Original Article

INVESTIGATING THE EFFECT OF LOW-DOSE KETAMINE IN PATIENTS WITH OPIOID-RESISTANT ACUTE CORONARY SYNDROME OR WITH UNSTABLE HEMODYNAMICS WHO REFERRED TO THE EMERGENCY DEPARTMENT OF SHAHID RAJAEI KARAJ HOSPITAL IN 2019

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Abstract

Background: The use of low dose ketamine is not without side effects, but the rate of these side effects is very low and transient at low doses, and it is safe to reduce the pain of patients who are resistant to opioids or have unstable hemodynamics. The aim of this study is to determine the effect of low-dose ketamine on pain control in patients with opioid-resistant acute coronary syndrome or with unstable hemodynamics who refer to the emergency room.

Material and Methods: This clinical trial study was conducted on 140 patients diagnosed with opioid-resistant acute coronary syndrome or with unstable hemodynamic status, who referred to the emergency department of Rajaei Karaj Hospital. After obtaining informed consent from eligible people, people were randomly divided into two groups (intervention and control). Then the visual pain questionnaire VAS (Visual Analogue scale) and NRS (Numeric Rating Scale) was completed by the patient with the help of the researcher. Patients of both groups after standard treatment in the intervention group of intravenous ketamine with a dose of 0.3-0.1 mg per kg and as a bolus and repeated 20 minutes later. Opioid was administered with the same dose to the control group. Systolic and diastolic blood pressure, heart rate and VAS and NRS visual pain questionnaire score before, 30 and 60 minutes after Prescription of ketamine and opioid was recorded, finally the data was collected and statistically analyzed with SPSS software. p value<5%.

Results: There was no significant difference between gender, type of disease, type of MI, anterior ischemia and inferior ischemia in two groups. The independent t-test showed that there was a significant difference between age and BMI trends in the two groups. According to the repeated measures test, there was a significant difference between the systolic and diastolic blood pressure trends in the two groups.

Conclusion: According to the findings, the use of ketamine has been effective in reducing the pain of patients with opioid-resistant acute coronary syndrome or with unstable hemodynamics.

Keywords: Acute Coronary Syndrome, Ketamine, Opium, Pain, Hemodynamics.

Introduction

Acute coronary syndromes (ACS) reflect a spectrum of pathological conditions compatible with acute myocardial ischemia or infarction that are usually due to an abrupt reduction in coronary blood flow (1). The morbidity and mortality due to ACS are substantial—nearly half of all deaths due to coronary heart disease occur following an ACS) (2).

Acute coronary syndrome includes myocardial infarction with an elevated ST wave segment (ST elevation myocardial infarction or STEMI), myocardial infarction without an elevated ST wave segment (Non-ST elevation myocardial infarction or NSTEMI) and unstable angina. Coronary artery disease (CAD) is the leading cause of premature death and disability in developed countries (3).

It has been estimated that acute pain accounts for more than half of all emergency department (ED) visits. Acute pain management in the ED is an important aspect of patient care and satisfaction. Currently, the most common group of analgesics used in the ED are opioids (4).

However, there are many patients who would benefit from an alternative to opioids for safe and effective pain control in the ED so an equally effective and safe analgesic option would be a helpful alternative for ED physicians (5-7).

Ketamine, a N-methyl-d-aspartate (NMDA) receptor antagonist, is a cheap and potentially opioid-sparing effect having drug, which in recent years attains more recognition for multimodal pain management (8-10).

Ketamine causes the release of more catecholamines and the reduction of the reabsorption of adrenaline, resulting in an increase in heart rate and arterial blood pressure. This property makes ketamine a useful analgesic in hemodynamically suppressed patients. Studies indicate that a low dose of ketamine can be an analgesic drug in the initial stages of painful stimuli and as a pre-anesthetic drug, it can reduce the patient's need for drugs. Ketamine is effective in post-surgical immune reactions through several mechanisms, one of which is its analgesic activity. Because pain by itself causes the creation of cytokine precursors and inhibits interleukin 6, as a result, this drug can be prescribed as a prodrug that is known to inhibit inflammation and stabilize hemodynamics (11).

For acute pain, low-dose ketamine has analgesic effects comparable to morphine, with similar need for rescue analgesia (12).Ketamine can be administered parenterally as an intermittent (over 10–15 min) or continuous infusion. Clinicians should start at a low dose (0.1 mg/kg every 4 hours for intermittent; 0.1 mg/kg/h for continuous infusion) and increase if needed, to a maximum dose of 0.35 mg/kg (intermittent) or 0.25 mg/kg/h (continuous) (13).

This study investigated the effect of low-dose ketamine in patients with opioid-resistant acute coronary syndrome or with unstable hemodynamics who referred to the emergency department of Shahid Rajaei Karaj Hospital in 2019.

Material and Methods

This study is a clinical trial, and after obtaining informed consent from the eligible people, the people were randomly divided into two groups (intervention and control).

144 patients diagnosed with opioid-resistant acute coronary syndrome or with unstable hemodynamics who referred to the emergency department of Shahid Rajaei Hospital in Karaj were examined based on the inclusion and exclusion criteria and were included in the study. At first, while explaining the study to the patients, the researcher asked them to complete a written consent form if they agree to participate in the study. Next, the demographic information of the patients, including age, sex, history of opioid use, history of drug sensitivity, and the drugs used, were recorded in the demographic information collection form. Then the VAS (Visual Analogue scale) and NRS visual pain in the following, for the patients of both groups, after the standard treatment in the intervention group, intravenous ketamine with a dose of 1/0-3/0 mg/kg and as a bolus was repeated 20 minutes later. Questionnaire was completed by the patient with the help of the researcher. Opioid was prescribed with the

same dose for the control group. Then again, VAS and NRS visual pain questionnaire was completed by the patient with the help of the researcher. Systolic and diastolic blood pressure, heart rate and VAS and NRS visual pain questionnaire scores were recorded before, 30 and 60 minutes after ketamine and opioid administration. Also, possible side effects that occurred for 120 minutes in patients following ketamine or opioid consumption were recorded. Finally, the data was collected and subjected to statistical analysis.

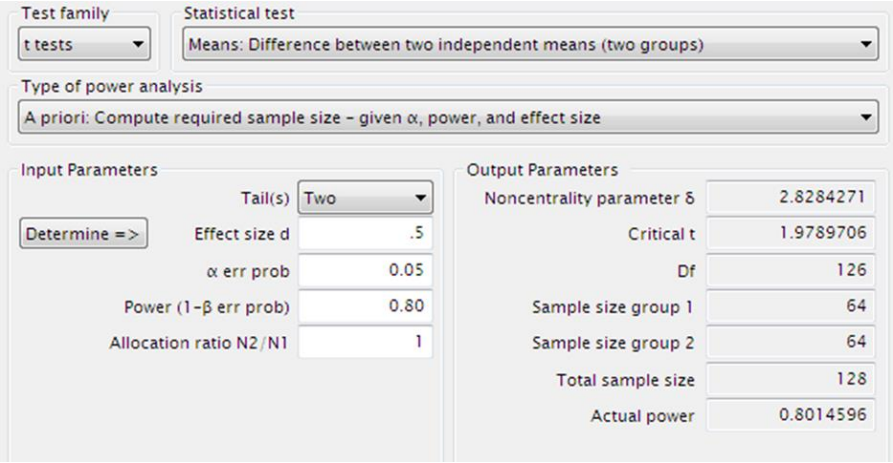
Among the study inclusion criteria: age over 18 years, age under 65 years, consent to participate in the study, no history of sensitivity to ketamine and patients with acute coronary syndrome (VAS greater than or equal to 9) and unstable patient hemodynamics. Systolic blood pressure less than or equal to 90 mm Hg or diastolic blood pressure less than or equal to 60 mm Hg or both) can be mentioned.

Exclusion criteria from this study: lack of consent to participate in the study, age less than 18 and more than 65 years, weight less than 40 kg, drug or alcohol poisoning, active psychiatric illness, history of sensitivity to ketamine and heart rate greater than 120 beats per It has been minutes.

The method of blinding was that the five-digit serial numbers generated in the random allocation process were placed in sealed envelopes and assigned by an independent person from the research team by telephone to each of the eligible subjects.

There were two intervention and control groups, for both groups, in addition to the standard treatment, which includes ACS treatment, cardiac markers and ECG, and paraclinical and analgesic measures with morphine (in case of stable hemodynamics). In the intervention group, in case of no response to intravenous opioids (with 9 mg of intravenous morphine or 50 mg of pethidine) and unstable hemodynamics, the desired drug (ketamine) was used. The samples were included in the study as available and were divided into intervention and control groups based on random allocation (random block). The sample size was calculated using G power software with $\alpha = 0.05$ and $\beta = 20$ and the average effect size was 0.5.

Figure 1: Determining the sample size using G-power software



The sample size was calculated to be 64 people in both groups, and 70 samples were selected by counting 10 drops in each group, and a total of 140 samples were studied in the two groups.

Data description was provided by SPSS software by mean and standard deviation, frequency and percentage. Independent and output t-tests, chi-square analysis of variance with repeated measurements and GEE (Generalized Estimation Equation) test were used. A p value smaller than 5% was considered significant.

Results

144 people were eligible to participate in the study and were randomly assigned to two intervention and control groups. There were 73 people in the intervention group and 71 people in the control group, 55 of whom were men and 18 were women.

Table 1: Distribution of the relative frequency of patients with acute coronary syndrome referred to the emergency department by type of disease in two intervention and control groups

Group / Type of disease	Control		intervention	
	Percentage	Num	Percentage	Num
Myocardial infarction	50/7 %	36	41/1 %	30
Unstable angina	49/3%	35	58/9 %	43
p=0/31				

Using the chi-square test and the obtained p value, there was no significant difference between the type of disease in the two groups

Table 2: Distribution of the relative frequency of patients with acute coronary syndrome referred to the emergency room by type of myocardial infarction in two groups

group / Type of myocardial infarction	Control		intervention	
	Percentage	Num	Percentage	Num
ST segment going up	100 %	35	86/7 %	26
ST segment not going up	0	0	13/3 %	4
p=0/04				

The chi-square test and the p value showed that there is a significant difference between the type of MI in the two groups and ST is more in the control group than in the ketamine group.

Table 3: Distribution of the relative frequency of patients with acute coronary syndrome referred to the emergency room by anterior ischemia, inferior ischemia, lateral ischemia Posterior ischemia and Right ventricular ischemiain two groups

Inferior Ischemia	Group	Control	intervention

		Percentage	Num	Percentage	Num
	No	68/6 %	48	67/1%	49
	Yes	31/4 %	22	32/9 %	24
	p=0/86				
Anterior ischemia	No	45/7 %	32	60/3 %	44
	Yes	54/3 %	38	39/7 %	29
	p=0/095				
Lateral ischemia	No	78/6 %	55	72/2 %	52
	Yes	21/4 %	15	27/8 %	20
	p=0/43				
Right ventricular ischemia	No	95/7 %	67	97/3 %	71
	Yes	4/3 %	3	2/7 %	3
	p=0/67				
Posterior ischemia	No	82/9 %	58	86/3 %	63
	Yes	17/1 %	12	2/7 %	10
	p=0/64				

Chi-square test showed that there is no significant difference between anterior ischemia, inferior ischemia, lateral ischemia Posterior ischemia and Right ventricular ischemia in two groups.

Chart 1: Distribution of the relative frequency of patients with acute coronary syndrome referring to the emergency room of the hospital by smoking in two groups

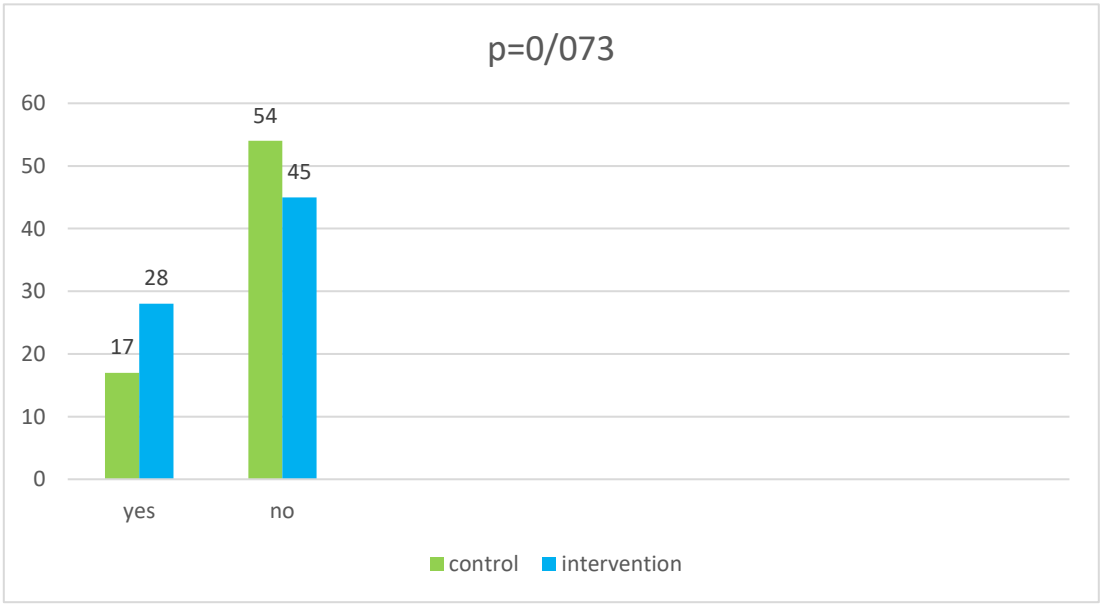


Chart 2: Distribution of the relative frequency of patients with acute coronary syndrome referred to the emergency room, according to opium use in two groups

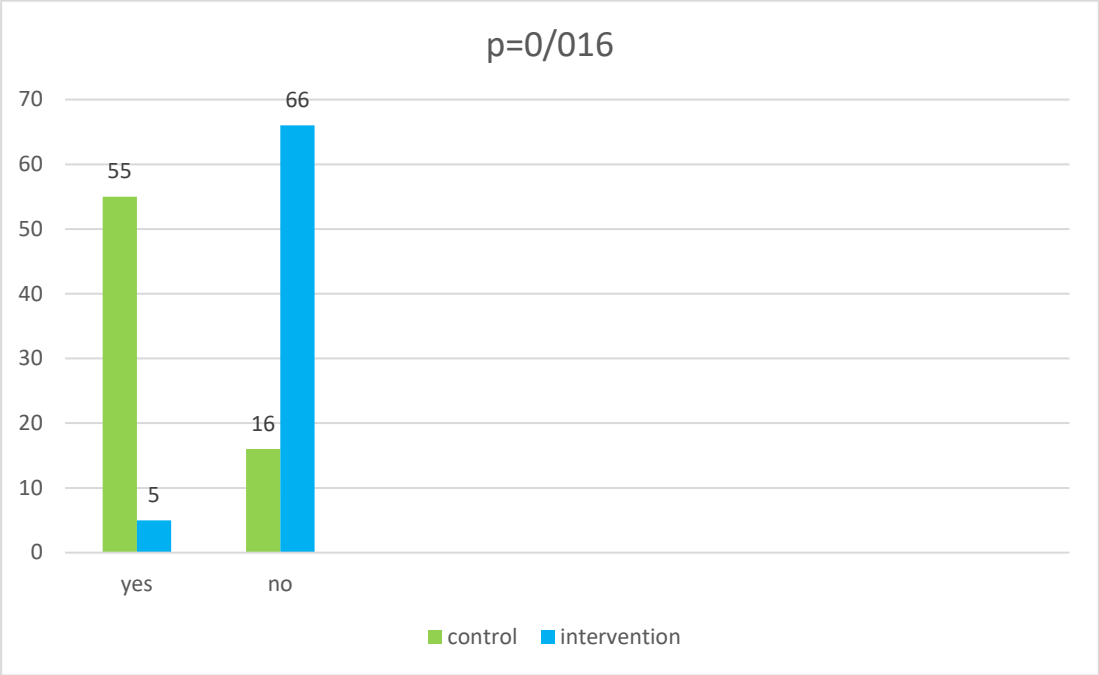


Table 4: Distribution of the relative frequency of patients with acute coronary syndrome referred to the emergency room, separated by the presence of diabetes, high blood pressure and ischemic heart disease in two groups

	Group	Control		intervention	
		Percentage	Num	Percentage	Num
Hyperglycemia	No	73/2 %	52	80/8%	59
	Yes	26/8 %	19	19/2 %	14
	p=0/32				
High blood pressure disease	No	71/8 %	51	78/1 %	57
	Yes	28/2 %	20	21/9 %	16
	p=0/44				
Ischemic heart disease	No	85/9 %	61	74 %	54
	Yes	14/1 %	10	26 %	19
	p=0/09				

Table 5: Investigating the trend of NRS (Numerical Rating Scale) in patients with acute coronary syndrome referred to the emergency room in the two investigated groups

Variable	group	Average	standard deviation	p

Primary Pain Numerical Rating Scale	intervention	8/89	0/8	
	Control	8/78	0/71	
30-minute numerical pain rating scale	intervention	5/83	0/98	0/00
	Control	6/28	0/95	
60-minute numerical pain rating scale	intervention	3/36	½	
	Control	4/84	1/56	
Total	intervention	6/03	0/09	0/00
	Control	6/63	0/11	

Table 6: Distribution of the relative frequency of patients with acute coronary syndrome referred to the emergency room by side effects in two groups

Group / side effects	Control		intervention	
	Percentage	Num	Percentage	Num
Not having complications	100 %	213	90/4 %	198
Drowsiness	0	0	8/2 %	18
dizziness	0	0	¼%	3
p=0/00				

Discussion

In the results of this research, 144 people were found eligible to participate in the study and were randomly assigned to two intervention and control groups. The number of people in the intervention group was 73 and the control group was 71.

GEE analysis (generalized estimating equation) showed that in the intervention group compared to the control group (group 2) there was a significant decrease in pain.

Out of 144 patients with heart attack, 75.3% men and 64.8% women in the intervention group and 64.8% men and 35.2% women were examined in the control group. The type of myocardial infarction was 41.1% in the intervention group and 50.7% in the control group, which was not significantly different from the type of unstable angina which was 58.9% and 49.3% in the two groups, respectively (P = 0/31).

The prevalence of myocardial infarction with ST segment elevation in the two groups was 86.7 and 100%, respectively, which according to P = 0.04, we conclude that there is a significant difference between the types of MI in the two groups, and ST elevation is higher in the control group than in the ketamine group.

Pain is a common condition among pre-hospital patients (14). EMS and emergency departments are faced with the challenge of providing effective pain management for both humanitarian reasons and to reduce the likelihood of chronic pain syndromes and pain-related anxiety and disability following the acute phase (15, 16).

Patients with unusual chest pain constitute a high proportion of emergency admissions. Often the symptoms remain or recur. Johansson et al concluded that morphine sulfate with the addition of low doses of ketamine

provided adequate pain relief in patients with bone fractures, an increase in systolic blood pressure, but without significant side effects (14).

JENNINGS et al found ketamine to be a safe and effective analgesic. The addition of ketamine as an analgesic agent may improve the management of patients presenting with acute traumatic pain in the prehospital setting, consistent with our finding that ketamine is effective in reducing pain in opioid-resistant or hemodynamically unstable patients. They are safe and aligned (17).

Galinski et al found that in the control group over a 30-minute time period, a greater proportion of the ketamine group than the morphine group had their pain reduced to less than 30 mm. However, this difference was not statistically significant, which is contrary to our study, where the difference between the two groups was significant in all three stages, and the pain score in the control group was higher than the intervention group (18).

In Svenson's (19) study, ketamine was used as a procedural sedative in five patients. Cottingham (20) and Johnson (14) concluded that ketamine provided effective pain relief, but Galinski (18) reported that ketamine reduced the amount of morphine required but was not associated with a reduction in pain intensity.

Galinski et al (18) reported that neuropsychological adverse effects were significantly greater in the ketamine group. These side effects included hallucinations, dizziness, diplopia, and dysphoria. Despite these side effects, the authors stated that they were mild and brief, none required treatment, and patient satisfaction did not differ between the two groups. The level of sedation, nausea, vomiting and itching did not differ between the two groups. Other studies reported no significant side effects and concluded that ketamine is safe.

Johansson's study (14) reported no other side effects other than nausea and vomiting experienced in either group. They reported an increase in mean systolic blood pressure in the ketamine group during hospitalization, which is not consistent with our study, which had dizziness and drowsiness in the intervention group.

In fact, it can be said that the use of ketamine with a low dose is not without side effects, but the amount of these side effects is very low and transient at a low dose, and it can be said that it is safe to reduce the pain of patients who are resistant to opioids or have unstable hemodynamics. But more studies are necessary to determine its effects on clinical results among the suggestions for future research, we can refer to the use of higher doses of ketamine, adjustment of accompanying factors, including the length of hospitalization in the emergency room and associated diseases, measuring the pain score in 120 minutes and more.

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