Original Contribution

Comparing the analgesic efficacy of morphine plus ketamine versus morphine plus placebo in patients with acute renal colic: A double-blinded randomized controlled trial☆

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ABSTRACT

Objectives: Renal colic (RC) is a common cause for emergency department visits. This study was conducted to compare the analgesic efficacy of morphine plus ketamine (MK) versus morphine plus placebo (MP) in patients with acute renal colic.

Method: Using a single center, double-blind, two-arm, parallel-group, randomized controlled trial, 200 patients were equally and randomly divided to receive 0.1 mg/kg morphine plus normal saline and 0.1 mg/kg morphine plus 0.2 mg/kg ketamine. The severity of renal colic was assessed by VAS at baseline, 20 and 40 min after drug injection. The number of adverse events also was recorded.

Results: Totally, 200 patients completed the study. Mean age of the patients was 35.60 ± 8.17 years. The patients were mostly men (68.5%). The severity of pain between the groups was not significantly different at baseline. Both groups showing a significant reduction in VAS scores across the three time points. The main effect comparing the two types of intervention was significant (F = 12.95, $p = 0.000$), suggesting a significant reduction in pain severity of patients in the MK group. The number of patients who suffered from vomiting was significantly higher in MP group than that of MK group (13 and 3, respectively ($P = 0.009$)). However, the risk of dizziness in the MK group was >2 times higher than MP group (relative risk: 2.282, 95% CI: 1.030–5.003, $P = 0.039$). The number of patients who needed rescue analgesia was significantly lower in the MK group (OR, 0.43 (0.22–0.83)).

Conclusion: Adding 0.2 mg/kg ketamine to 0.1 mg/kg morphine can reduce the renal colic pain, nausea and vomiting more than morphine alone; however, it was associated with higher number of patients with dizziness.

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1. Introduction

Renal colic (RC) is a common cause for emergency department (ED) visits, worldwide [1]. Renal colic is caused by an increase in pressure within the upper urinary system or due to the dilatation of the kidney and pelvic capsules above the blockage site, which is often caused by stones. This pain is suddenly felt on the patient's flank and radiates to the groin and genital area [1]. Due to the severe and intermittent nature of renal colic, one of the main priorities in the ED is to provide quick and effective analgesia for patients. However, several factors such as efficacy, safety, the ease of rapid administration, and availability must be considered in analgesia selection [2]. In most clinical settings, the choice of medication to reduce pain is determined by the local policies of the given health care system and there is no consensus guideline regarding the best analgesic option for patients presenting with renal colic to the ED [1,3-5].

Several medications are available for the treatment of renal colic pain, including, but not limited to, NSAIDs, antidepressants, anesthetic agents, anti-epileptics and opioids [3-13]. As frequent therapies, both non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are usually used for the prompt pain relief of patients in the ED. However, due to the unwanted adverse events of opioids, NSAIDs, particularly in

Enrollment

Assessed for eligibility (n= 230)

Excluded (n= 30)
- Not meeting inclusion criteria (n= 20)
- Declined to participate (n=5)
- Other reasons (n=5)

Randomized (n= 200)

Allocation

Allocated to intervention (n= 100)
- Received allocated intervention (n= 100)
- Did not receive allocated intervention (give reasons) (n=0)

Allocated to intervention (n=100)
- Received allocated intervention (n= 100)
- Did not receive allocated intervention (give reasons) (n= 0)

Follow-Up

Lost to follow-up (give reasons) (n= 0)

Discontinued intervention (give reasons) (n= 0)

Lost to follow-up (give reasons) (n= 0)

Discontinued intervention (give reasons) (n=0)

Analysis

Analysed (n=100)
- Excluded from analysis (give reasons) (n=0)

Analysed (n=100)
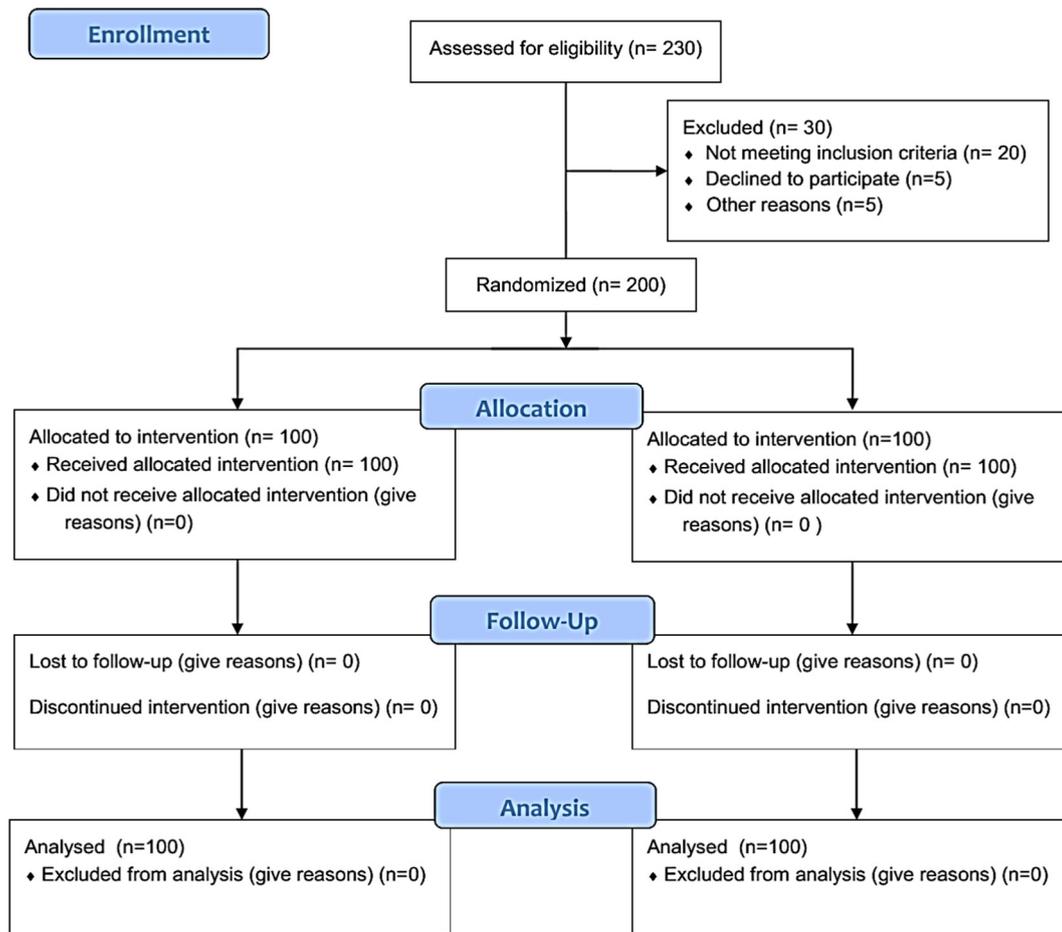- Excluded from analysis (give reasons) (n=0)

Fig. 1. CONSORT 2010 flow diagram.

intravenous forms, become very attractive agents for acute pain relief in the ED [5]. In this regard, a recent Cochrane review of non-opioid analgesia for acute renal colic showed that NSAIDs could improve pain control compared with placebo [3].

Regarding the management of acute pain in ED, finding alternatives to opioids has become increasingly interesting, both in practical applications and in theoretical studies, for emergency medical professionals. Ketamine, a noncompetitive N-methyl-D-aspartate receptor antagonist, is recently used at sub-anesthetic doses as a supplementary medication

for treatment of various therapy-resistant pain syndromes [14]. A number of studies have evaluated the effects of ketamine for reducing pain in patients with renal colic and found some promising results that ketamine may be effective to reduce the severity of pain in renal colic as well as morphine consumption and therefore, it can reduce the number of opioid-related adverse events [11,12,15-18]. Accordingly, based on the available evidence, we hypothesized that the combination of morphine and ketamine can reduce the pain intensity and the number of adverse events better than that of morphine alone in patients with renal colic.

Table 1
baseline demographic and clinical characteristics for the total sample and each group

Items	Total	MP ($n = 100$)	MK ($n = 100$)	Test, p-value
Male (n)	137 (68.5%)	70	67	$\chi^2 = 0.20, 0.64$
Female (n)	63 (31.5%)	30	33	
Age (mean $\pm$ SD)	35.6 $\pm$ 8.17	35.91 $\pm$ 9.13	35.29 $\pm$ 7.12	$T = 0.53, 0.593$
Weight (mean $\pm$ SD)	70.08 $\pm$ 7.81	69.86 $\pm$ 8.56	70.3 $\pm$ 7.02	$T = -0.39, 0.692$
History of stone (n)	105 (52.5%)	47	58	$\chi^2 = 2.42, 0.11$
History of psychosis (n)	0	0	0	1
Abnormal para-clinical findings (n)	54 (27%)	30	24	$\chi^2 = 0.91, 0.34$
Gross (visible) hematuria (n)	32 (16%)	23	9	$\chi^2 = 7.29, 0.007$[a]
Microscopic hematuria (n)	47 (23.5%)	25	22	$\chi^2 = 0.25, 0.61$
Nausea (n)	64 (32%)	36	28	$\chi^2 = 1.47, 0.225$
Vomiting (n)	31 (15.5%)	17	14	$\chi^2 = 0.34, 0.55$
Dizziness (n)	18 (9%)	10	8	$\chi^2 = 0.24, 0.621$
Rash (n)	0	0	0	1
RR (mean $\pm$ SD)	15.95 $\pm$ 1.31	16.46 $\pm$ 1.35	15.44 $\pm$ 1.04	$T = 5.94, 0.000$[a]
DBP (mean $\pm$ SD)	78.85 $\pm$ 6.94	79.7 $\pm$ 8.40	78.0 $\pm$ 4.97	$T = 1.741, 0.083$
SBP (mean $\pm$ SD)	122.40 $\pm$ 14.73	123.65 $\pm$ 17.27	121.15 $\pm$ 11.60	$T = 1.201, 0.231$

[a] Significant; n: number; SD: standards deviation; MP: morphine plus placebo; MK: morphine plus ketamine; T: independent samples test.

Table 2

Comparing the mean of VAS scores between groups at different time points (MP, $n = 100$; MK, $n = 100$).

Time points	At baseline	At 20 min	At 40 min	Tests of within-subjects		
				F	*p*-Value	PES
MP (mean ± SD)	8.11 ± 1.01	5.26 ± 1.13	3.13 ± 1.06	681.68	0.000	0.873
MK (mean ± SD)	7.98 ± 1.01	4.75 ± 0.93	2.67 ± 0.99	1647.9	0.000	0.943
MD (95% CI)	0.13 (−0.15–0.41)	0.51 (0.22–0.80)	0.48 (0.17–0.74)			
Test, *p*-value	$T = 0.906$, 0.366	$T = 3.469$, 0.001[a]	$T = 3.163$, 0.002[a]			

[a] Significant; *n*: number; SD: standards deviation; CI: confidence interval; MD: mean difference; PES: partial eta squared; T: independent samples test.

Therefore, the aim of this study was to compare the analgesic efficacy morphine plus ketamine versus morphine alone in patients with acute renal colic in the ED.

2. Methods

2.1. Design and study setting

This study was a single-center, double-blind, two-arm, parallel-group, randomized controlled trial, which was performed in the ED of Imam Khomeini Hospital, Sari, Iran, between 20 September 2015 and 22 May 2017. This study was carried out according to the Helsinki Declaration on ethical principles for research involving human subjects. The Ethics Committee of Mazandaran University of Medical Sciences approved the study on 09 April 2017 (ID: IR.MAZUMS.REC.94-1719). Written informed consent was obtained from all participants. The study was registered at Iranian registry of clinical trial (IRCT ID: IRCT2015080523517N1). The study design and report were followed by the Consolidated Standards of Reporting Trials guideline.

2.2. Sample size

Using a Student *t*-test for two independent samples and a significance level of 5% (two-sided), the sample size of at least 86 participants in each group (total of 172) was calculated using G*Power (ver. 3.1) with a medium effect size of 0.5, and power (β) of 0.90. Considering the possible withdrawal of patients for any reason, the number of patients in each group increased to 100 patients.

2.3. Selection of participants

Inclusion criteria were age between 18 and 65 years; initial visual analog (VAS) scale of pain intensity of at least 6 out of 10; the presence of kidney stones has been confirmed by ultrasonography or computed tomography scan; patients' vital signs are stable and lack of sensitivity to morphine and ketamine. Exclusion criteria were pregnancy or probable pregnancy; breastfeeding; contraindications for morphine usage; history of opium addiction; taking any analgesics or narcotics during last 6 h prior to admission; peritoneal signs and symptoms in the abdominal examination; history of known chronic cardiovascular, liver and kidney diseases; psychosis; refusal of the patients from the participation.

2.4. Randomization and blinding

At the time of enrollment, each participant was assigned an identification number using a computer-generated random number table. Two hundred patients who met the eligibility criteria were randomly assigned at a 1:1 ratio to either the morphine plus ketamine group (MK, $n = 100$) or morphine plus normal saline group (MP, $n = 100$) by an external person who was blinded to each group allocation and had no other role in the study. Researchers were blinded to the randomization table, code assignments, and procedure. Preparation and injection of drugs were done by two nurses so that the nurse who prepared the medication was not aware of the patient receiving the medication and the nurse who injected the drug was not aware of the drug name. Meanwhile, all syringes and medications were prepared in similar form. Data collection and patients pain evaluation was done by an emergency physician who was not aware of the prescribed medications.

2.5. Intervention

After confirming the diagnosis of stone-related renal colic by ultrasonography or computed tomography scan, patients in the MK group received the dose of 0.1 mg/kg morphine plus 0.2 mg/kg ketamine intravenously. At the same time, patients in the MP group received 0.1 mg/kg morphine plus normal saline, as a placebo, intravenously.

Ketamine hydrochloride from Rotexmedica (50 mg/ml) was used to prepare a concentration of 5 mg/ml. This solution was then administered at 0.2 mg/kg intravenously. Morphine sulfate from Irandaru (10 mg/ml) was used to prepare a concentration of 5 mg/ml. This solution was then administered at 0.1 mg/kg intravenously. Due to the severity of the patient's pain after 20 min, if necessary, patients received an additional dose of morphine (0.05 mg/kg) as a rescue analgesia. Patients who had pain after 40 min were classified as resistant pain, and then, they were referred to a urologist for possible recommendations.

2.6. Measurements

VAS scores were assessed at baseline, 20 and 40 min after injection of medications. The possible adverse events including nausea, vomiting, dizziness, rash or hives were recorded at baseline, 20, and 40 min after intervention. As well, blood pressure and respiratory rate were

Table 3

Patients' clinical characteristics 20 min after drug injection.

	MP ($n = 100$)	MK ($n = 100$)	Test, *p*-value	OR/MD
Nausea (*n*)	34	30	$\chi^2 = 1.710$, 0.19	OR: 0.83 (0.45–1.50)
Vomiting (*n*)	13	3	$\chi^2 = 6.793$, 0.009[a]	OR: 0.20 (0.05–0.75)
Dizziness (*n*)	11	22	$\chi^2 = 4.391$, 0.036[a]	OR: 4.83 (0.19–0.96)
Rash (*n*)	0	0	1	–
Need for rescue (*n*)	35	19	$\chi^2 = 6.49$, 0.011[a]	OR: 0.43 (0.22–0.83)
RR (mean ± SD)	15.1 ± 1.15	14.65 ± 0.62	$T = 3.347$, 0.001[a]	MD: 0.45 (0.19–0.70)
DBP (mean ± SD)	78.05 ± 7.13	77.50 ± 4.52	$T = 0.651$, 0.516	MD: 0.55 (−1.11–2.21)
SBP (mean ± SD)	120.65 ± 12.64	119.10 ± 9.27	$T = 0.988$, 0.324	MD: 1.55 (−1.54–4.64)

[a] Significant; *n*: number; SD: standards deviation; CI: confidence interval; MD: mean difference; T: independent samples test.

Table 4
patients' clinical characteristics 40 min after drug injection.

	MP	MK	OR/MD (CI 95%)
Nausea (*n*)	45	43	OR: 0.92 (0.53–1.61)
Vomiting (*n*)	38	32	OR: 0.77 (0.43–1.37)
Dizziness (*n*)	45	42	OR: 0.88 (0.50–1.54)
Rash (*n*)	34	37	OR: 1.14 (0.63–2.03)
Need for rescue (*n*)	19	7	OR: 0.32 (0.12–0.80)[a]
RR (mean ± SD)	14.62 ± 1.83	14.02 ± 1.70	MD: 0.58 (0.08–1.07)
DBP (mean ± SD)	80.74 ± 15.21	77.96 ± 13.95	MD: 2.78 (−1.29–6.85)
SBP (mean ± SD)	119.30 ± 13.22	117.84 ± 14.35	MD: 1.46 (−2.39–5.30)

[a] Significant; *n*: number; SD: standards deviation; CI: confidence interval; MD: mean difference;

recorded. The number of patients who needed an additional dose of rescue analgesia also recorded.

2.7. Outcomes

The primary outcome was pain intensity scores as calculated by VAS. Criteria for treatment response was determined as pain reduction level by 50% based on the primary VAS score or VAS score of four or lower. The secondary outcomes were the number of patients who need rescue analgesia in addition to the number of adverse events.

2.8. Data analysis

Data were analyzed by IBM SPSS Statistics version 23. Descriptive variables have been reported as frequency and percentage while quantitative variables have been reported as the mean, standard deviation, mean difference (MD), and confidence interval (CI) of 95%. Chi-squared test was utilized to compare treatment adverse effects between groups. An independent-samples *t*-test was conducted to compare the mean of VAS scores between two groups. A mixed between-within subjects' analysis of variance was conducted to assess the impact of two different interventions (MP and MK) on VAS scores, across three-time points (baseline, 20 and 40 min after drug injection). A *p*-value of <0.05 was considered statistically significant. Shapiro-Wilk statistic and ANOVA diagnostics, including the test of Sphericity were generated to verify the assumptions of normality and homoscedasticity. The effect size for each outcome was measured by partial eta squared. Cochran's Q test was utilized to compare adverse effects within groups across the three time points.

3. Results

3.1. Participants' characteristics

230 participants were assessed for eligibility criteria and finally, 200 patients completed the study (Fig. 1).

Mean age of the patients was 35.60 ± 8.17 years. The patients were mostly men (68.5%). The MP and MK groups exhibited roughly similar demographic and clinical characteristics. However, the number of patients with gross hematuria was significantly higher in the MP group compared with the MK group (*p* = 0.007). In addition, the respiratory

rate of patients in the MP group was significantly higher than that of the MK group (MD: −1.020; 95% CI: −1.356 to −0.683, *p* = 0.000). In total, the incidence of nausea and vomiting at baseline were 32% and 15%, respectively. Table 1 shows the baseline demographic information and clinical characteristics for each group.

3.2. Study outcomes

The total mean of VAS scores at baseline and at the end of the study were 8.05 ± 1.01 and 2.90 ± 1.05, respectively. As depicted in Table 2, the severity of pain between the two groups was not significantly different at baseline. However, there was a significant difference between the two groups regarding the mean VAS scores at 20 and 40 min (*p* = 0.000 and *p* = 0.002, respectively). At both these time points, patients in the MK group had significantly lower pain than MP group. The severity of pain in the MP group at 20 and 40 min were significantly lower than that of baseline (*P* < 0.001 and *P* < 0.001, respectively). In the MK group, the severity of pain at 20 and 40 min was significantly lower than that of baseline (*P* < 0.001 and *P* < 0.001, respectively). Table 2 shows the comparison of the mean of VAS scores between two groups at different time points.

A mixed between-within subjects' analysis of variance was conducted to assess the impact of two different interventions (MP and MK) on VAS scores, across three time points (baseline, 20 and 40 min after drug injection). Mauchly's Test of Sphericity indicated that the assumption of Sphericity had been met ($\chi2^{(2)} = 4.45$, *p* = 0.108). There was a statistically significant effect for time (F = 1662.02, *p* = 0.000, partial eta squared = 0.89), with both groups showing a significant reduction in VAS scores across the three time points (see Table 2). In addition, there was no significant interaction between groups × time (F = 2.64, *p* = 0.072, partial eta squared = 0.01). The main effect comparing the two types of intervention was significant, F = 12.95, *p* = 0.000, partial eta squared = 0.06, suggesting a significant reduction in pain severity of patients in the MK group.

At 20 min, two groups were statistically different in terms of vomiting, dizziness, need for rescue analgesia and RR. The number of patients who suffered from vomiting was significantly higher in MP group than that of MK group (13 and 3, respectively (*P* = 0.009)). However, the risk of dizziness in the MK group was >2 times higher than MP group (relative risk: 2.282, 95% CI: 1.030–5.003, *P* = 0.039). The number of patients who need rescue analgesia was significantly lower in the MK group (OR, 0.43 (0.22–0.83)). The total mean of the respiratory rate of patients in both groups decreased over time (from 15.95 to 14.31). However, the between groups deference was only significantly lower in the MP group at 20 min (*P* = 0.001). Table 3 shows clinical characteristics of patient 20 min after drug injection.

At 40 min, no significant differences were observed between the two groups regarding nausea, vomiting, dizziness, rash, RR, DBP, and SBP. However, the number of patients who need for rescue analgesia was significantly lower in the MK group (OR: 0.32 (0.12–0.80)). Table 4 summarizes the clinical characteristics of patients 40 min after drug injection.

Table 5 compares the number patients with adverse events within groups. Table 6 compares the clinical characteristics of patients between-within groups across the three time points. Fig. 2 illustrates

Table 5
Comparing the number patients with adverse events within groups across the three time points.

Time point	Nausea		Vomiting		Dizziness		Need for rescue	
	MK	MP	MK	MP	MK	MP	MK	MP
Baseline	28	36	14	17	8	10	–	–
20	30	34	3	13	22	11	19	35
40	43	45	32	38	42	45	7	19
p-Value[*]	=0.027	=0.175	<0.001	<0.001	<0.001	<0.001	=0.019	=0.021

[*] Cochran's Q;

Table 6
Comparing the clinical characteristics of patients between-within groups across the three time points using repeated-measures analysis of variance.

Clinical characteristics	Time points	Group			Test	F[a]	p	Eta squared
		MK (n = 100)	MP (n = 100)	Total (n = 200)				
RR	Baseline	15.44	16.46	15.95	Time	91.39	0.000*	0.316
	20	14.65	15.10	14.88	Group	28.90	0.000*	0.127
	40	14.02	14.60	14.31	Time * group	2.93	0.069	0.015
DBP	Baseline	78.00	79.70	78.85	Time	1.47	0.231	0.007
	20	77.50	78.05	77.77	Group	0.706	0.494	0.004
	40	77.96	80.74	79.35	Time * group	3.50	0.063	0.017
SBP	Baseline	121.15	123.65	122.40	Time	6.81	0.001*	0.033
	20	119.10	120.65	119.87	Group	1.64	0.201	0.008
	40	117.84	119.30	118.57	Time * group	0.149	0.862	0.001

RR: respiratory rate; DBP: diastolic blood pressure; SBP: systolic blood pressure; MK: morphine plus ketamine; MK: morphine plus placebo.

[a] Greenhouse-Geisser.

* p-Value was significant.

the interaction between the two groups regarding the clinical characteristics of patients.

4. Discussion

The results from this single-center, randomized controlled trial showed that the combination of ketamine with morphine compared to morphine alone could better reduce the severity of renal colic pain at both 20 and 40 min after drug injection. In addition, this combination reduced the need for rescue analgesia such that the number of patients in MK group who needs for extra doses of rescue analgesia was lower at both 20 and 40 min after the start of the intervention. Moreover, using this combination reduced the number of adverse events; however, more patients who received ketamine suffered from dizziness. Despite

the difference in the implementation of the intervention, the outcomes, and reported adverse events, our findings are partially similar to the previous studies [12,15-20].

Due to the high incidence of opioid-related adverse events, their use for controlling acute pain in the ED has been controversial. In recent years, many drugs with similar or more potent analgesic effects than opioids have been used in clinical settings. Ketamine, N-methyl-D-aspartate receptor antagonist, is a safe and widely available anesthetic drug with analgesic effects at sub-anesthetic doses, which has been used in several pain-related conditions [11,14]. Previous studies have revealed that low-dose ketamine, either alone or in combination, can provide safe and effective analgesia [12,14,15,18]. In a most comparable study, Abbasi et al. compared the efficacy of low-dose ketamine (0.1 mg/kg) with morphine (0.1 mg/kg) to reduce renal colic and
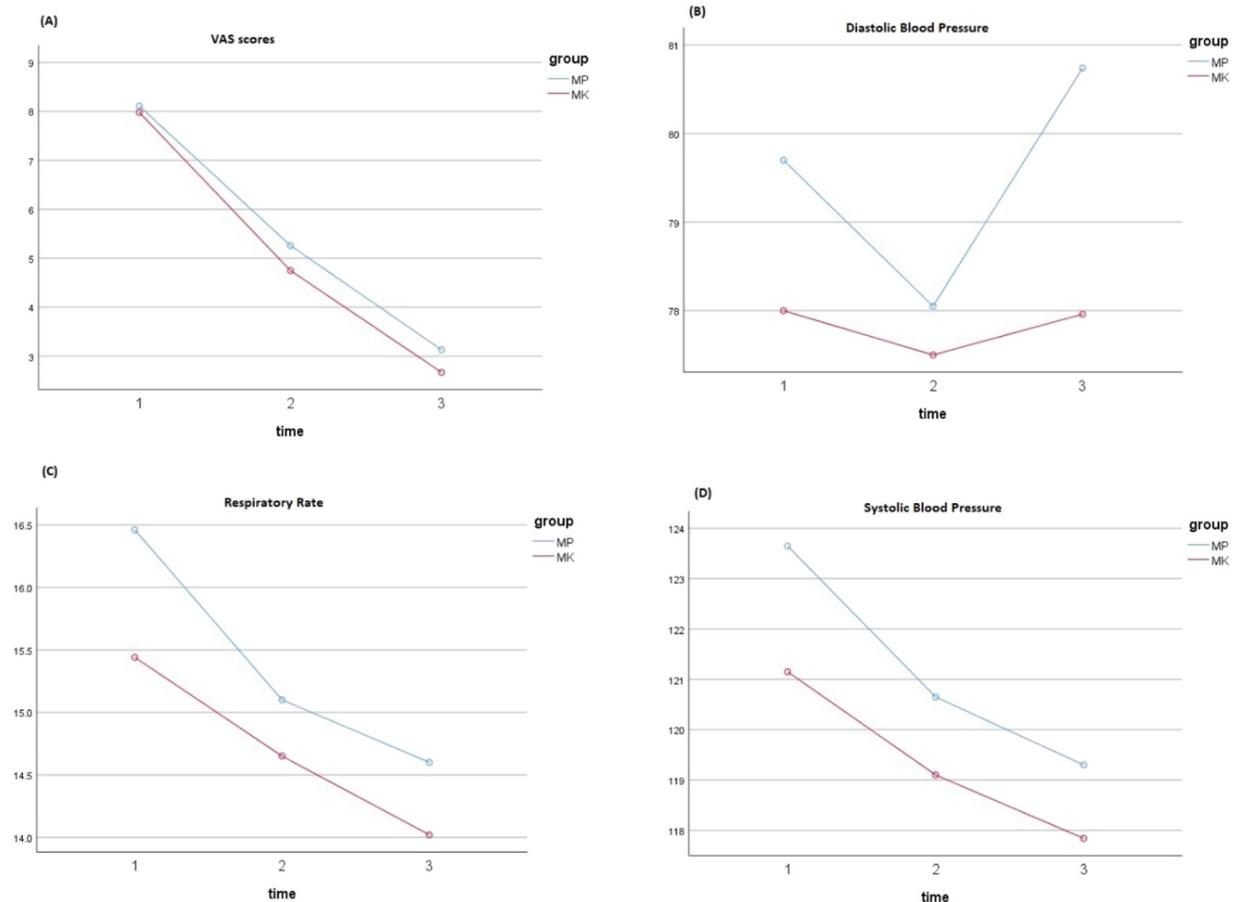

Fig. 2. The interaction between the two groups regarding the (A) VAS scores; (B) diastolic blood pressure; (C) Respiratory rate; (D) systolic blood pressure.

found that patients who received the combination of ketamine and morphine were significantly experienced lower pain than that of morphine alone. They also found that adding low doses of ketamine to morphine can reduce the morphine consumption [15]. In contrast with our findings, there is a study contradicting the superiority of ketamine to morphine in reducing renal colic pain over time. Miller et al. found that low-dose ketamine (0.3–0.6 mg/kg) could not reduce the severity of pain compared with morphine (0.1 mg/kg). Although it is not superior, ketamine was able to decrease acute renal colic pain faster than morphine [18]. It seems that the rapid analgesic effects of ketamine can decrease the need for rescue analgesia. In contrast to Miller's study, we found that the analgesic effects of ketamine when combined with morphine last at least 40 min. In another study, Sin et al. found that the use of ketamine was associated with lower pain severity at 15 min and higher mean satisfaction score when compared with morphine. However, similar to our findings, ketamine was associated with higher number of patients with dizziness [20]. In a non-blinded, non-controlled observational study of patients with different painful conditions, Ahern et al. found that low-doses of ketamine plus hydromorphone could produce quick and deep pain relief without significant adverse events [19]. The main difference among the mentioned studies was the use of different doses of ketamine.

Although ketamine is a safe analgesic and anesthetic drug, several dose-related adverse events have been reported including neurological and cardiovascular effects [11,21]. In the present study, the adverse events rate and vital signs between the two groups were partially comparable. The addition of ketamine to morphine in comparison to morphine alone caused less vomiting but more dizziness. In addition, the respiratory rate of patients in the MK group, although in the normal range, had a significant reduction from baseline compared with 20 min, which means that adding ketamine to morphine could reduce the respiratory rate. In terms of adverse events, our findings were relatively different from previous studies [12,15,18,20], likely due to the different dosage, duration or timing of injection as well as the type of opioid used.

Previous studies have used deferent ketamine doses. It is documented that the subdissociative-dose of Ketamine with analgesic effects is <1 mg/kg [22]; however, higher doses are associated with higher incidence of adverse events. There is no consensus regarding the optimal dose with analgesic properties for acute pain management [11]. In the present study, we used the dose of 0.2 mg/kg. It seems that higher doses may have better analgesic properties. This assumption could be tested in future studies.

The present study has several limitations that warrant consideration. First, the generalization of our findings to other populations is limited, as we only evaluated patients from a single center hospital; however, the sample size was well-powered. Due to the acute nature of renal colic pain, we only chose three time points for assessing the efficacy of the proposed intervention. In addition, due to the unknown optimal analgesic dose of ketamine, we selected the lowest dose. Therefore, further multi-center, large-scale trials are needed to expand the time points as well as other dosages of ketamine.

5. Conclusion

Adding 0.2 mg/kg ketamine to 0.1 mg/kg morphine appears to reduce the renal colic pain, nausea, and vomiting as well as the requirements for additional rescue analgesia. However, this combination increased the risk of dizziness. Further well-designed studies are needed to identify the optimal adjuvant analgesia, the optimal dose, duration, and timing of ketamine administration.

Conflicts of interest

None.

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