Original Article

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Comparison of Efficacy of Nebulized Ketamine plus Lidocaine versus Morphine in Pain Management in Patients referred to Emergency Department: A Randomized triple-blind Clinical Trial

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ABSTRACT

Background & Objective: Pain is a common cause of patients referred to the emergency department (ED). The current study was performed to compare the efficacy of ketamine and lidocaine administration instead of intravenous morphine to alleviate acute limb pain in patients.

Materials & Methods: In the current triple-blind clinical trial, 40 included patients were divided into two separate groups. The intervention group received ketamine (5mg/kg), lidocaine (2mg/kg), and normal saline (0.1 ml/kg) intravenously (IV), while the control group received 0.1 mg/kg of morphine and nebulizer normal saline. A 10-point pain scale was performed to measure the pain level and its effects before and after treatment. At intervals of 5-60 minutes, the pain was evaluated.

Results: The average pain relief between the two groups was not statistically different. For the first 5-10 minutes after the drug administration, similar pain relief was observed in both groups. In the first 15 minutes, ketamine and lidocaine nebulizer pain relief was better than morphine. The reaction to pain-relieving medication in both groups was more extensive than the three numerical pain assessments. There was no noticeable adverse effect in the studied groups.

Conclusion: The ketamine and lidocaine nebulizers in emergency departments can be used as a practical and simple approach to managing acute limb pain. Given that lidocaine was utilized in this investigation to boost ketamine mucosal absorption and prevent probable adverse effects, more trials lacking lidocaine could be conducted to remove lidocaine's effect and better evaluate ketamine's effect. Ketamine can also be used at a higher dose to evaluate its effects and possible side effects.

Keywords: Numerical rate of scale (NRS), Nebulized, Acute limb pain, Ketamine

Introduction

Pain is the prevalent reason among patients referred to emergency departments (EDs) **(1)**; 70% of patients are admitted to the EDs with some form of pain **(2)**. Pain is a mental and unpleasant sensory criterion with no objective criterion and is experienced based on the patient's statements. ED practitioners extensively use pain rating scales to assist them in checking for acute pain and assessing the efficacy of treatments **(3).** There is no conclusive clinical evidence that patient satisfaction is linked to pain intensity **(4, 5)**. Patient satisfaction is significantly linked to reduced pain

intensity, influenced by the speed of analgesic impact **(6)**.

CI-581 was identified in 1962 as a multi-purpose drug having unique features as a non-competitive N-Methyl-D-aspartate (NMDA) antagonist of the central nervous system (CNS) on glutamate receptors. This drug contains pain-relieving and anesthetic properties due to opioid receptors opposing Ketamine. Through opioid receptors, this medication has pain-relieving and anesthetic properties **(7)**. Moreover, ketamine has become more common in mucosal absorption methods due to its greater fat solubility and low pharmaceutical side effects **(8)**. Ketamine's effectiveness has been demonstrated in traumatic brain injury, acute pain services, patients with high intraocular pressure, tumor pain, chronic pain, alcohol withdrawal, critical care medicine, status epilepticus, electroconvulsive therapy, sore throat, cardiopulmonary bypass (CPB) surgery, and uropathy **(9, 10)**.

The available literature describes current clinical uses of ketamine with moderate scientific evidence according to the resurgent interest in low-dose ketamine therapy as follows: A) Procedural sedation for both adults and children: The previous studies are robustly supportive of the safety and effectiveness of ketamine for ED dissociative sedation for a diversity of brief painful or emotionally bothering methods in children as well as adults, for example, Laceration mending, fracture decrease, abscess drainage, urgent cardioversion, amputation, and chest tube placement. That is helpful for approaches in the mentally disabled, who are usually uncooperative. This dissociative sedation can be easily obtained through the management of a single IV or IM loading dose of ketamine and then titration. Intranasal ketamine is being applied in a broad area of clinical doses (0.5-9 mg/kg) for procedural sedation in children **(11)**. It is applied to sedation or general anesthesia for pediatric procedures like cardiac catheterization, radiotherapy, and radiological investigations, including magnetic resonance imaging (MRI), dressing changes, and dental activities **(12)**. Low-dose ketamine combined with low-dose propofol leads to efficient and safe sedo-analgesia for urgent short surgical procedures in children, adults undergoing colonoscopy, and short gynecological strategies **(13)**. B) Sedation and analgesia in the critical care unit (CCU): Ketamine utilized for patients in CCU supplies combined sedation and analgesia and has beneficial outcomes on hemodynamics and can also treat continual bronchospasms. Constant IV infusion of ketofol provides sufficient and sure short-term sedation **(14)**. C) Co-induction and total IV anesthesia (TIVA): Ketamine as a co-induction agent in low doses combined with other drugs such as propofol/midazolam/dexmedetomidine/lidocaine for TIVA method in the operating room has become increasingly popular. This combination has some advantages including retention of constant hemodynamics, decreased injection pain, and minimal respiratory depression while allowing ventilation spontaneously. Erdogan et al. conducted a study on elderly patients (n= 80) and reported that the ketofol (ketamine plus propofol 1:1, i.e., 5 mg/ml each) provides better proseal laryngeal mask airway (PLMA) insertion conditions. They discovered that the ketofol group had an increased apnea duration, fewer patients who needed ephedrine and a lower total dose of ephedrine **(15)**.

One of the most well-known opioid pain relievers is morphine. It is used to treat both children and adults with moderate to severe pain. It has specific adverse effects, including drowsiness and respiratory depression **(16)**, and the standard dose (0.1 mg/kg) is ineffective at repressing severe pain. In 2012, Tsze et al. found that using intranasal ketamine for wound healing in children at a dose of 9 mg/kg was efficiently successful **(17)**.

Another study by Acworth et al. on the combined intravenous midazolam and ketamine with intranasal midazolam in emergency pediatric sedation showed that the rate and persistence of the intranasal midazolam effect and the use of its inhaler spray has been effective in many clinical trials **(18)**. Cioacă et al. conducted a further study and discovered that using ketamine in the oral mucosa had a calming effect on children **(19)**. Thus, the current study aimed to use combined ketamine and lidocaine using a nebulizer and comparing it with IV morphine administration and to examine the differences in terms of individual and demographic variables and the required minimum dose and speed of onset. This method might likely be recommended as an alternative to aggressive procedures such as IV morphine prescription in patients who suffered from acute limb trauma. In the present clinical trial, the analgesic effect of nebulized combination of ketamine (5mg/kg) and lidocaine (2mg/kg) with intravenous morphine (0.1 mg/kg) was compared. In addition, we evaluated the side effects of drugs.

Materials and Methods

Study Design

In the present randomized triple-blind clinical trial, the side effects of a nebulized combination of ketamine and lidocaine were compared with those of IV morphine in ED patients along with acute limb injuries. The ethics code (no. 9405) was obtained from the Clinical Ethics Board of Zanjan University of Medical Science. The randomized clinical trial (RCT) was registered and approved by the blinded Registry of Clinical Trials (IRCT 2012111701585N1). Ketamine administration was done with the approval of the joint commission and the authorization of the drug board officials of hospitals affiliated with the Iran University of Medical Sciences.

This study was performed to compare the effectiveness and safety of nebulized Ketamine with intravenous morphine for pain handling of patients

with trauma in the ED of a university teaching hospital (7th Tir) in Tehran, Iran, from September to November 2015. In this study, trauma patients were included with aged 16 to 50 years. Participants also had an acute limb trauma score≥ 5 on a standard 0-10 numeric rating scale who were referred to the emergency departments. Patients were excluded from this investigation if they had the following criteria: instability in vital signs, head trauma, Glasgow coma scale score< 15, patients using opioids, psychiatric or cardiac trouble, sensitivity to ketamine or morphine, pregnancy, breast-feeding, renal and hepatic failure, and Upper respiratory tract infections or hypersensitivity, which are contraindications for both medications. All patients who participated were volunteers, and informed consent was obtained from all of them.

Study Instrument

A 10-cm line with tick marks spaced 1 cm apart was utilized to measure pain. The leftmost mark is labeled with a minimum of "0" and means "no pain," and the rightmost mark is labeled with a maximum of "10" and means "the worst pain ever".

Participants

This study included 40 patients with acute limb pain who met seven criteria: non-consume continuous paregoric, non-alcoholic, non-drug addict, non-pregnancy, non-breastfeeding, stable vital signs (SBP≥90, HR═60-120, RR═8-22, O_2 saturation≥90, GCS═15/15, in 16-50 aged with the Numerical Rating Scale (NRS) higher 5 out of 10, also an allergic to morphine, ketamine and lidocaine, head trauma, optic trauma, Chronic Obstructive Pulmonary Disease (COPD), liverish, nephron, cardiovascular disease, blood disease, psychological chronic disease and psychiatry drug consume, consume of Selective serotonin reuptake inhibitor (SSRI), Monoamine oxidase inhibitor (MAOI), trichloro acetic acid (TCA), hypnagogic drugs, phenothiazine, asthma), and the 1st group with comorbid disease of American Society of Anesthesiologist classification(ASA >II)were considered exclusion criteria. The research was conducted at Tehran Hafte-Tir Hospital from October to November 2015.

Randomization

The block randomization algorithm generated the following random sequence: AABB, ABAB, BBAA, BABA, BAAB, and ABBA (A: intervention group, B: control group). Every fourth block had a 16.6% chance of having a patient.

The intervention group was given normal saline as a placebo for 1 minute before receiving 5 minutes of nebulized ketamine and lidocaine. The control group was given 1 minute of IV morphine sulphate, followed by 5 minutes of normal saline as a placebo.

Patient Allocation and Blinding

Based on the patients' self-statement NRS, two equal groups were treated with one medical package. According to Ramsay III, the cut-off medication threshold was regarded as the highest level of mitigating (the patient was sleepy but could follow the instructions; it is a criterion: the patient's level of awareness is based on the patient's visual and verbal reactions as well as the individual's motion in reaction to sound and external and internal stimuli).

Interventions

Baseline pain grade was assessed with a numeric rating scale (NRS). Patients who had a pain score≥ 5 were included in the study. Baseline characteristics of studied patients, including gender, age, BMI, and matrimony status, were recorded using patients' interviews. Subsequently, the patients were randomized into two groups. Blocked randomization was the method employed for randomization. Three 10cc syringes with the 10cc medicine or the identical placebo (normal saline) were included in each pharmaceutical box. The control group received normal saline from two placebo syringes via nebulizer, 0.1 mg/kg morphine (1cc per 10 kg patient's weight from 1 mg/ml solution) within 5 minutes, and the case group received 5 ml/kg ketamine (1cc per 10 kg patient's weight from 50 mg/ml solution) and 2 mg/kg lidocaine (1cc per 10 kg patient's weight from 20 mg/ml solution). Then, the participants in the first group received ketamine (5mg/kg) with lidocaine (2mg/kg), and the second group received morphine (0.1 mg/kg). Each group received IV medication injections by a nurse blind to the study process. The adequate pain score decrease in patients was determined as a reduction in pain score ≥ 3 **(20)**. In case of patients did not get enough pain reduction, rescue analgesia was injected every 5 minutes. Pain score, blood pressure (BP), heart rate (HR), pulse oxygen saturation, and side effects of drugs were evaluated at 0,5,10, 15, 30,45, and 60 minutes after injection. Patients' nausea during the study period was controlled by using antiemetic drugs. When the blood pressure of the patients decreased to 90 mmHg, it was considered hypotension and was treated with a fluid bolus. Oxygen saturation less than 92% is defined as desaturation and is typically managed using head tilt-chin lift and bag-mask ventilation. Bradycardia was considered when the HR was reduced to less than 60/min and controlled via 0.5 mg atropine intravenously. Patient satisfaction with drug injection was recorded with a qualitative level of 5 points after 1 hour of injection, where points 5-1 were considered excellent, very good, good, fair, and poor, respectively. The intended analgesic effect was to be achieved through excellent and very good responses.

The severity of pain in participants was recorded before administration and also 5, 10, 15, 30, 45, and 60 minutes after nebulizer and intravenous drug administration. Respiratory rate, HR, blood pressure, pulse rate, pain severity, and drug side effects were recorded before and 5, 10, 15, 30, and 60 minutes after administration. All included patients in the study were randomly assigned to a group and monitored by HR and pulse oximetry.

To respond to the treatment due to the NRS criterion, a reduction of at least 3 points of the pain intensity was

considered, provided that the final number is less than 5, although achieving to some measure analgesia level with no side effects was the ultimate goal.

Outcome

In terms of pain intensity, HR, blood pressure, and drug side effects, three times were monitored: the first before therapies (on arrival), the second five minutes after intravenous drug and nebulizer injection, and the third in the sextet times 2-6 (10, 15, 30, 45, and 60 minutes after the first time). When the individuals did not respond to the medication, one milligram of morphine was administered every five minutes (morphine was injected at time three, 15 minutes after the end of the drug injection, if there was no response to treatment). It falls within the category of life-saving therapy.

In an emergency, 0.1 mg/kg of midazolam IV was administered (it causes adverse reactions on awakening (hallucinations, delirium, color vision impairment, etc.). When the patient's sedation level resulted in non-response or adverse effects, the patient was removed from the trial. Each group was given three syringes. One group received two syringes containing ketamine (RotexMedica Germany), lidocaine (Abu Reyhan Pharmaceuticals, Iran) for nebulizer administration, and a third syringe containing normal saline for intravenous delivery. The other group includes two syringes that carry normal saline via a nebulizer and a third syringe that contains intravenously administered morphine sulphate (Abu Reyhan Pharmaceutical, Iran). These categories were coded and used at random.

The patient's self-statement of pain intensity was recorded at sextet intervals. The Novin S100 pulse oximeter was used to monitor arterial blood oxygen saturation below 90% from the first finger of the right or left hand. Any O2 saturation reduction below 90% for 60 seconds was deemed reasonable. In the sextet-defined times, its absolute value was also recorded. The total life-saving dosage of morphine was measured in ml until satisfactory analgesia was achieved. Sixty minutes after getting the medicine or at the time of prescribing life-saving therapy, overall satisfaction was measured using a 5-point criterion (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent).

Statistical analysis

The data was evaluated quantitatively using SPSS Inc.'s Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) version 21 for Windows by performing Repeated Measures one-way ANOVA, Paired T test, and Post Hoc Scheffe test, if necessary. Results were shown as mean ± SD for quantitative variables, and a p-value < 0.05 was considered significant, statistically. The sample size in this study was computed by the following formula: $N = \frac{\left[Z_{1-\alpha/2}+Z_{\beta}\right]^2\left[S_1^2+S_2^2\right]}{(M_1-M_2)^2}$

Results

140 patients were included in this clinical trial, but 100 were excluded because they did not meet the inclusion criteria. All the remaining 40 patients in the study were randomly subjected to two LDK and morphine groups. The CONSORT diagram of the patient is depicted in Figure 1. Only 40 patients met the criteria for inclusion in the research out of 140 acute limb trauma patients (16–50 years old) referred to the Hafte-Tir Hospital emergency department. The main thing that happened was that the NRS decreased, but there were no big changes in the sextet times of the NRS in the two groups. As indicated, age, gender, and body mass index (BMI) had no significant coefficients **(Table 1).** Both groups were observed to have a significant decrease in mean pain intensity 15 minutes after drug injection (T15) when compared to initial pain (T5, T0). Also, no significant differences in the mean pain intensity (P=0.56) were not found between groups at baseline and T15 at 30, 45, and 60 minutes. In addition, no life-threatening complication (including nausea, dizziness, nystagmus, emergency phenomena, restlessness, and flushing) was found in both und.

To examine the pain causes four categories were considered as the content of Table 2.

The NRS is a qualitative indicator that measures patient satisfaction. The patients were divided into two desired satisfaction and non-desired satisfaction groups. Although there was no statistically significant difference between the two groups (p = 0.4), the desired level of sensually satisfactory satisfaction was present.

Table 1. Baseline Demographic information of patients

Demographic		Intervention group	Control group	P-value(NRS)
Gender	**Female No. (%)**	6(30%)	6(30%)	0.99
	Male No. (%)	14(70%)	14(70%)	0.99
Age mean± SD	**Age (≥35)**	6(30%)	12(60%)	0.11
	Age (≤34)	14(70%)	8(40%)	0.11
BMI(kg/m^2) mean± SD	**Female**	6(30%)	6(30%)	0.99
	Male	14(70%)	14(70%)	0.99
	Total	24.6	25.4	0.66
Matrimony status	**Single**	9(45%)	4(20%)	0.67
	Married	11(55%)	16(80%)	0.67

Table 2. Causes of acute pain in the experimental and control groups

Items	Intervention group (Nebulized ketamine)	Control group (IV morphine)	Total
Wound and soft tissue injuries	4	3	7
Fractures	9	13	22
Sprains and strains	5	3	8
Dislocation	2	1	3
Total	20	20	40

Table 3. Decrease of NRS

Times	Group	5min	10min	15min	30min	45min	60min
Control group (n=20)	Mean	6.42	5.52	4.94	4.52	3.94	3.73
	CI	5.5-7.2	4.6-6.3	4.1-5.7	3.7-5.3	3.2-4.6	2.9-4.4
Intervention group (n=20)	Mean	6.10	5.05	4.65	4.20	3.70	3.20
	CI	5.2-6.9	4.2-5.8	3.8-5.4	3.4-4.9	2.9-4.4	2.4-3.9
Total (n=40)	Mean	6.26	5.28	4.79	4.36	3.82	3.46
	CI	5.6-6.8	4.7-5.8	4.2-5.3	3.8-4.9	3.3-4.3	2.9-3.9

Table 4. The frequency of drugs side effects.

Side effects	Restlessness	Flushing	Nystagmus	Emergency phenomenon	Vertigo	Vomit	Brochorea	Total
Control group	0	2	0	0	4	3	0	9
Intervention group	0	0	6	0	2	0	0	8
Total	0	2	6	0	6	3	0	17

Table 5. The patients' satisfaction following treatments in patients with acute limb pain

Items	Scale	Groups		P-value	Total
		Control	Intervention		
Desired Satisfaction	Satisfied	1(5%)	4(20%)	0.4	33(82.5%)
	Extremely	6(30%)	9(45%)		
	Very good	8(40%)	5(25%)		
Non desired satisfaction	Good	4(20%)	2(10%)	0.4	7(17.5%)
	Moderate	1(5%)	0		

Discussion

This study found that ketamine at a dose of 5mg/kg,15 minutes after nebulization, had a significant pain reduction in the patients with trauma. In comparison with morphine, a significant difference was not discovered in T15. The use of ketamine in mucosal absorption methods is becoming more common due to its acceptable solubility and low complications. One-fifth of prescription medications can reach circulation if 20% of nebulizer drugs enter circulation. In the trial, this substance was used to boost mucosal absorption. In recovery, patients were followed for 60 minutes, with any problems or changes in vital signs being noted. Heart rate (HR), systolic blood pressure (SBP), oxygen saturation, and respiratory rate (RR) did not alter significantly. Rapid postoperative treatment of sore throat and asthma therapy are some of the study topics for ketamine administration by nebulizer **(21-23).** Few investigations have been performed to assess the analgesic impact of ketamine in emergency departments (EDs). For instance, Acworth et al. **(18)** conducted a retrospective case series research during 2 years and evaluated the efficacy of ketamine in several acute and chronic pain in ED. They used 0.1 to 0.3 mg/kg (5 to 25 mg IV or IM) dose of ketamine alone or in conjunction with another tranquilizer for pain management in ED. In the study mentioned, 92% of patients were given 10 to 15 mg of Ketamine. The results indicated that about 6% of patients met complications. They concluded that the use of LDK can be clinically useful as an analgesic drug in a diverse population of ED patients to treat many types of pain safely and with high efficacy. Majidinejad et al. **(24)** conducted another investigation comparing a 0.5 mg/kg dose of ketamine with 0.1 mg/kg of morphine in patients (n=126) with long bone fractures who were in an emergency. The authors found that the ketamine-receiving group experienced a significant reduction in pain 10 minutes after drug injection, similar to the morphine-receiving group. In addition, the ketamine-receiving group experienced a significant increase in the rate of complications. In another study, Motov et al. **(25)** investigated 90 patients along with various pains with NRS≥ 5. The study was conducted with 45 subjects in each group, and the analgesic effects and complications of ketamine (0.3 mg/kg) and morphine (0.1 mg/kg) were compared 120 minutes after injection. In the mentioned study, LDK similar to morphine, was effective in a short time on pain reduction. On the other hand, they observed that the ketamine-receiving group experienced a significantly higher complication rate than the morphine-receiving group. Additionally, several investigations have also assessed the safety and painkiller impacts of ketamine in pre-hospital conditions. In this regard, Jennings et al., in a review literature, reported the safety and efficacy of ketamine as an analgesic drug in pain reduction in pre-hospital trauma patients **(26)**. In another research, analgesic effects were compared between ketamine (0.2 mg/kg) and pentazocine (0.4 mg/kg) and placebo in a separate investigation conducted in pre-hospital people in the war region of Iraq **(27)**. According to the study, intravenous ketamine is effective in both lowering blood pressure and reducing pain. In a study by Mahshidfar et al. comparing the LDK with morphine for pain alleviation in patients with trauma **(28)**. This group concluded that LDK (0.2 mg/kg) in the early minutes caused to remarkable decrease in pain in comparison with intravenous morphine. It is also less likely to cause complications than morphine. In a randomized, double-blind clinical trial, studied patients (n=300) with trauma from the ED of two separate teaching hospitals (including Tehran and Iran) were included and divided into two groups. The pain intensity, as well as complications, were evaluated and compared every 15min to 1h between the groups receiving 0.2 mg/kg of ketamine and 0.1 mg/kg of intravenous morphine. The finding shows that LDK, compared to intravenous morphine, causes a significant reduction of pain in the earlier minutes.

Based on the current study, it can be concluded that ketamine's analgesic effect is identical to that of morphine 15 minutes following injection. Compared to the morphine group, ketamine's effect on reducing pain decreased in the next few minutes. The previous literature mentioned above also proved the effects of ketamine in the initial few minutes following injection. These findings are by those of the present study. Our study revealed that complications caused by ketamine were less severe than those caused by morphine. The morphine group experienced a significantly higher rate of flushing and a significant drop in BP. In contrast, the ketamine group necessitated additional tranquilizers; also, morphine recipients were further content with analgesic effects. Huge samples and various doses of ketamine are needed for further studies.

Conclusion

The research suggests that reducing pain with nebulized LDK (5mg/kg) in the early minutes is a significant improvement over intravenous morphine. Furthermore, it results in fewer complications than morphine. The safety and efficacy of a nebulized version of ketamine as an anodyne have yet to be established. Ketamine is equally as effective as intravenous morphine for pain relief. Ketamine is a quick, low-cost, side-effect-free, easy-to-use, and effective pain reliever for any injury. Although the combination of nebulizing ketamine and lidocaine did not significantly reduce pain, it is preferred to combine nebulizing ketamine and lidocaine since it has fewer adverse effects. Because no negative effects were

found with the ketamine dosage specified, it can be tested without the use of lidocaine.

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Authors' Contribution

Conceptualization, methodology, and investigation, EP, SSh, HP; data curation, writing (original draft preparation and review and edition, BGh, JH, ES.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

The study protocol was approved by the Clinical Ethics Board of Zanjan University of Medical Sciences (ethical code: 9405). The RCT was registered and approved (IRCT 2012111701585N1) by blinded Registry of clinical Trials Administration of Ketamine, subject to the joint commission's authorization from the directors of the board of narcotics of the Hospitals affiliated with the Iran University of Medical Sciences.

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