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ORIGINAL ARTICLE

Intranasal ketamine versus intravenous morphine for pain management in patients with renal colic: a double-blind, randomized, controlled trial

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Abstract

Background Urinary stones are a common urologic problem that can be manifested as an intense pain, known as renal colic. Pain control is an important intervention for the emergency treatment of renal colic patients. Intranasal ketamine can form a crucial part of such interventions by offering a new route for a widely-used analgesic drug.

Methods In a double-blind, randomized, clinical trial, adults with renal colic admitted to a tertiary hospital emergency department were examined. The intervention group received 1 mg/kg intranasal (IN) ketamine and 1 ml of saline as a placebo. The control group received 0.1 mg/kg intravenous (IV) morphine and four puffs of saline as the placebo. The pain score was measured on the Numerical Rating Scale (NRS) 0, 15, 30 and 60 min after the drug administration.

Results A total of 184 patients enrolled in this study in two parallel groups. The two groups did not differ significantly in terms of pain intensity at the time of their referral ($P=0.489$), 15 min post-dose ($P=0.204$), 30 min post-dose ($P=0.978$) and 60 min post-dose ($P=0.648$).

Conclusion IN ketamine is as effective as IV morphine for pain control in renal colic patients. No remarkable side-effects were observed for IN ketamine use in these patients.

Keywords Ketamine · Morphine · Kidney stones

Introduction

Renal colic is a common urologic problem that can affect approximately 1–5% of the general population annually [1]. It is the most common urologic cause for Emergency Department (ED) visits [2]. This pain can be very severe and have a tremendous emotional impact on both patients and emergency physicians. Relieving this pain is an important part of renal colic treatment in EDs [3]. Different medications are used for pain control in renal colic patients. Opioids, NSAIDs, corticosteroids, alpha-blockers, magnesium sulfate, lidocaine and acetaminophen are some of these drugs that have yielded different pain reduction outcomes in different studies [4-7]. Although NSAIDs are the preferred analgesics in renal colic patients and the European Association of Urology guidelines on nephrolithiasis emphasize the benefits of NSAIDs over opiates, this drug has some restrictions for use in specific groups of patients [8], as patients with coronary artery disease, asthma or COPD have restrictions in NSAID use. Opiates are the second analgesic of choice in this group of patients. Opiates are associated with significant side-effects, including nausea and vomiting [9]. Some studies have shown that ketamine can replace opiates in renal colic patients. Forouzan et al. studied intravenous (IV) ketamine for pain relief in renal colic patients and found this drug more effective than morphine [10]. Farnia et al. also studied intranasal (IN) ketamine in renal colic patients and found it effective and safe [11].

Since its introduction to medicine in the 1960s, ketamine has been widely used for inducing anesthesia because of its

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safe hemodynamic profile [12]. This *n*-methyl-D-aspartate (NMDA) antagonist is used both as a single drug or in combination with other drugs for the induction of anesthesia and analgesia [13]. In its intravenous use, the analgesic effects of ketamine start in doses 10–15 times lower than the anesthetic dose; therefore, it often keeps patients awake and has a minimal effect on respiration or hemodynamics [14, 15]. The intranasal (IN) route of ketamine administration has recently been studied for analgesic purposes. Ketamine's bioavailability in the IN route is approximately 45% [16]. The onset of the analgesic effects of ketamine is 2 min after administration and this effect lasts for approximately 3 h [17, 18]. The IN route offers a fast and non-invasive technique for drug administration that might have certain advantages for EDs. This study examined the IN administration of ketamine to renal colic patients in EDs.

Materials and methods

This double-blind, randomized, clinical trial was conducted at Imam Reza Hospital in Tabriz, Iran, as a tertiary hospital with annually 110,000 ED visits. After approval from the Ethics Committee of Tabriz University of Medical Sciences (Approval No. IR.TBZMED.REC.1398.006), the study was registered at the Iranian Registry of Clinical Trials under the registration code IRCT20121010011067N4. In the 3 months from 15 May 2019 to 15 July 2019, 186 eligible consecutively-selected patients were investigated. After explaining the research objectives and protocol to the patients in a simple language, their written consent was obtained if they were willing to take part in the study.

The patients over age 18 years with a history of nephrolithiasis and complaints of flank pain similar to their previous pain and patients with acute flank pain suggesting renal colic were included in the study. A pain meeting the following criteria was considered suggestive of renal colic pain: Flank pain with radiation to the groin or genitalia accompanied by frequency, hematuria or hydronephrosis in the ultrasound. The patients who had received analgesics before their ED admission and those with a history of psychosis, rhinitis or common cold or hypersensitivity to ketamine or morphine were excluded from the study. After ensuring pain control, all the patients with flank pain underwent a non-contrast CT scan for the confirmation of nephrolithiasis, and the patients with confirmed renal stones entered the study.

Considering a test power of 95% for the study and according to previous studies, the sample size was estimated as 73 per group according to Cochrane's formula. To achieve a higher test power, the sample size was increased to 100 per group.

The patients were randomly divided into two parallel groups using a random number generator website. A simple individual randomization protocol was used in this study. The patients were randomly divided into two groups. Group I was taken as the intervention group and received 1 mg/kg IN ketamine (RotexMedica Pharmaceutical Co., Germany) by a nasal spray. One milliliter of normal saline was injected intravenously to this group as the placebo. Group II was taken as the control group and was administrated 0.1 mg/kg IV morphine (Darupakhsh Pharmaceutical Co., Iran) and four puffs of IN saline was used in them as the placebo.

The drugs were administered in both groups by different nurses who were blinded to the patients' grouping and type of administered drug. All the patients were also blinded to their study group. The questionnaires were filled out by a single physician who was also blinded to the patients' grouping.

The pain score was measured in the patients before the drug administration and then 15, 30 and 60 min after the beginning of treatment using a Numerical Rating Scale (NRS). Reduction in pain score was taken as the primary outcome in this study.

For the patients who did not respond to the drugs, the intervention was stopped and the pain management protocol advised in urology guidelines was used.

The qualitative data were analyzed using the Chi-square test. The independent *t* test and Mann–Whitney's *U* test were used for analyzing the quantitative data. The data normality was assessed with the Kolmogorov–Smirnov test. The qualitative data were reported as frequency and percentage and the quantitative data as mean, median and standard deviation. All the data were analyzed in SPSS-16 and $P < 0.05$ was taken as the level of statistical significance.

Results

Two hundred patients entered this study in two parallel groups with one hundred patients in each group. The mean age of the patients was 40.30 ± 7.6 years. The youngest patient was 22 years old and the oldest was 58 years old.

Fourteen patients did not complete the 60 min observation time and were excluded from the study. Two patients in the ketamine group had no change in their pain severity after 15 min and were administered morphine to abort their pain and were excluded from the study (Fig. 1). Ultimately, 95 patients enrolled in the ketamine group and 89 enrolled in the morphine group. The mean age of the patients was 41.27 ± 5.2 years in the morphine group and 39.39 ± 3.7 years in the ketamine group. There was no statistically significanct difference between the two groups ($P = 0.095$).

There was no significant difference in the pre-treatment pain score between the two groups ($P = 0.489$); (Table 1). The mean pain scores were 5.22, 2.97 and 1.28 after 15,

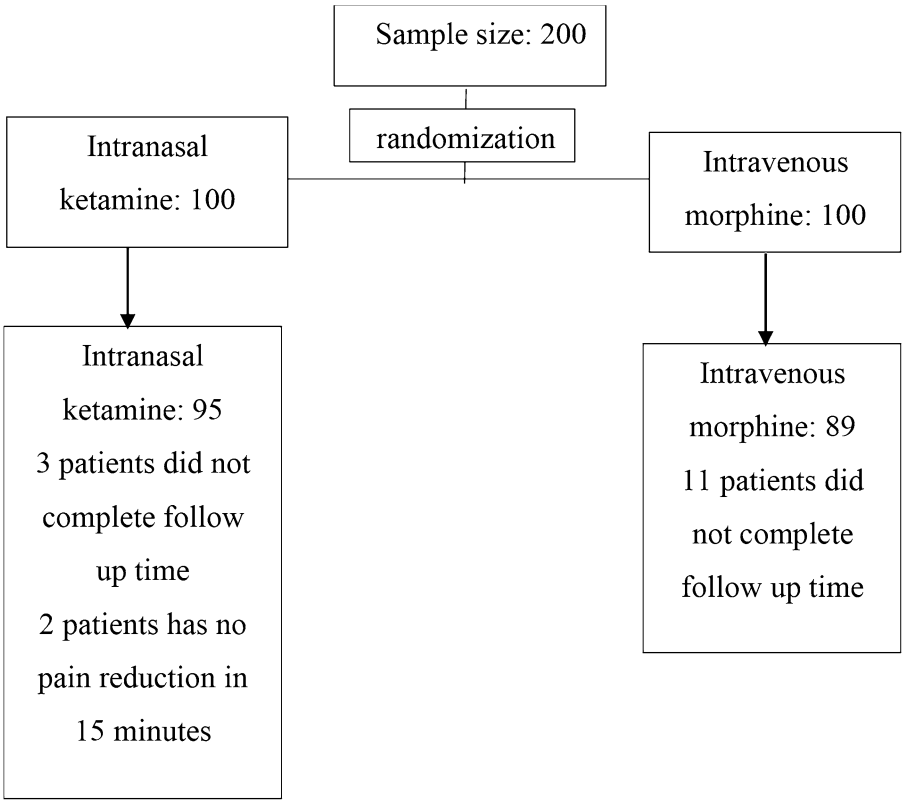

Fig. 1 The study flow chart. Three patients did not complete the follow-up; two patients showed no pain reduction after 15 min. Eleven patients did not complete the follow-up.

Table 1 Pretreatment NRS in the patients

NRS	Frequency	Percentage
4	11	6.0
5	15	8.2
6	19	10.3
7	28	15.2
8	50	27.2
9	26	14.1
10	35	19.0

Table 2 The NRS 0, 15, 30 and 60 min after the drug administration in the two groups

Variable	Group	Mean	*P* Value
Age	Morphine	41.27	0.095
	Ketamine	39.39	
Initial pain	Morphine	8.24	0.489
	Ketamine	8.11	
15-min pain	Morphine	5.22	0.204
	Ketamine	4.85	
30-min pain	Morphine	2.98	0.978
	Ketamine	2.97	
60-min pain	Morphine	1.67	0.648
	Ketamine	1.53	

30 and 60 min in the morphine group and 4.85, 2.97 and 1.53 in the ketamine group (Table 2). No significant difference was observed in the pain scores between the two groups 15, 30 and 60 min after drug administration.

Twenty-one patients in the ketamine group (21.1%) had complaints of dizziness. This symptom was resolved in less than 15 min and did not require the administration of any medications.

In the morphine group, 85 patients (95.5%) experienced nausea without vomiting, which was not severe enough to administer medications.

Discussion

The present findings showed that IN ketamine is as effective and safe as IV morphine in pain reduction in patients with renal colic admitted to EDs.

Ketamine has analgesic properties that work through different mechanisms. Its main mechanism of effect is antagonizing the NMDA receptors. It also has agonist effects on opioid receptors and interacts with sigma receptors [19].

Many studies have shown significant analgesic effects for IV ketamine in comparison with opioids. In 2015, Motov et al. studied IV ketamine versus IV morphine in a double-blind, randomized, clinical trial and found ketamine to be as effective as morphine in pain control and also reported that it had fewer side-effects [20]. In a double-blind RCT in 2016 conducted on children who had undergone bone marrow biopsy, Abdolkarimi et al. found IV ketamine a safe and effective analgesic in comparison with IV meperidine [21].

Although these studies plus many others have shown the efficacy of IV ketamine in analgesia induction, the intranasal route of ketamine administration is a relatively novel method that has recently been studied in emergency settings. Andolfatto et al. studied IN ketamine in 40 emergency patients in 2013 and found that IN ketamine reduces the Visual Analog Scale (VAS) score in 88% of patients in a clinically significant manner. They also reported minor side-effects for IN ketamine [22]. In 2019, Andolfatto et al. also studied IN ketamine as a prehospital pain control drug in combination with nitrous oxide and reported a better outcome in comparison with a placebo [23]. In a prospective RCT in 2016, Shimonovich et al. studied 90 patients with trauma and compared IN ketamine with IV and IM morphine in emergency patients. Their trial examined adult patients with moderate to severe traumatic pain who were administered 1 mg/kg IN ketamine or 0.1 mg/kg IV morphine or 0.15 mg/kg IM morphine. They found IN ketamine to be efficient for pain control and safe in hemodynamically fragsile or otherwise unstable patients [24]. The doses of IN ketamine and IV morphine administered in their study were similar to the doses in the present study, which also found similar effects for ketamine in renal colic patients' pain control.

In another double-blind RCT conducted in 2016 for studying IN ketamine in renal colic patients, Farnia et al. examined 40 patients 5, 15 and 30 min after administering 1 mg/kg IN ketamine or 0.1 mg/kg IV morphine. They found similar pain control outcomes in the IN ketamine and IV morphine groups [11]. They noted their small sample size as a limitation of their study. The present study used the same doses of the medications, assessed the patients for 60 min and used a larger sample size to improve the test power and still achieved the same pain reduction outcomes in both groups.

Shrestha et al. investigated IN ketamine administration at a lower dose in emergency patients in 2015. They used 0.7 mg/kg of IN ketamine and an additional 0.3 mg/kg dose only if VAS was more than 50 mm after 15 min of the drug administration. They studied 34 consecutively-selected patients and found IN ketamine a safe and effective choice for pain control in overcrowded and low-resource EDs [19].

In the present study, similar to the aforementioned studies, no remarkable side-effects occurred after IN ketamine administration, which shows the advantages of ketamine use in EDs, especially since many ED patients may have hemodynamic instability. Also, there are more challenges for respiratory and hemodynamic monitoring in overcrowded EDs that may restrict opioid use but not ketamine use in such conditions. Although this study did not show a better pain control outcome for IN ketamine versus IV morphine, the benefits of the IN route of drug administration should be emphasized, as it can reduce the time of starting pain medication for patients and also helps avoid the pain of intravenous injection. The IN route is also easier for out-of-hospital care and has a lower cost for the health system, both in terms of its safer hemodynamic profile and more simple administration. According to the EAU guidelines for the treatment of renal colic, the first-line treatment agent consists of non-steroidal anti-inflammatory drugs (NSAIDs) such as Diclofenac Sodium. NSAIDs have a better effectiveness in controlling the pain of renal stone than opioids. Furthermore, opioids have some uncomfortable side-effects, such as dizziness and vomiting (4). The use of low-dose ketamine is recommended for controlling pain in old patients, patients with a history of asthma, pregnant patients and others who cannot use NSAIDs and in whom opioids are rarely administered.

Limitations

The limitations of this study include being a single-center study. In addition, the time dedicated for follow-up of the patients was 60 min, since most patients were discharged after their pain was mitigated. This limitation means that the recurrence of pain and potential long-term adverse effects of the drug were not examined. The NRS was used in this study because many of the patients did not cooperate in using the VAS.

Our study has a potential strength in other studies. The present study had a large sample size in comparison with previous studies, which might have improved its test power. Also, the patients were followed up for a longer period of time in comparison with previous studies on the same subject. Meanwhile, a multicenter study with a larger sample size is needed to assess the efficacy and the safety of IN ketamine.

Conclusion

IN ketamine has the same efficacy as IV morphine in renal colic pain control. It has a good hemodynamic profile and is safe for use in emergency patients. IN Ketamine can, therefore, be administered to patients with contraindication for NSAIDs and opioids and also for all patients as a second-line treatment for renal colic.

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Author contributions All the authors have read and approved the manuscript. MP, ZVR and HS were responsible for data collection, literature review, and drafting the manuscript. PM and SPP undertook major parts of the study design and performed the statistical analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval The study was approved by the Ethics Committee of Tabriz University of Medical Sciences and registered under the code IR.TBZMED.REC.1398.006.

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