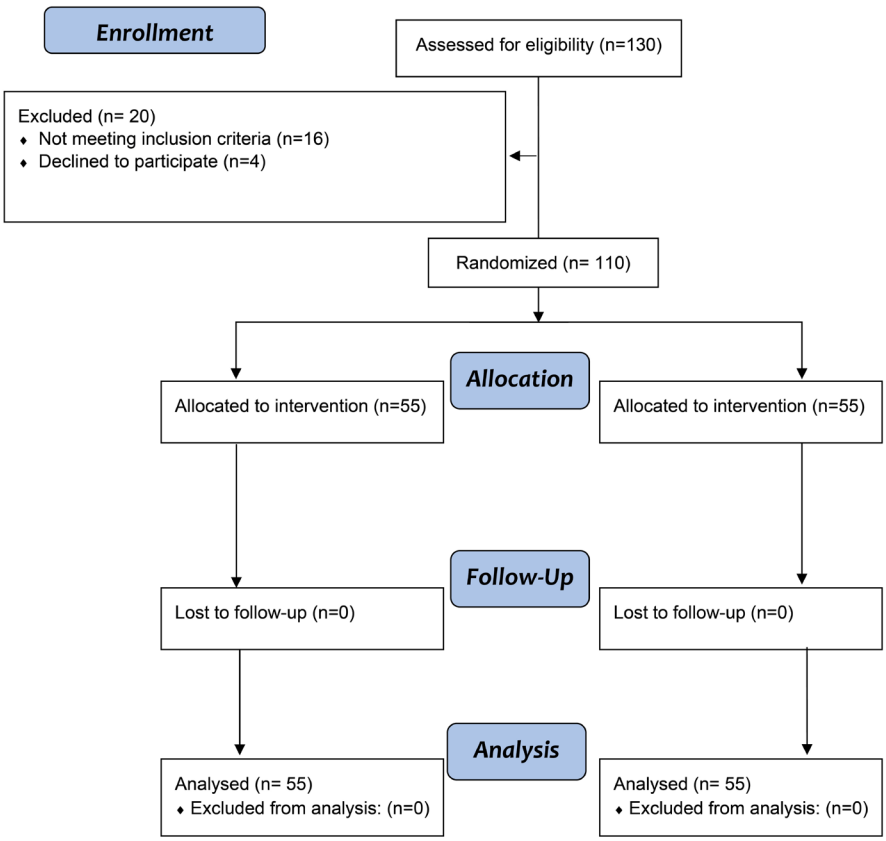

Figure 1. CONSORT flow diagram of the study.

Pain assessment tool

Pain intensity was measured using the VAS (10-point scale) (9).

Data collection

Primary information was collected using a checklist, which included:

- Demographic information: age, gender, underlying diseases, history of similar pain, history of urinary system stones, time from symptom onset to emergency room visit, and pain level.
- Clinical assessment: History and clinical examination are consistent with renal colic pain.
- Measurements: Pain intensity (based on a 10-point VAS scale), respiratory rate, heart rate, blood pressure, and body temperature.

Respiratory rate, heart rate, blood pressure, and VAS scores were recorded at baseline (before the start of treatment) and subsequently at 20, 40, and 60-minute intervals. Patients were also monitored for adverse events potentially associated with acute fentanyl use, including respiratory depression, allergies (such as rash, itching, edema, and bronchospasm), nausea, vomiting, tachycardia, and altered level of consciousness. Information regarding pain intensity, adverse events, and demographic data were recorded in the study questionnaire (5, 10).

Outcomes

The primary objective of this study was pain relief within 60 minutes, defined as a 50% or greater reduction in the VAS score from baseline (11). For this purpose, differences in VAS scores were assessed at 20, 40, and 60 minutes. Secondary objectives included comparing hemodynamic parameters (blood pressure, pulse rate, and respiratory rate) and complications between the two groups.

Statistical analysis

Quantitative variables were described using the mean and standard deviation, if the data distribution was non-normal. Categorical variables were described using frequency and percentage. The distribution of continuous variables was compared between the two treatment groups using either the independent samples T-test or the Mann-Whitney U test. Similarly, categorical variables were compared using the chi-square test. Changes in pain intensity from baseline were compared between the two groups using Mann-Whitney U, and ANOVA for repeated measures. Changes in hemodynamic parameters including systolic and diastolic blood pressure, pulse and respiratory rate were compared by paired T-test before and after intervention and by independent T-test between the two groups. The confidence level was set at 95%, and statistical significance was defined as $P<0.05$. SPSS version 22 software was conducted for all analysis.

Results

In this study, 130 patients with renal colic were included in the study, 16 patients were excluded due to lack of inclusion criteria and 4 patients were excluded due to lack of consent to participate in the study, finally, 110 patients experiencing acute renal colic pain were divided into two groups: ketorolac group (n = 55) and fentanyl group (n = 55) (Figure 1).

The two groups were well-matched for both gender and age. There was no significant difference in the patients' body temperature before the intervention between the two groups (Table 1).

Pain intensity

Pain intensity in the treated patients in both groups was assessed at the time of admission and then at 20, 40, and 60 minutes after receiving the medication. There was no significant difference in the initial pain intensity (at admission) between the two study groups ($P=0.959$). Furthermore, both drugs effectively reduced the patients' pain with a similar pattern over time (Table 2 and Figure 2).

Hemodynamic changes

Hemodynamic changes, including systolic and diastolic blood pressure, heart rate, and respiratory rate, were assessed in both study groups at admission and before and after the therapeutic intervention. While changes in systolic and diastolic blood pressure, as well as heart rate, did not differ significantly between the two treatment groups, changes in respiratory rate were statistically significant ($P=0.006$; Table 3).

Complications

Among the anticipated side effects following therapeutic intervention with ketorolac and fentanyl in the study

Table 1. Comparison of demographic, clinical, and paraclinical characteristics between two intervention groups

Characteristics		Intervention		*P* value
		Ketorolac	Fentanyl	
Gender No. (%)	Female	25 (45.5)	16 (29.1)	0.076*
	Male	30 (54.5)	39 (70.9)	
Age (years, Mean ±SD)		39.64 (9.46)	36.20 (9.44)	0.062**
Body temperature (°C, mean ±SD)		37.11 (0.34)	37.10 (0.36)	0.729**
Size of stone (mm, mean ±SD)		5.95 (3.54)	4.73 (2.55)	0.041**

* Chi-square test; ** Independent T-test.

Table 2. Frequency of pain intensity levels by visual analog scale (VAS) in two groups of patients with acute renal colic

Pain intensity (Mean ±SD)	Groups		*P* value*
	Ketorolac	Fentanyl	
Before Intervention	8.8 (1.1)	8.8 (1.1)	>0.999
After 20 minutes	6.5 (1.8)	6.7 (1.6)	0.471
After 40 minutes	4.5 (2.0)	4.3 (1.9)	0.732
After 60 minutes	2.7 (2.1)	2.6 (2.4)	0.700
P value**	<0.001	<0.001	
P value***	0.957		

* Mann-Whitney U, ** ANOVA, *** ANOVA for repeated measure.

groups, the observed side effects were: decreased blood pressure, dry mouth, tachycardia, nausea and vomiting, sweating, drowsiness, and headache. The frequency of these side effects is detailed in Table 4. As indicated by the frequency of side effects, the incidence of hypotension was significantly higher in the fentanyl-treated group ($P<0.001$). However, the frequency of the other complications did not show a statistically significant difference between the two study groups.

It is important to note that none of the patients experienced a pathologically severe drop in blood pressure; the observed decrease remained within the normal range throughout the treatment period. Furthermore, complications such as respiratory depression, allergy (including rash, itching, edema, and bronchospasm), and shortness of breath did not occur in any of the studied subjects.

Discussion

At admission, the two treatment groups showed no statistically significant differences in age, gender, and body temperature. However, the size of the urinary stones in the ketorolac-treated group was significantly larger than in the fentanyl-treated group. Despite this difference in stone size, the degree of pain relief achieved did not differ significantly between the two groups. This finding aligns with some studies indicating that the size of urinary stones does not necessarily correlate with the level of pain experienced by the patient (12).

According to the results, while the pain intensity based on the VAS criterion showed no significant difference between the two groups at the time of admission and during the three subsequent stages of the study (20-, 40-, and 60-minutes post-injection), the amount of pain reduction was similar in both groups. This suggests that both ketorolac and fentanyl are effective in reducing pain in patients with renal colic and exhibit comparable potency, making them potentially interchangeable in situations where one might be contraindicated.

In contrast to our findings, Darling et al (13) reported a significant difference between the analgesic effects of ketorolac and fentanyl; ketorolac demonstrating a better effect and greater reduction in pain intensity without any notable complications. However, it is important to note that the study by Darling et al included all form administration for fentanyl and ketorolac such as slow IV drip, IV push, intranasal and intramuscular, whereas our study employed the intravenous form, and its analgesic effect was compared between ketorolac and fentanyl. Imamoglu et al (5) found that intravenous fentanyl provided faster and more potent pain relief compared to inhaled fentanyl in patients with renal colic. This difference in administration routes likely explains the discrepancy between the findings of Darling et al and our current study.

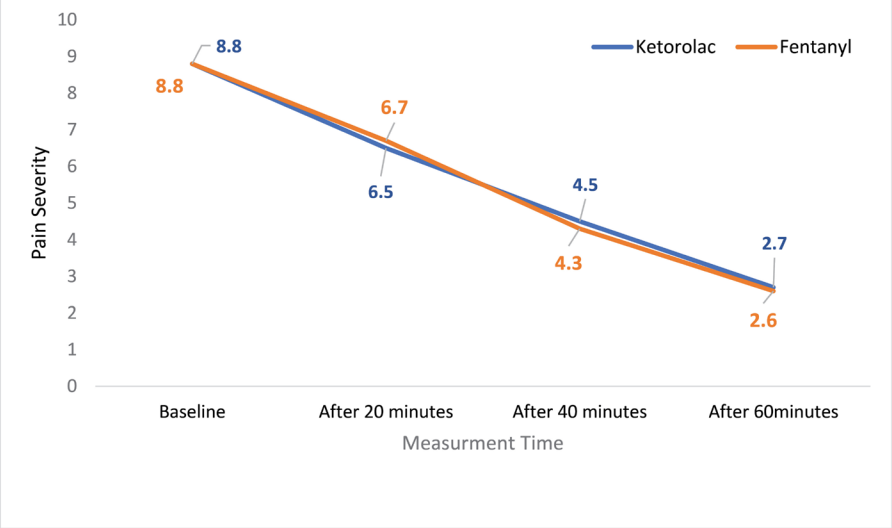

Figure 2. Frequency of pain intensity based on VAS in two groups of patients with acute renal colic pain during the study duration. The vertical axis represents the pain score, and the horizontal axis represents the time intervals of pain assessment at 0, 20, 40, and 60 minutes. Ketorolac is represented by 'K', and fentanyl is represented by 'F'.

Table 3. Frequency distribution of vital sign changes in two groups of patients with acute renal colic pain

Parameters	Groups	Time of Measurement		Difference (Mean ±SD)	*P* value*
		Before (Mean ±SD)	After (Mean ±SD)		
Systolic BP (mm Hg)	Ketorolac	132.5 ± 13.4	124.4 ± 10.7	8.09 ± 9.05	<0.001
	Fentanyl	130.1 ± 15.5	121.4 ± 13.7	8.74 ± 11.36	<0.001
P value**		0.396	0.707	0.739	
Diastolic BP (mm Hg)	Ketorolac	82.6 ± 9.9	78.4 ± 9.3	4.27 ± 8.74	<0.001
	Fentanyl	82.1 ± 9.4	79.7 ± 9.4	2.32 ± 8.88	<0.001
P value**		0.981	0.994	0.250	
Pulse rate (/minute)	Ketorolac	91.0 ± 11.3	80.6 ± 7.0	10.43 ± 8.18	<0.001
	Fentanyl	87.6 ± 12.4	79.6 ± 8.0	7.98 ± 8.28	<0.001
P value**		0.706	0.921	0.121	
Respiratory rate (/minute)	Ketorolac	18.4 ± 1.9	15.9 ± 1.7	2.5 ±1.91	<0.001
	Fentanyl	17.3 ± 2.2	15.9 ± 1.8	1.45 ±2.04	<0.001
P value**		0.974	>0.999	0.006	

BP: Blood pressure. * Paired T-test; **Independent T-test.

Kim et al (14) compared the analgesic effects of intravenous fentanyl and intravenous ketorolac in patients following ophthalmic surgery. Their findings indicated that fentanyl provided better pain relief than ketorolac, and that ketorolac was significantly associated with a higher incidence of postoperative nausea and vomiting. Despite the differences in the underlying cause and primary source of pain between their study and ours, the analgesic effects of intravenous ketorolac and fentanyl differed between the two studies.

Other studies have indicated that combining NSAIDs and opioids can provide superior pain relief in patients with renal colic compared to using either medication alone (10,15). However, it is important to note that opioid use is associated with side effects such as respiratory depression, nausea, vomiting, dizziness, and fatigue (16). Furthermore, the potential for dependence, as well as constipation, drowsiness, respiratory depression, and hypotension at higher doses, has led physicians to explore alternative options (17). Ketorolac is a valuable alternative for opioids, even potent options with fewer side effects like fentanyl, for managing pain in patients with renal colic.

Table 4. Frequency distribution of expected adverse events after therapeutic intervention in two groups of patients with acute renal colic pain

Complications, No. (%)	Groups		*P* value*
	Ketorolac	Fentanyl	
Hypotension	4 (7.3)	31 (56.4)	< 0.001
Dry mouth	0 (0)	5 (9.1)	0.057
Tachycardia	0 (0)	1 (1.8)	> 0.999
Nausea and vomiting	7 (12.7)	2 (3.6)	0.161
Sweating	0 (0)	2 (3.6)	0.495
Drowsiness	2 (3.6)	0 (0)	0.495
Headache	4 (7.4)	0 (0)	0.118

* Chi-square test.

The results of this study indicated no significant difference in the mean systolic and diastolic blood pressure and heart rate of patients in the two groups before and after the therapeutic intervention, suggesting that both ketorolac and fentanyl have a relatively low incidence of hemodynamic complications. Contrary to some studies that highlight potential complications associated with opioid use (18,19), fentanyl in this study provided favorable analgesic effects in relieving renal colic pain without significantly affecting patients' blood pressure and heart rate. However, it is important to note that a statistically significant difference in respiratory rate was observed between the groups ($P = 0.006$), although no instances of severe respiratory depression were reported.

Similarly, Imamoglu et al (5) demonstrated that fentanyl use was not associated with significant changes in patients' respiratory status or blood pressure, and any complications observed during the treatment period were minor and did not require intervention. The literature presents conflicting evidence regarding the superiority of NSAIDs versus opioids in terms of their side effect profiles, as well as the optimal use of these drug classes in combination. This ongoing disagreement underscores the need for further research in this area (13,14,20,21).

Notably, the mean respiratory rate at admission was higher in the ketorolac group compared to the fentanyl group, and this difference was statistically significant. However, following the intervention, there was no significant difference in the mean respiratory rate between the two groups. This observation is particularly important considering that the mean initial pain level was also not significantly different between the groups. Therefore, it can be inferred that ketorolac may have contributed to a greater reduction in respiratory rate compared to fentanyl in this study.

Conclusion

Both ketorolac and fentanyl demonstrate comparable effectiveness in relieving pain in patients with renal colic, suggesting they are suitable alternatives to each other for acute pain management. While fentanyl did not show a significant effect on pulse rate in this study, a statistically significant difference in respiratory rate was observed between the groups, with ketorolac potentially contributing to a greater reduction. Fentanyl was associated with a higher incidence of hypotension, warranting cautious use in patients with pre-existing hypotension. Further research is warranted to comprehensively investigate the side effect profiles of these two drugs in the treatment of renal colic pain.

Limitations of the study

One limitation of this study was the inability to investigate other factors that could influence changes in pain intensity and vital signs. Given the multitude of variables affecting pain perception, it was not feasible to examine all potential contributors within the scope of a single study. Another limitation was the potential influence of variations in patients' education levels and health awareness, which may have affected their interpretation and reporting of pain intensity using the VAS.

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Authors' contribution

Conceptualization: Davood Arab, Arash ArdestaniZadeh, Mohammadreza Moonesan.
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Writing–original draft: Majid Mirmohammadkhani, Mohammadreza Moonesan.
Writing–review & editing: Davood Arab, Arash ArdestaniZadeh, Mohammadreza Moonesan.

Data availability statement

The dataset generated and analyzed during this study is available from the corresponding author upon reasonable request, either during the submission process or after publication.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and the Ethics Committee of Semnan University of Medical Sciences. Approval was obtained from the Ethics Committee (reference number IR.SEMUMS.REC.1399.067). Prior to data collection and intervention, the objectives and methods of the study, along with potential complications, were explained to all patients, and written informed consent was obtained from each participant. The study was registered with the Iranian Clinical Trial Registration Center (identifier: IRCT20150902023855N3; (https://irct.behdasht.gov.ir/trial/31789). This study is extracted from the M.D, thesis of Reihane Ghanipour at this university (Thesis #1815).

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