

Low-dose intravenous ketamine versus intravenous ketorolac in pain control in patients with acute renal colic in an emergency setting: a double-blind randomized clinical trial

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Background: This study was conducted to compare the effectiveness of low-dose ketamine versus ketorolac in pain control in patients with acute renal colic presenting to the emergency department (ED).

Methods: This is a double-blind randomized clinical trial. The initial pain severity was assessed using the numerical rating scale (NRS). Then, ketamine or ketorolac was administered intravenously at a dose of 0.6 mg/kg and 30 mg respectively. The pain severity and adverse drug reactions were recorded 5, 15, 30, 60, and 120 min thereafter.

Results: The data of 62 subjects in the ketamine group and 64 patients in the ketorolac group were analyzed. The mean age of the patients was 34.2 ± 9.9 and 37.9 ± 10.6 years in the ketamine and ketorolac group, respectively. There was no significant difference in the mean NRS scores at each time point, except for the 5 min, between the two groups. Despite a marked decrease in pain severity in the ketamine group from drug administration at the 5 min, a slight increase in pain was observed from the 5 min to the 15 min. The rate of adverse drug reactions, including dizziness ($P = 0.001$), agitation ($P = 0.002$), increased systolic blood pressure (> 140 mmHg), and diastolic blood pressure (> 90 mmHg) was higher in the ketamine group.

Conclusions: Low dose ketamine is as effective as ketorolac in pain management in patients with renal colic presenting to the ED. However, it is associated with a higher rate of adverse drug reactions. (Korean J Pain 2019; 32: 97-104)

Key Words: Acute pain; Blood pressure; Double-blind method; Drug-related adverse reactions; Hospital emergency service; Ketamine; Ketorolac; Pain management; Randomized controlled trial; Renal colic; Urinary calculi.

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INTRODUCTION

Urinary stone pain, also known as renal colic, is one of the most frequent causes of emergency department (ED) visits. Renal colic is the most common manifestation of urinary stones, which is very excruciating [1]. Renal stones usually cause a very severe colicky pain. It is reported that it affects about 1%–5% of the population in developed countries, inflicting pain on about 2.1 million individuals every year. Renal stones affect about 5%–12% of the people in industrial societies at least once in their lifetime and may relapse in about 50% of the patients [2–4]. Effective and prompt pain management is one of the priorities and the basis of treatment in patients presenting to ED with renal colic. Since more than 90% of the stones are expelled spontaneously, the best approach with these patients is to manage their pain [5–8].

Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for pain management of these patients in the ED; however, their administration is associated with side effects and limitations [9–16]. NSAIDs, like ketorolac, are the drug of choice for pain management of patients with renal colic. Intravenous (IV) administration of these drugs has a better and faster effect compared to intramuscular (IM) injection or oral use. However, these drugs should be administered with caution in patients at risk of gastrointestinal bleeding, and those with underlying renal problems. Moreover, NSAIDs may cause a delay in lithotripsy due to inducing platelet function disorders [17,18].

Several studies are investigating the use of other drugs in patients worldwide [19–21]. IV ketamine is a rather safe analgesic compared to opioids, but its effectiveness in renal colic has not been investigated extensively. Ketamine binds to N-methyl-D-aspartate (NMDA) receptors in the posterior horn of the spinal cord and blocks the transmission of painful stimuli. It is also used as a pre-intubation drug in asthmatic patients, due to its relaxing effect on smooth muscles, and has analgesic and anxiolytic effects at the time of injection [22–25]. Ketamine can be administered IV, IM, orally, buccally, epidurally, nasally, and subcutaneously [22,26]. A review of its applications suggests that it may also be used in renal colic because management of pain and anxiety in these patients, together with the occurrence of smooth muscle spasms, may resolve the symptoms. However, the use of ketamine is al-

so associated with different side effects, including tachycardia, increased blood pressure, and emergence phenomena following its administration [23,27,28]. Using a low dose of a drug to minimize its side effects has always been a matter of debate. Several studies have shown that low-dose ketamine, administered orally, is effective in reducing acute pain, but no study has investigated its effectiveness in management of renal colic [26,29,30].

The authors of the current study believe that administration of low-dose ketamine may be useful in avoiding its side effects. Therefore, this study was conducted to compare the effect of low-dose IV ketamine versus IV ketorolac in acute pain management of renal colic in an emergency setting.

MATERIALS AND METHODS

1. Study design

This double-blind randomized clinical trial was conducted from 1 March 2016 to 30 February 2017 in Imam Khomeini Hospital Complex and Sina Hospital, Tehran, Iran. The Ethics Committee of Tehran University of Medical Sciences approved the protocol of the study (approval number: IR.TUMS.REC.1394.786), and the study was registered in the Iranian Registry of Clinical Trials at www.irct.ir (registration code: IRCT2017021932660N1). This trial was carried out in accordance with the tenets of the Declaration of Helsinki. The objective and protocol of the study were explained to the subjects who met the inclusion criteria in simple language and their informed consent was obtained in writing if they were willing to join the study. Participation in this research caused no disorder in diagnostic and therapeutic procedures and no additional costs were imposed on the patients.

2. Study population

Patients over 18 years of age who presented to the ED with acute renal colic and clinical symptoms suggesting renal stones, as well as patients with a history of renal calculus, whose symptoms were similar to previous attacks, were included in this study. The exclusion criteria were sensitivity to ketamine or ketorolac, ischemic heart disease, hypertension, intracerebral vascular abnormalities, fibromyalgia, chronic pains managed with morphine, use of

analgesics within 4 h before presenting to the ED, pregnancy, lactation, renal or hepatic failure, psychosis, trauma to the head or eye, and unstable vital signs. An emergency medicine specialist evaluated the physical examinations and past medical histories of the patients to determine the presence of the above criteria.

According to $\alpha = 0.05$ and $\beta = 0.9$, 63 patients were required in each group to detect any significant difference in pain between the two groups (a total of 126 patients). The patients who met the inclusion and exclusion criteria were randomly assigned to one of two groups: either low-dose IV ketamine (group A) or IV ketorolac (group B), using a computer-generated random numbers table. **Fig. 1** presents the CONSORT flowchart of the patients.

3. Intervention

The baseline data and demographic characteristics of the patients were recorded in predesigned checklists. Before drug administration, one of the researchers assessed the initial pain severity using the numerical rating scale (NRS). Then, ketamine at a dose of 0.6 mg/kg or ketorolac at a dose of 30 mg was administered by another person/nurse. In the next step, the same researcher who initially as-

sessed the pain, re-assessed pain severity using the NRS and the rate of adverse drug reactions at 5, 15, 30, 60, and 120 min after drug administration. The investigator, who was responsible for pain assessment, was kept blinded to the type of the administered drug. If pain was intolerable despite administration of ketorolac or ketamine, morphine was injected at a dose of 0.1 mg/kg as a rescue medicine. Lack of effective pain management within 120 min of two ketamine injections at a dose of 0.6 mg/kg and an NRS score above 5 indicated treatment failure [31].

4. Statistical analysis

A chi-square and Fisher exact test were applied to analyze qualitative data, and the independent *t*-test and Mann-Whitney tests were used to compare quantitative variables between case and control groups. The Friedman test was administered to analyze pain changes over time. Qualitative data are presented as frequency and percentage, and quantitative data are reported as mean, median, standard deviation, and interquartile range. The Kolmogorov-Smirnov test and Q-Q plot were applied to assess data normality. Data were analyzed with IBM SPSS ver. 22 (IBM Corp., Armonk, NY) and $P < 0.05$ was considered significant.

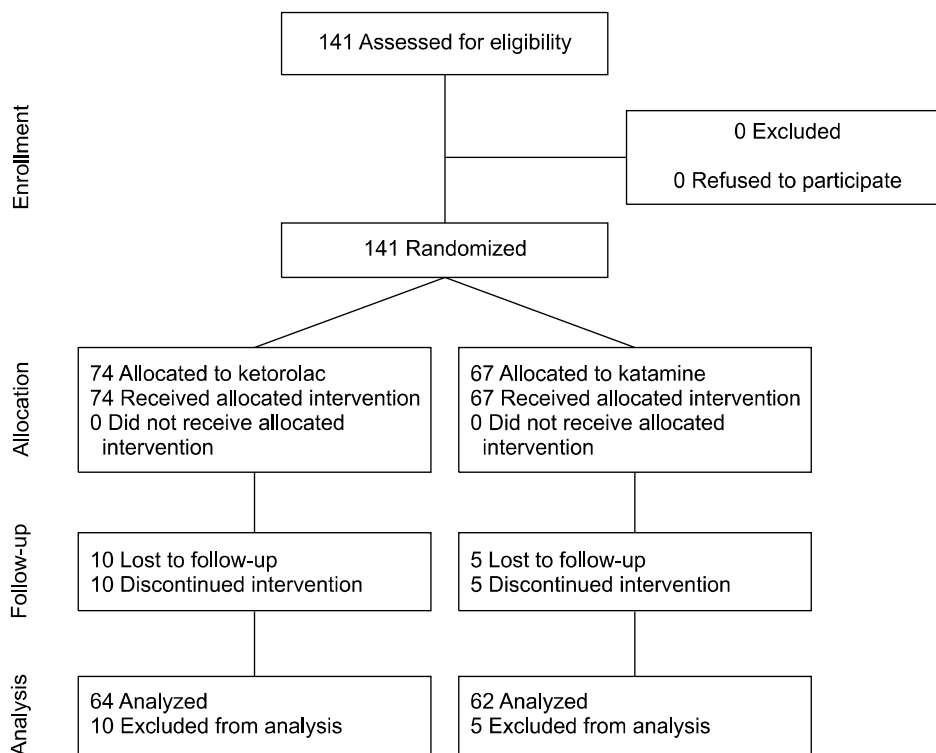


Fig. 1. CONSORT flowchart of the patients.

RESULTS

The data of the 62 patients in the ketamine group and 64 subjects in the ketorolac group were analyzed. The mean age of the patients was 34.2 ± 9.9 and 37.9 ± 10.6 years in ketamine and ketorolac groups, respectively ($P = 0.092$). Moreover, there was no significant difference in age categories between the two groups (Table 1).

1. Pain assessment

There was no significant difference in the mean NRS scores at different time points, except for the 5 min, between the two groups ($P > 0.05$) (Table 2). Despite a substantial decrease in pain severity from injection to the 5 min in the ketamine group, a slight increase was reported from min 5 to min 15. Moreover, in patients receiving ket-

amine, the pain severity decreased by 4 points from injection to 15 min, compared to the initial pain severity, while the pain severity never decreased by 3 points compared to the previous time point in the ketorolac group; however, the pain score was 2 at 30 min in patients receiving ketorolac. The pain severity decreased significantly in both groups over time ($P < 0.001$) (Fig. 2).

2. Side effects

A significant difference was observed in the mean systolic blood pressure and heart rate at 5, 15, and 30 min between the two groups ($P < 0.05$) (Fig. 3). Total side effects were reported in 39 patients (62.9%) in the ketamine group and 9 patients (14.1%) in the ketorolac group. The rate of side effects was significantly higher in the ketamine group ($P = 0.001$). Details of reported side effects were summarized

Table 1. Baseline Characteristics of Studied Patients with Renal Colic in Current Study

Characteristic	Ketamine (n = 62)	Ketorolac (n = 64)	P value
Sex			0.175
Male	44 (71.0)	52 (81.2)	
Female	18 (29.0)	12 (18.8)	
Age (y)			0.092
≤ 30	31 (50.0)	18 (28.1)	
31-40	15 (24.2)	19 (29.7)	
41-50	12 (19.4)	18 (28.1)	
> 50	4 (6.5)	9 (14.1)	
History of renal stone			0.367
Yes	51 (82.3)	48 (75.0)	
No	11 (17.7)	16 (25.0)	

Values are presented as number (%).

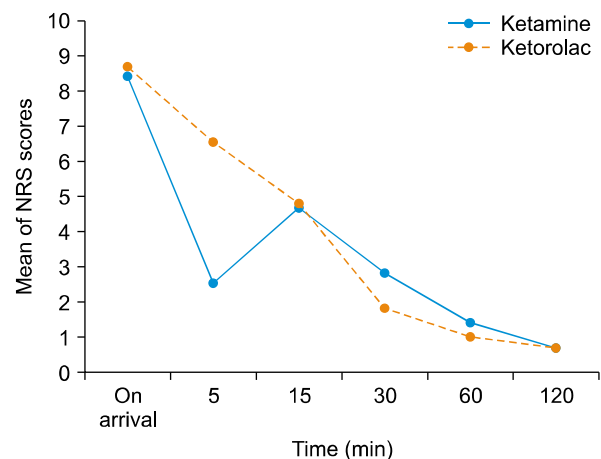


Fig. 2. Changes of pain severity in patients receiving ketorolac and ketamine during the study period. NRS: numerical rating scale.

Table 2. Pain Score of Subjects at Different Time Intervals Based on Numerical Rating Scale

Time (min)	Ketamine (n = 62)		Ketorolac (n = 64)		P value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
On arrival	8.4 ± 1.5	8.0 (3.0)	8.7 ± 1.4	8.0 (2.0)	0.217
5	2.5 ± 2.7	3.0 (5.0)	6.5 ± 2.1	6.0 (3.0)	< 0.001
15	4.7 ± 3.1	5.0 (4.0)	4.8 ± 2.5	5.0 (3.0)	0.998
30	2.8 ± 2.9	3.0 (5.0)	1.8 ± 2.3	0.0 (4.5)	0.072
60	1.4 ± 2.4	0.0 (3.0)	1.0 ± 2.2	0.0 (0.8)	0.476
120	0.7 ± 1.9	0.0 (0.0)	0.7 ± 1.6	0.0 (0.0)	0.591

SD: standard deviation, IQR: interquartile range.

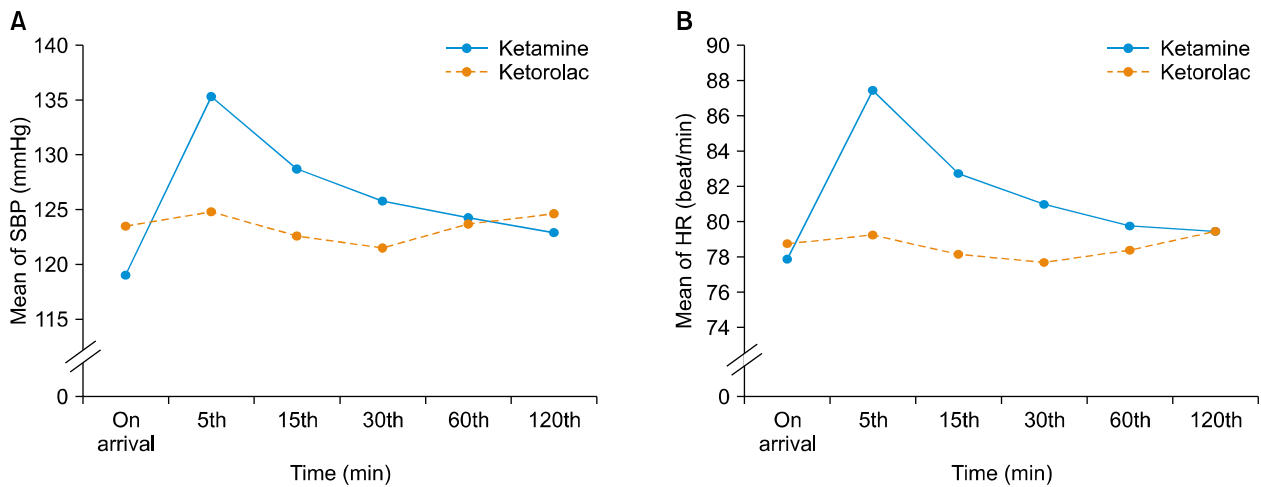


Fig. 3. Vital signs changes in patients receiving ketorolac and ketamine during the study period. Mean of (A) systolic blood pressure (SBP) and (B) heart rate (HR).

Table 3. Frequency of Side Effects in the Study Population

Side effect	Ketamine (n = 62)	Ketorolac (n = 64)	P value
Tachycardia	2 (3.2)	0	0.240
Blood pressure rising	15 (27.8)	1 (1.9)	< 0.001
Nausea	7 (11.3)	9 (14.1)	0.640
Dizziness	25 (40.3)	0	< 0.001
Agitation	9 (14.5)	0	0.002
Other	7 (11.3)	0	0.006

Values are presented as number (%).

in **Table 3.**

DISCUSSION

This study was done to compare low-dose ketamine versus IV ketorolac in acute pain management of patients with renal colic presenting to the ED. According to the results of this study, low-dose ketamine was as effective as IV ketorolac in pain management of these patients, but its use was associated with a higher rate of side effects. In the present study, ketamine and ketorolac were equally effective in controlling pain severity but the occurrence of complications like tachycardia, increased blood pressure, dizziness, and agitation was higher following ketamine administration.

Sadove et al. [32] was one of the first researchers who proposed the analgesic effects of ketamine at subdisso-

ciative low doses. However, after several years, the effectiveness of ketamine as an analgesic is still a matter of debate and discussion. Some researchers believe that its antihyperalgesic effects are stronger than its analgesic properties, and a number of studies are being conducted in this regard [24,33]. Few studies have investigated the effect of ketamine on pain management of patients with renal colic, although its effects in other study populations have been more frequently studied. Some previous investigations have shown that ketamine is as effective as opium in post-surgical pain management. Moreover, it has proved very effective in burn patients [24]. The results of a study by Galinski et al. [34] on the management of acute pain in trauma patients showed that administration of low-dose ketamine and morphine reduced the need for morphine by about 26% for 30 min. Moreover, Beshpalov et al. [35] reported that blockade of NMDA receptors by ketamine inhibits hyperalgesia and prolongs the duration of the antinociceptive effect of opioids. Some other studies have claimed that intranasal ketamine may be as effective as IV morphine in pain management of renal colic patients [36]. However, some studies have reported contradictory results. For example, Vosoughin et al. [37] reported that NSAIDs were more effective than ketamine in women undergoing elective gynecologic laparoscopy.

Ketamine exerts its analgesic effects through different mechanisms, including NMDA receptor antagonism, opioid receptor agonism, sigma receptor interaction, local anesthetic action, cholinergic effects, monoamine effects, and

supraspinal mechanisms [24]. It is obvious that these mechanisms are associated with different clinical manifestations that can be desirable or undesirable [38]; for example, unlike NSAIDs, ketamine does not induce platelet function disorders [39]. Moreover, it plays an undeniable role in patients with opioid tolerance [40]. In addition, it may be a proper alternative in asthmatic patients in whom histamine release induced by morphine is a problem. One of the advantages of ketamine is its diverse administration routes [24]; for example, Andolfatto et al. [41] studied the analgesic effect of intranasal ketamine in the ED.

In the present study, the frequency of side effects, including dizziness, and increased systolic blood pressure and diastolic blood pressure (> 90 mmHg), was higher in the ketamine group. Physicians are not willing to prescribe ketamine because it induces agitation and dissociation [36,37]. The threshold of consciousness impairment following ketamine administration is very low and loss of consciousness is reported even at a dose of 0.25 mg/kg. It is recommended to administer titrated doses of ketamine starting from 0.1 mg/kg to a maximum of 0.5 mg/kg [24,42]. Tachycardia and increased blood pressure are other side effects of ketamine that require attention despite being transient [43].

The most common limitations of objective studies are diversity in subjective responses regarding pain perception and encouraging the patients to participate in the study. The patient's perception of pain is extensively affected by the drug's pharmacogenetics and is different from time to time. Another limitation of the study was adverse drug reactions, including disorientation in time and place, dissociative disorders, and hallucination; however, it seems that IV administration of low-dose ketamine is not associated with psychotomimetic effects or adverse pharmacologic reactions. More studies are required to assess whether ketamine has long-term benefits in decreasing the occurrence or severity of the pain. Moreover, the stone size and location and the level of hydronephrosis, which were not investigated in this study, may affect interpretation of the results. As another limitation, emergency revisits and the outcomes of these patients were not evaluated, either.

According to the results of the present study, low-dose ketamine is as effective as IV ketorolac in pain management of IV renal colic patients presenting to the ED, but its use is associated with a higher rate of side effects. The advantages and disadvantages of ketamine admin-

istration in comparison with ketorolac should be studied and discussed to determine its indications. As of now, there is no justification for using ketamine instead of ketorolac as a first line of treatment in patients with renal colic in the emergency setting. However, ketamine may be administered as an alternative when ketorolac is contraindicated.

A published systematic review conducted by Ghate et al. [44] in 2017 reported that there is broad variation in the dose and route of low dose ketamine used in previous studies ranging from 0.1 to 0.7 mg/kg administered subcutaneously, intravenously, or intramuscularly. It seems that determination of the exact sub-dissociative dose of ketamine still requires further investigations, so reducing the side effects but benefit from advantages.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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