

Ketamine in Acute Abdominal Pain in Patients with Lead Poisoning

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Abstract: *Introduction:* In this study, we investigated the effect of intravenous ketamine administration on acute abdominal pain in lead poisoning patients. *Methods:* In this cross sectional study, we evaluated 20 patients with opium abuse with acute abdominal pain due to lead poisoning. With cardiac monitoring, 0.25 mg/kg ketamine (maximum dose was considered as 20 milligrams) was administered during 30 to 60 seconds. To control ketamine complications such as psychological irritability 0.03 mg/kg midazolam (2 milligrams was considered as maximum dose) was injected slowly during one or two minutes. Patients were observed in the ED for the next 6 hours. Pain score was assessed with VAS method, serially. Pain was measured before ketamine administration, every one hour for the next two hours and every two hours for four hours. *Results:* In this study 20 patients were enrolled with mean age of 37.2 ± 4.2 years (range from 30 to 44 yrs.). Repeated measurement test shows significant reduce in pain score after ketamine administration ($P=0.001$). Five patients report no pain 4 hours after ketamine injection, and 3 of them left the hospital with personal consent before the end of the study. From 17 remaining patients, 13 ones (76.4%) had no pain, and mean VAS score in other 4 patients was less than 2 after 4 6 hours. *Conclusion:* our results show that low dose ketamine administration can reduce abdominal pain related to lead poisoning in opium abusers.

Keywords: Acute Abdominal Pain, Lead Poisoning Patients, Ketamine

1. Introduction

Pain is the most common symptom that forces a patient to look for emergency medical care. As a fact, pain does not depend on a particular age, gender or culture [1]. Pain is an unpleasant sensation and experience that is caused by actual or potential tissue damage and is a common phenomenon in the emergency that can have adverse effects on the patient's hemodynamic status [2].

Today, ketamine is introduced as a dramatic pain relief in many patients and associated with lowering the consumption of systematic opioids. Ketamine is an antagonist of NMDA receptors (N-methyl dispartate, one of the pain-related receptors) and is used as a general anesthetic for short-term

surgeries or diagnostic procedures that do not require skeletal muscle relaxation. This drug may act by blocking the afferent nerve pain messages and decrease spinal cord activity [3]. Ketamine is rapidly distributed throughout the body's tissues, including the brain. Its metabolism is hepatic and its half-life is 2-3 hours. After 15-30 seconds from intravenous injection and 3.4 minutes after intramuscular injection, ketamine begins to act [4-6].

Hallucinations, dreams, increased saliva production, hypertension, tachycardia, tonic and colonic muscle movements and tremor are common side effects of ketamine that can be seen in cases with high doses injection.

Concomitant use of low doses benzodiazepines such as diazepam and midazolam can prevent these complications [5].

Drug abuse is one of the major public health problems in all societies, including Iran. The prevalence of drug abuse in the world has been reported about one to two percent, this estimation seems to be much higher than the global scale in Iran [7]. Nowadays, opium is a new source of lead contamination, drug distributors are mixing it with lead for greater profit and increased volumetric mass. Lead absorption depends on the volume of particles, so the smaller particles are absorbed earlier [8]. On the other hand, higher amount of lead will be absorbed in iron deficiency patients. Divalent metal transporter 1 (DMT1) is iron and lead adsorbent, and its production increases in the case of iron deficiency. Lead disrupts cellular activity, lipids membrane structure and damage the vessel wall, so, lead to vascular obstruction and necrosis [9]. Therefore, the consumption of these substances, especially oral use of opium, can cause lead poisoning (LP). The clinical symptoms of acute lead poisoning vary in individuals, some of them are: abdominal pain (lead colic), constipation, musculoskeletal pain, headaches, decreased libido, short-term focus and memory impairment, hypochromic or microcytic anemia and nephropathy [10].

Chronic exposure to small amounts of lead can also increase the risk of hypertension and cognitive disorders in adults. Most cases happen due to workplace lead exposure such as; Batteries, Painting, Soldering, Ammunition, Radiators, Wiring Cables, Cosmetics, Ceramics, Motor Oil and Gasoline and Handmade Alcohol. Inhalation is one of the most important way of lead entrance and 40% of lead absorbs at this site [11]. Gastrointestinal absorption rate of lead is 10-15%, this rare increases in fasting conditions or deficiency of iron, calcium, phosphorus or zinc in the diet. Although gastrointestinal absorption is not the main route of lead absorption, it is an important site of entry in children as well as in adults consuming lead-contaminated drugs or food ingredients. The kidney is the main route by which lead is eliminated and in normal renal function cases lead has about 30 days half-life. However, the rate of lead clearance is lower in people who have been exposed to lead for a long time. The cause of opium contamination with lead is unknown. And there are two theories explain it; drug traffickers perform it or the possibility of geographical vicinity of the opium fields and lead mines [11-14].

In published records of opium-tinged in Iran, all cases of LP occur in male patients and there is no report of lead poisoning in female or children. Mean age of abusers of lead contaminated opium is between 25 and 68 years and abdominal pain and nausea were observed in all cases [7]. Abdominal pain associated with lead poisoning is one of the main causes of drug abusers' referral to the emergency department (ED). Suppressing this pain is one of the most important challenges, because their pain is resistant to conventional antispasmodic or analgesic drugs like hyoscine and high doses of opioids.

Lead poisoning related abdominal pain is a challenging issue in emergency department. There is no previous report about the

efficacy of ketamine in lead poisoning colic. Although, previous studies demonstrated the efficacy of ketamine in acute and chronic pain or surgical pain, there is no study about the impact of ketamine on acute pain in drug abusers. And to best of our knowledge, this study is the first one.

In this study, we investigated the effect of intravenous ketamine administration on the treatment of acute abdominal pain in lead poisoning patients.

2. Method

In this cross sectional study, we evaluated 20 patients with opium abuse who referred to our academic hospital ED with acute abdominal pain. Study was conducted after ethical approval of Mashhad University of medical sciences (98/4321). Lead poisoning was considered in patients with serum lead level more than 60 micrograms/ deciliter based on agency for toxic substance and disease registry information [15].

2.1. Patients' Selection

Patients were enrolled the study with a history of drug abuse and acute abdominal pain purposeful sampling. Due to the lack of similar studies and the percentage of emergency referrals, our sample size was estimated at least 20 patients during one year. Although, three patients leaved ED before 6 hours of admission because of dramatic pain relief, we analyzed their data in final evaluation. Written consent was obtained from all patients. Inclusion criteria were:

- 1) History of opium use regularly for the last 6 months until now.
- 2) Acute abdominal pain for the last 24 hours with visual analogue scale (VAS) more than or equal to 7 which was not suppressed by routine analgesics.
- 3) Serum lead level higher than 60 micrograms/ deciliter.
- 4) Aged between 18 and 45.
- 5) ED stay for at least 4 hours after ketamine administration.
- 6) Patients were excluded with the following criteria:
- 7) Abnormal findings in patents serial examination (such as abdominal tenderness, rebound tenderness, gastrointestinal bleeding...).
- 8) Elevated liver function tests, positive viral hepatics serum markers.
- 9) Abnormal serum creatinine, lactate dehydrogenase levels, abnormal arterial blood gas analyses.
- 10) Abnormal radiologic findings.
- 11) Need for further investigations based on surgery consult.
- 12) Dramatic response after administration of 10 milligrams morphine.
- 13) History of chronic renal, liver, pulmonary diseases or diabetes mellitus, hypertension, etc.
- 14) History of psychological disorders or using synthetic drugs.
- 15) History of head and neck or facial trauma in the last month.

2.2. Method of Administration and Evaluation of Severity of Abdominal Pain

An intravenous access was obtained from antecubital fossa in all patients. In all 10 milligram morphine sulfate was administered intravenously one hour before ketamine injection, but none of them report a significant pain relief. After careful patient selection and absence of known contraindication and complete patient satisfaction, under cardiac monitoring, 0.25 mg/kg ketamine (maximum dose was considered as 20 milligrams) was administered during 30 to 60 seconds. To control ketamine complications 0.03 mg/kg midazolam (maximum dose was considered as 2 milligrams) was injected slowly during one or two minutes. Patients were observed in the ED for the next 6 hours. Pain score was assessed based on VAS with a serial method, before ketamine administration, every hour for the next two hours and every two hours for four hours. After pain relief patients referred to toxicology clinic for lead poisoning treatment.

2.3. Statistical Analyses

Data were coded and entered Statistical Package for the Social Sciences (SPSS) version 16. In order to maintain the confidentiality of the study, the patients' checklists were coded and only were available to the project leader. Average of pain score was obtained and correlation between pain score and ketamine dose was evaluated with Pearson test. Mean VAS score were compared with repeated measurement analytic test. Significance level was considered as p-value less than 0.05 in all tests.

3. Results

In this study 20 patients were enrolled with mean age of 37.2 ± 4.2 years (range from 30 to 44 yrs.). Pain score based on VAS before ketamine injection was 8.7 ± 0.8 . Patients abused opium for 8.1 ± 4.1 years (range from (3 to 19 years). Table 1 shows the mean VAS score in different time after injection.

Table 1. Demographic characteristics of patients.

	Mean \pm SD
Age (yrs.)	37.2 ± 4.2
Pain score (VAS)	8.7 ± 0.8
Opium abuse years	8.1 ± 4.1

Mean ketamine dosage was 14.3 ± 3.4 milligram (range from 10 to 20 milligrams). Repeated measurement test shows significant reduce in pain score after ketamine administration ($P=0.001$). Five patients report no pain 4 hours after ketamine injection, and 3 of them left the hospital with personal consent. From 17 remaining patients, 13 ones (76.4%) had no pain, and mean VAS score in other 4 patients was 1 or 2. The mean VAS score in different time after ketamine injection is summarized in table 2.

Table 2. The mean VAS score in different time after ketamine injection.

Time	Mean \pm SD
Zero	8.7 ± 0.8
First hour	5.1 ± 0.7
Second hour	3.1 ± 0.3
Fourth hour	2.3 ± 1.1
Sixth hour	1 ± 1

There was no correlation between duration of drug abuse and VAS score. 16 patients were discharged after 6 hours and pain relief. We followed up patients for 72 hours after discharge by telephone calls, and only one patient readmitted for abdominal pain.

In one patient apnoeustic respiration occurred, so he was transferred to cardiopulmonary resuscitation unite. Supportive intervention was taken immediately, regard to the history of opium abuse, naloxone was administered and after 4 ampule injection, respiratory rate was normalized. This patient received maintenance dose of naloxone and admitted to toxicology unite for the next 48 hours.

4. Discussion

4.1. Summary

Although, previous studies demonstrated the efficacy of ketamine in acute and chronic pain or surgical pain, there is no study about the impact of ketamine an acute pain in drug abusers. And to best of our knowledge, this study is the first one. Our results show that single dose injectable ketamine is one of the best methods with the least side effects to alleviate acute abdominal pain in patients with drug abuse. Because of differences in individual susceptibility, symptoms of lead exposure and their onset may vary. And it is not clear why these patients experienced diffuse abdominal pain. So, there is not an established method for treatment of abdominal pain in lead poisoning patients, and symptomatic treatment might be useful in these population.

4.2. Strengths and Limitations

This study was a cross-sectional study without a control group with a limited number of patients. Further clinical trials are needed to use its results in EDs. Although ketamine complications have been reported to be uncommon, but these effects appear to be rare after its oral administration due to slower absorption. And, future studies can evaluate the efficacy of this method also.

Comparison with existing literature:

The number of patients with chronic pain increased in recent decades. Antidepressants, anticonvulsants and opioids are widely used for treatment of these patients. Patients with lead-induced abdominal colic are one of the most challenging patients in the emergency department because their abdominal pain is -in many cases- resistant to high doses of opioids [14, 16].

Ketamine is a derivative of Phenylpiperidine, which is chemically similar to phencyclidine. Today, ketamine has been shown to be very effective in treating neuropathic pain by

inhibiting N-Methyl-D-aspartate receptor (NMDAR). Lead related abdominal colic has not been well studied and may also have a neuropathic basis [11]. Our study showed the efficacy of single dose ketamine in LP patients' acute abdominal pain. Ketamine also has anti-inflammatory effects that can be effective in lead poisoning patients. Acute analgesic effects of ketamine are mediated by effects on presynaptic neurons of the dorsal horn of the spinal cord. Ketamine also affects the downstream pathways of pain, which may be one of the reasons for longer pain control in patients, and described the cause of only one readmission of our cases. Magnetic resonance and behavior studies revealed that ketamine activated cingulate and frontal orbital cortex in normal individuals, so pain modulates and inhibits the downstream reactivation of pain receptors [10]. But we cannot completely decline the theory of colicky nature of LP abdominal pain, which might be the cause of longer pain relief in LP pain!

It has recently been suggested that ketamine also affects opiodergic, muscarinic, and monoaminergic receptors. Other studies in mice have shown that ketamine can induce analgesia by acting on the μ -opioid receptor, which may justify apnea and its response to naloxone in one of our patients [11].

4.3. Implications for Research

Considering the lethality of lead poisoning in high doses, it is important to always intend lead poisoning in the differential diagnosis of drug abusers with unexplained abdominal pain, and measuring lead levels in addicts with specific symptoms is necessary.

5. Conclusion

Our results show that low dose ketamine administration can reduce abdominal pain related to lead poisoning in opium abusers which can increase patient satisfaction and reduce the dose of injectable analgesic and decrease the readmission of patients in emergency department.

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