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The analgesic effect of intranasal ketamine and intravenous morphine in patients with flank pain (renal colic) in the emergency department; a clinical trial study

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Abstract

Introduction: Renal colic is the most common clinical manifestation of urinary stones.
Objectives: This study was aimed to compare the effect of intranasal ketamine versus intravenous morphine on renal colic.
Patients and Methods: In this clinical trial study, 100 patients with renal colic were entered into the study and randomly divided into two groups. Patients in treatment group received intranasal ketamine (1.5 mg/kg) and the other group was given intravenous morphine (0.1 mg/kg). The pain was measured at 0, 5, 15, 30 and 60 minutes after therapy.
Results: In this study, 32% of patients were female and 68% were male. In addition, the difference between the initial pain with the pains at all subsequent times was significant in the two groups ($P<0.001$). The duration of the ketamine effect to control pain was longer; since, with the administration of morphine, a faster effect on pain relief was achieved.
Conclusion: Low-dose ketamine is considered as an analgesic with low side effects, with simple and uncomplicated usage that reduces the risk of the needle stick in pre-hospital conditions. Therefore, intravenous (IV) morphine has a faster effect; therefore its administer in patients with severe pain should be given priority.
Trial Registration: The trial protocol was approved in the Iranian Registry of Clinical Trial (identifier: IRCT20171229038132N1; https://irct.ir/trial/28821, ethical code; IR.ZAUMS.REC.1396.271).

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Introduction

The risk of developing urinary tract stones in societies is increasing and the risk of life-span sickness varies from 6% in women to 12% in men(1). Renal colic is a complex of symptoms caused by urethral obstruction due to stones (2). Generally, it is an acute onset and severe flank pain, which can be accompanied by one-sided extension to the groins, nausea and vomiting(3). Most patients experience the first occurrence of urinary stones in the late 20s and with the peak age between 40-60 years old in both genders, with the difference that the starting age in women is slightly earlier than men (4). Failure to control pain and provide adequate analgesia is the main criteria for the referral of a patient with renal colic to a hospital (5).

The classic and standard routine for pain relief in renal colic are nonsteroidal anti-inflammatory drugs (NSAIDs) or opiates (4). Several studies have been conducted to compare the effects of opiates and NSAIDs on relief renal colic pain and it has been shown that NSAIDs and opioids are more effective than placebo in reducing pain (6). However, the numerous complications of these two drugs (nausea, vomiting and increased risk of bleeding) can limit their usage in some patients (7).

One of the drugs that have been employed as an analgesic for various types of pain, including postoperative pain, renal colic pain and also chronic pain, is ketamine. In addition to the anesthetic effects, it also has analgesic and sleeping properties, which distinguishes it from other anesthetics.

Key point

In this clinical trial study, 100 patients with renal colic were divided into two groups. Patients in the first group received the intranasal ketamine (1.5 mg/kg) and the second group received the intravenous morphine (0.1 mg/kg). The results of this study showed that low-dose ketamine is considered as an analgesic with low-side effects, with simple and uncomplicated administration that reduces the risk of the needle stick in pre-hospital conditions.

Additionally, the side effects of this medication are reduced in the analgesic dosage. This drug conducts its analgesic effect by attaching to the receptors in the posterior horn of the spinal cord and blocking the N-methyl-D-aspartate (NMDA) painful stimulus. Ketamine can be used in a variety of ways, including injection, oral, skin, topical, epidural, intranasal and subcutaneous (8-10). Ketamine is rapidly distributed in all tissues of the body, including the brain. Its metabolism is through the liver and its half-life is 2 to 3 hours. The onset of the effect after intravenous injection is 15 to 30 seconds and after muscular injection is 3 to 4 minutes. Duration of the drug after intravenous administration is 5 to 10 minutes after the intramuscular injection is 12 to 25 minutes (11) and the bioavailability of the nasal form is 45% (12).

Opiates due to their excessive side effects, lack of access to in all medical centers, the route of administration only through injections and the limited use of them in some diseases, including asthma and pregnant women, faces some difficulties (7,13). Studies have shown that the administration of ketamine in sub-anesthetic doses can be considered as a safe and with low complications option for the treatment of acute (10,14,15) and chronic pain (16). Therefore, due to some difficulties with the use of first-line and intravenous drugs and also a small number of studies on the effects of ketamine on renal colic pain relief, we decided to investigate the effect of administration of intranasal ketamine compared with intravenous morphine to reduce the pain of patients with renal colic who are referred to the emergency department in this study.

Objectives

Therefore, we decided to investigate the effect of administration of intranasal ketamine compared with intravenous morphine to reduce the pain of patients with renal colic who are referred to the emergency department in this study.

Patients and Methods

Study design

This clinical trial study was carried out from 23 September 2017 to 20 March 2018 in the emergency department of Khatam-al-Anbia hospital in Zahedan. The participants were included the study after obtaining informed consent.

Statistical analysis

Samples were entered into the study from among those referring to the emergency department with flank pain after an initial physical examination and bed-side ultrasonography by an emergency specialist and rejection of critical causes, including aortic dissection or gynecologic disorders. Patients were selected from those with a previous history or diagnosis of kidney stones and were ruled out for acute renal diseases. Inclusion criteria include patients with known history of renal stone, acute renal pain with score ≥four based on visual analogue scale (VAS) and with age between 20 to 50 years and with no other underlying diseases. Exclusion criteria include drug addiction based on patient's own declaration, pregnant and lactating women, narcotic allergy, nasal obstruction, systolic blood pressure less than 100 mm Hg, respiratory distress, history of seizure, history of glaucoma, previous use of the pain-killer drug before visiting the hospital and critical diseases such as aortic dissection. The sample size was calculated as 100 patients in both case and control groups based on the study by Cyrus et al (17). Sampling was conducted with simple and convenience method.

Intervention and information gathering

This clinical trial was conducted without blindness that both investigators of treatment response and the patients were aware of the type of treatment received. After a physical examination, ultrasonography, initial investigations and rule outing of other differential diagnosis patients were randomly divided into two groups. VAS criteria were employed to measure pain in this study that is psychometric response instrument consist of a straight line graded from 0 to 10. The number 0 is for the complete no-pain state and the number 10 is for worst possible pain. Patients rate their pain depending on the severity of it with one of the numbers on this scale. In fact, this number is a numerical measure of the patient's pain (16). The pain was measured at 0, 5, 15, 30 and 60 minutes after medication administration. One group of patients received intranasal ketamine with a dose of 1.5 mg/kg plus intravenous distilled water as placebo and the other group was given a 0.1 mg/kg intravenous morphine plus intranasal distilled water as placebo. If the patient does not report relief of pain for at least 30 mm lower than initial pain after 30 minutes, 2 µg/kg (18) of fentanyl was given in each group. Pain-control results information, together with the demographic data of patients, including age and gender were recorded for each patient.

Statistical analysis

After gathering data, they were entered for statistical analysis in SPSS version 25. Then regarding descriptive indexes (mean, standard deviation, frequency and percentage) were analyzed. The relationship between variables measured using *t* test and chi-square test and determining changes in pain score over time repeated ANOVA test was employed at the significance level of 0.05.

Results

In this study, 100 patients with renal colic were studied and assigned in the two groups of morphine and ketamine (Figure 1). Thirty-two patients (32%) were female and 68 (68%) were male. The mean age of the patients was 34.15 ± 11.80 years, which was 32.87 ± 10.82 years in the morphine group and 35.43 ± 12.68 years in the ketamine group. Based on the independent t-test, mean age in the two groups did not show a significant difference ($P = 0.29$).

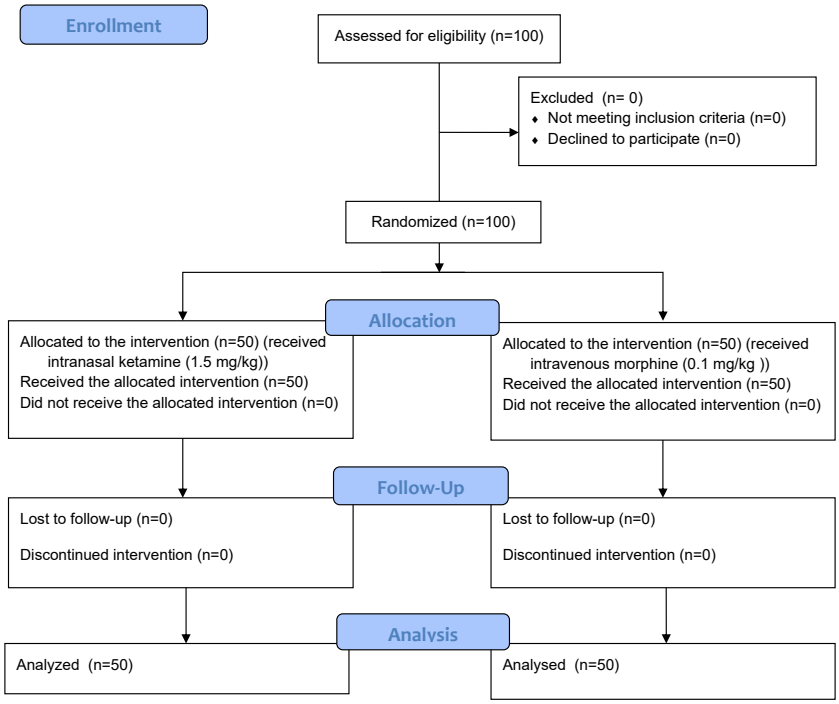

Figure 1. Consort flowchart of patients.

The average weight of the patients was 68.32 ± 11.22 kg, which was 68.78 ± 9.31 kg in the morphine group and 68.00 ± 12.96 kg in the ketamine group. Based on independent *t* test, mean weight in the two groups did not show a significant difference ($P = 0.75$). Additionally, between the two groups in the initial examinations with kidneys, ureters and bladder (KUB), ultrasonography and history of kidney stones there was no statistically significant difference (Table 1).

Independent *t* test was utilized to evaluate the mean score of pain at different times between the groups. Accordingly, as Table 2, the mean of initial pain and pain at 30 minutes after the administration of the drug in the two groups were significantly different. In addition, the difference between the initial pain with pain at all subsequent times in the two groups were significant. By reviewing Table 2, it is shown that the duration of the action of ketamine is longer for pain control, while morphine has a faster effect in pain relief.

Finally, concerning the significance of Mauchly's test results ($P < 0.001$), Greenhouse-Geisser test was used that again significant differences were observed in these groups. This significant difference was related to intra-group effect ($P < 0.001$) and interaction ($P < 0.001$); while the intergroup effect ($P < 0.8787$) was not significant. Then to investigate further intra-group difference, independent t-test was employed in the two groups (Tables 3 and 4).

Based on the results, the need for drug re-administration

Table 1. Frequency distribution of demographic indicators & primary criteria in the patients

Characteristics		Group				*P* value
		Morphine		Ketamine		
Gender	Female	16 (32.0)	-	16 (32.0)	-	χ2=11.44, df=1, *P*= 1.00
	Male	34 (68.0)	-	34 (68.0)	-	
Age (year)		-	32.88 ± 10.82	-	35.44 ± 12.69	t= -1.06, df= 94, *P*= 0.29
Weight (kg)		-	68.78 ± 9.31	-	68.00 ± 12.96	t= 0.31, df= 80, *P*= 0.75
KUB	Negative	8 (66.7)	-	7 (53.8)	-	χ2=0.43, df=1, *P*= 0.51
	Positive	4 (33.3)	-	6 (46.2)	-	
Sonography	No kidney stone	6 (24.0)	-	9 (50.0)	-	χ2=7.19, df=3, *P*= 0.07
	Kidney stone	0 (0.0)	-	2 (11.1)	-	
	Mild hydronephrosis	3 (12.0)	-	1 (5.6)	-	
	Ureter stones	16 (64.0)	-	6 (33.3)	-	
History of kidney stone	Negative	18 (38.3)	-	15 (34.9)	-	χ2=0.11, df=1, *P*= 0.73
	Positive	29 (61.7)	-	28 (65.1)	-	

Data are shown as mean ± SD or n (%).
KUB: kidney-ureter-bladder.

Table 2. Comparison of the mean pain at 0, 5, 15, 30 and 60 minutes, and comparison of the initial pain (VAS 0) with the next times based on the VAS scale in the two groups

Pain based on time	Group		*P* value
	Morphine	Ketamine	
VAS 0	8.32±1.42	6.94±2.14	t= 3.79, df= 98, *P*= 0.001
VAS 5	6.46±1.85	6.10±2.31	t= 0.86, df= 98, *P*= 0.39
VAS 15	5.28±1.70	5.48±2.56	t= -0.46, df= 98, *P*= 0.64
VAS 30	4.46±2.03	5.50±2.83	t= -2.11, df= 98, *P*= 0.03
VAS 60	4.20±2.42	5.00±2.85	t= -1.51, df= 98, *P*= 0.13
VAS 5-0	1.86±1.47	-.84±1.25	t= -3.73, df= 98, *P*= 0.001
VAS 15-0	3.04±1.74	-1.46±1.90	t= -4.34, df= 98, *P*= 0.001
VAS 30-0	3.86±2.19	-1.44±2.16	t= -5.57, df= 98, *P*= 0.001
VAS 60-0	4.12±2.34	-1.94±2.47	t= -4.52, df= 98, *P*= 0.001

Data are shown as mean ± SD.

in the morphine group was 36% and in the ketamine group was 17%; which is based on chi-square test, it was not statistically significant ($P=0.83$; Table 5). Comparison of the data obtained from the two groups showed that the drug side effects (nausea, dizziness, hypotension and dissociation), need for drug re-administration to achieve optimal analgesia, as well systolic blood pressure and heart rate were not statistically significant between the two groups (Table 6). However, changes in diastolic pressure and blood oxygen saturation (SpO2) were significantly different in these two groups; hence, diastolic blood pressure changes in the morphine group and changes in SPO2 in the ketamine group were more than another group. These findings can be an effective factor in the appropriate selection of each of these medications by the health team based on patient conditions, especially in patients with unstable hemodynamics and respiratory problems.

Discussion

Renal colic is one of the most commonly diagnosed diseases in emergency departments and affects 5% to 15% of the population around the world(19). Pain management in these patients is essential and most commonly administered drugs for this purpose are NSAIDs and opioids. Ketamine is utilized as an acute pain-killer (14) by various routes, including inhalation (10, 20-23).

In the current study, patients were treated with intravenous morphine and intranasal ketamine. Based on independent t-test, there was no significant difference in demographic indicators of the two groups. However, the difference between the mean of initial pain and pain at 30 minutes after the drug administration in the two groups was significantly different. It is noteworthy that initially less pain was reported in the ketamine group; however, with passing of time, the amount of pain in the morphine group is reduced more and after 15 minutes of the drug injection, it was always less than the morphine group; and therefore this can be expression of faster and more effective of morphine's analgesic action. Contrary to the low and

Table 3. Intra-group pain difference at 0, 15, 30 and 60 minutes after intervention, based on the VAS scale in the morphine group in the patients

	VAS 0	VAS 5	VAS 15	VAS 30	VAS 60
VAS 0	-	t = 8.94, *P* = 0.0001	t = 12.37, *P* = 0.0001	t = 12.48, *P* = 0.0001	t = 12.42, *P* = 0.0001
VAS 5		-	t = 5.68, *P* = 0.0001	t = 6.02, *P* = 0.0001	t = 6.03, *P* = 0.0001
VAS 15			-	t = 4.11, *P* = 0.0001	t = 3.80, *P* = 0.0001
VAS 30				-	t = 1.17, *P* = 0.24
VAS 60					-

Table 4. Intra-group pain difference at 0, 15, 30 and 60 minutes after intervention, based on the VAS scale in the ketamine group in the patients

	VAS 0	VAS 5	VAS 15	VAS 30	VAS 60
VAS 0	-	t = 4.74, *P* = 0.0001	t = 5.44, *P* = 0.0001	t = 4.71, *P* = 0.0001	t = 5.55, *P* = 0.0001
VAS 5		-	t = 4.53, *P* = 0.0001	t = 3.28, *P* = 0.002	t = 4.09, *P* = 0.0001
VAS 15			-	t = -0.15, *P* = 0.88	t = 2.09, *P* = 0.04
VAS 30				-	t = 2.57, *P* = 0.01
VAS 60					-

Table 5. Comparison of the need for re-use of the drugs in the two groups

Reuse of drugs		Group		P value
		Morphine	Ketamine	
Reuse of drugs	Yes	18 (36.0)	17 (34.0)	χ2=0.04, df=1, *P*= 0.83
	No	32 (64.0)	33 (66.0)	

Data are shown as No. (%).

Table 6. Comparison of the frequency distribution of side effects, the need for re-administration of the drugs and the mean of vital signs in the two study groups

Variables		Group		*P* value
		Morphine	Ketamine	
Complications	Nausea	8 (40.0)	6(30.0)	χ2=4.68, df=3, *P* = 0.21
	Dizziness	10 (50.0)	12(60.0)	
	Dissociation	0 (0.0)	2(10.0)	
	Hypotension	2 (10.0)	0(0.0)	
Re-administration	Positive	18 (52.9)	17(47.2)	χ2=0.23, df=1, *P* = 0.63
	Negative	16 (47.1)	19(52.8)	
Blood pressure (mm Hg)	Systole before intervention	112.02 ± 13.62	115.41 ± 16.77	t=0.09, df=98, *P* = 0.92[a]
	Systole after intervention	113.16 ± 9.82	114.33 ± 14.25	
	Diastole before intervention	72.48 ± 10.03	73.33 ± 10.78	t=3.05, df=98, *P* = 0.003[a]
	Diastole after intervention	73.16 ± 9.55	73.09 ± 9.88	
Pulse rate (bpm)	Before intervention	81.50 ± 14.32	81.37 ± 9.08	t=0.48, df=98, *P* = 0.63[a]
	After intervention	80.14 ± 9.33	82.38 ± 8.11	
SPO2 (%)	Before intervention	96.15 ± 2.27	96.45 ± 2.76	t=-4.50, df=98, *P* = 0.001[a]
	After intervention	96.09 ± 2.56	96.20 ± 2.83	

Data are shown as mean ± SD or n (%).
[a] Based on the means difference before and after the intervention in each group.

slow rate of ketamine analgesic induction, the duration of ketamine action is longer for the pain control and provides prolong analgesia.

Almost consistent with our study, Huge et al, showed that the effect of ketamine in reducing the pain lasts for three hours (24). Carr et al showed that the intranasal ketamine reaches its blood-level detection rate after two minutes while its peak level after 30 minutes. Both studies showed that ketamine inhalation was effective in induction of analgesia while its side effects were minor and transient (16). Since, we found no significant difference in pain relief from ketamine in both inhalation and intravenous routes; therefore, it is important to choose this medication for patients with special conditions.

Various studies have been conducted to evaluate postoperative analgesia with ketamine. For example, in the study of Christensen et al, doses of 10, 30 and 50 mg of ketamine in relieving pain after third molar removal, can induce optimal analgesia with minimal side effects than placebo (25). Elia and Tramèr examined various methods and routes for ketamine administration and its dosage regimens. They did not see any clinical effect on pain score by visual analogue scale 48 hours after surgery. This study showed that ketamine could reduce the dose of the opioid drug without altering its side effects (26). The results of the above-mentioned studies support the administration of ketamine, while our research on morphine has been shown to be more effective in reducing patients' pain faster.

Although analgesia is achieved faster in the administration of morphine, it should always be considered the potential side effects of opioids, especially in high-risk patients. Although the employment of non-opioid drugs such as ketamine for achieving optimal analgesia, may delay the recovery process, by reducing opioid requirement, it can reduce side effects, increases respiratory and hemodynamic stability of the patient (27) and reduce nausea and vomiting caused by opioid use (28). This approach can be very important, especially in recurrent cases of renal colic; because frequent use of opioids, in addition to side effects on the respiratory system hemodynamic, can also cause opioid-induced hyperalgesia in the patient (29) and reduces patient complications.

In our study, changes in diastolic pressure and SPO2 were significantly different in these two groups. The findings indicated that the changes in diastolic pressure and SpO2 were higher in the morphine and ketamine groups, respectively. In the study of Nesher et al, respiratory rate and SPO2 in the morphine + ketamine group were higher than the morphine alone treatment group. According to this study, cardiovascular stability and respiratory parameters along with a decrease in the need for morphine, are the priority points for the use of ketamine alongside opioids (30).

Conclusion

Low-dose ketamine is considered as an analgesic with low side effects; especially when the administration of this drug through intranasal is simple and uncomplicated and its analgesia is comparable with intravenous administration and in the pre-hospital condition reduces the need for establishing IV access and therefore the risk of the needle stick. According to the results, the administration of intravenous morphine to reduce the renal colic pain has a faster effect than intranasal ketamine and its use in these patients should be given priority.

Limitations of the study

One of the challenges of our study was that we were

unable to determine the blood level of ketamine to control its analgesia effect. In addition, our sample size was not sufficient to detect the accurate effects of the drugs and their side effects. Therefore, clinical trials with larger sample size and longer follow-up should be conducted to provide better prospective and to identify side effects. Another challenge in our research was that we did not choose a time point as the main result, but we decided to study VAS score changes for 60 minutes. It is recommended that in the future studies that are conducted on two different drug groups regarding pain, their initial pain levels are somehow be matched.

Authors' contribution

MM, MB and MA were the principal investigators of the study. MA was included in preparing the concept and design. ZV and ZV revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Zahedan University of Medical Sciences approved all study protocols (IR.ZAUMS.REC.1396.271). This study has been registered in the Iranian Registry of Clinical Trials (identifier: IRCT20171229038132N1, https://irct.ir/trial/28821). Accordingly, written informed consent was taken from all participants before any intervention. This study is a dissertation by Marzieh Ziaei at this university (Thesis #396271). Ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors. Besides, ethical issues (including plagiarism, data fabrication, double publication) were completely observed by the authors.

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