

Original Article

DOI: 10.22114/ajem.v0i0.75

Intranasal Ketamine Administration for Narcotic Dose Decrement in Patients Suffering from Acute Limb Trauma in Emergency Department: a Double-Blind Randomized Placebo-Controlled Trial

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Published online: 2018-04-03

Abstract

Introduction: pain management is an important and challenging issue in emergency medicine. Despite the conduct of several studies on this topic, pain is still handled improperly in many cases.

Objective: This study investigated the effectiveness of low-dose IN ketamine administration in reducing the need for opiates in patients in acute pain resulting from limb injury.

Method: This randomized, double-blind, placebo-controlled trial was conducted to assess the possible effect of low-dose intranasal (IN) ketamine administration in decreasing patients' narcotic need. Patients in emergency department suffering from acute isolated limb trauma were included. One group of patients received 0.5 mg/kg intravenous morphine sulfate and 0.02 ml/kg IN ketamine. The other group received the same dose of morphine sulfate and 0.02 ml/kg IN distilled water. Pain severity was measured using the 11 points numerical rating scale at 0, 10, 30, 60, 120, and 180 minutes.

Results: Ninety-one patients with mean age of 31.62 ± 9.13 years were enrolled (54.9% male). The number of requests for supplemental medication was significantly lower in patients who received ketamine (12 patients (30%)) than those who received placebo (27 patients (67.5%)) ($p = 0.001$).

Conclusion: It is likely that low-dose IN ketamine is effective in reducing the narcotic need of patients suffering from acute limb trauma.

Key words: Analgesics; Emergency medicine; Ketamine; Morphine; Pain management

Cite this article as: Mohammadshahi A, Abdolrazaghnejad A, Nikzamir H, Safaie A. Intranasal Ketamine Administration for Narcotic Dose Decrement in Patients Suffering from Acute Limb Trauma in Emergency Department: a Double-Blind Randomized Placebo-Controlled Trial. *Adv J Emerg Med.* 2018;2(3): e30.

INTRODUCTION

Pain is one of the most common complaints among patients visiting the emergency department (ED); more than half of patients visiting ED complain about pain to some extent (1, 2). Hence, pain management is an important and challenging issue in emergency medicine. Despite the conduct of several studies on this topic, pain is still handled improperly in many cases (3-6). There are several analgesics for pain control, and opiates are still among the oldest and most commonly used medications (7, 8). Despite the strong analgesic effect of opiates, their possible side effects such as nausea, vomiting, hypoventilation, hypotension, constipation, and risk of dependence limit their use in some cases. In some instances, a high dose of opiate may be required, that could lead to increased risk of complications (9). Accordingly, many surveys have been conducted to find an alternative to opiates or an adjuvant medication

that reduces the opioid dose required. An approved method is the use of sedatives (e.g., benzodiazepines) for breakthrough acute pain, which unfortunately is associated with complications such as increased central nervous system depression and hypoventilation (10, 11). So, the search for an alternative analgesic agent is still on, at least for cases with the risk of complication and no clinical response to opiates (7).

Ketamine, a derivative of phencyclidine, is well-known as a dissociative anesthetic agent, available in various medicinal forms. It is among the few anesthetics that provide all the three components of desirable anesthesia, namely anti-nociception, immobility, and amnesia (12). Based on available evidence, the intranasal (IN) form of ketamine has adequate bioavailability and desirable clinical effect compared with other non-intravenous

formulations (13). This study investigated the effectiveness of low-dose IN ketamine administration in reducing the need for opiates in patients in acute pain resulting from limb injury.

METHODS

Study design

This was a randomized, double-blind, placebo-controlled trial (phase 3) conducted from March 2015 to June 2016 in the academic ED of Besat Hospital, Army University of Medical Sciences, Tehran, Iran. The protocol of the study was approved by the ethics committee of Army University of Medical Sciences on February 19, 2013, and ID:9209 was assigned. The investigators were committed to the Helsinki Declaration principles at all stages of this study. Written consent was obtained from all patients, and they were free to leave the study at any time.

Study population

Patients with acute isolated limb trauma, visiting the ED, were enrolled based on inclusion and exclusion criteria using convenience sampling technique. Patients of either gender older than 18 years with limb pain resulting from traumatic injuries within the last 24 hours and baseline numeric rating scale (NRS) ≥ 7 were included. The exclusion criteria were as follows: open fracture; closed fracture in more than one site; fracture plus dislocation; acute traumatic pain in more than two limbs; unstable hemodynamics (blood pressure (BP) $< 90/60$ mmHg or BP $> 160/100$ mmHg, pulse rate (PR) > 120 /min or PR < 60 /min); Glasgow Coma Scale (GCS) < 15 ; non-limb traumatic injuries (head, neck, chest, etc.); pregnancy; history of allergic reaction to ketamine or morphine; patients reluctant to participate; patients leaving the hospital for any reason within three hours after drug administration.

According to $n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times \sigma^2}{(\mu_1 - \mu_2)^2}$, at least 38 patients were needed in each group, namely treatment and placebo, for making a statistical comparison ($\alpha = 0.05$, $Z_{1-\frac{\alpha}{2}} = 1.96$, power = 0.8, $Z_{1-\beta} = 0.84$, $\sigma = 2$, $\mu_1 = 7$, $\mu_2 = 5.7$) (14).

Randomization and blinding

Patients were randomly assigned to ketamine (K) and placebo (P) groups using computer-assisted randomization table. Similar containers (in terms of size and color) were filled with ketamine and distilled water, marked with computer-generated random codes comprising of a Latin word and four digits, and allocated to the ketamine (K) or placebo (P) groups.

The injection team and patients were unaware of

the mechanism of assigning the codes. A paper packet, containing a sheet with a Latin word and four digits written on it, was provided for each sample. The codes were equally assigned to the treatment and placebo groups. The researcher picked a packet by chance and administered the coded medicine.

Intervention

The administered medicines in each group were: Ketamine Group (K): intravenous (IV) morphine sulfate (0.05 mg/kg) and 0.02 ml/kg IN ketamine solution (containing 50 mg/ml ketamine), using a dropper; Placebo Group (P): IV morphine sulfate (0.05 mg/kg) plus 0.02 ml/kg IN distilled water, using a simple dropper prepared for the intervention. We measured the volume needed for each patient (0.02 ml/kg) with a syringe and then administered the volume with the dropper to the patient.

Ketamine bioavailability was determined to be around fifty percent in past studies (15). We administered 1 mg/kg (0.02 ml/kg) IN ketamine to patients in the ketamine group. We expected this dose to be bioequivalent to 0.5 mg/kg IV dose. If any patient requested more analgesics at any time after 10 minutes of primary drug administration, we gave them 0.05 mg/kg IV morphine sulfate.

Outcome

The primary outcome was a request for a supplemental analgesic. The secondary outcomes included NRS reduction, hemodynamic changes, and side effects in both groups. Information regarding making or not making a request and time of the request for a supplemental analgesic were recorded.

NRS was used to measure the severity of pain in the current survey. This scale can be used for verbal or visual expression of pain level. In this self-report battery, the patient scores his/her severity of pain on a scale from 0 (without pain) to 10 (the most severe pain). The patient can report the pain verbally, by making a mark on the scale, or by pointing with fingers. NRS was measured at 10, 30, 60, 120, and 180 minutes after drug administration.

Age, gender, systolic blood pressure (SBP), heart rate (HR), arterial oxygen saturation (O₂sat), and consciousness level were also recorded at 10, 30, and 60 minutes after drug administration. Any adverse effects that occurred within three hours after drug administration were noted.

Statistical analysis

The collected data were analyzed using statistical package for social sciences (SPSS) software version 18.0 (SPSS Inc., Chicago, USA). Qualitative data

were analyzed with the chi-square test. For quantitative data analysis, parametric and non-parametric data were first specified with Kolmogorov-Smirnov test. Then, parametric and non-parametric data were analyzed with t-test and Mann-Whitney test, respectively. One-way analysis of variance (ANOVA) and Kruskal-Wallis test were used for the analysis of parametric and non-parametric longitudinal data (SBP, HR, O2sat, and NRS), respectively. P-values less than 0.05 were considered significant.

RESULTS

Demographic and baseline findings

The CONSORT flowchart of the studied patients is presented in figure 1. Seventeen out of the 97 patients admitted to the ED with limb injuries that required analgesics were excluded. Finally, 80 patients with mean age of 31.62 ± 9.13 years were enrolled (54.9% male) and randomly assigned to either the K group (n = 40) or P group (n = 40). The demographic and baseline characteristics of the participants are summarized in table 1. The mean age (p = 0.899) and sex ratio (p = 0.818) of the two groups were not statistically significantly different. The mean baseline HR, O2sat, and GCS were not significantly different between the two groups (p > 0.05), but the mean NRS (K: 8.50 vs. P: 9.05; p = 0.034) and SBP (K:111.62 vs. P:119.50; p = 0.011) were significantly lower in the ketamine compared with the placebo group at baseline.

Primary outcomes

The number of requests for a supplemental analgesic was significantly lower in patients who received ketamine (12 patients (30%)) than those who received placebo (27 patients (67.5%)) (p = 0.001). The difference regarding the time of the

Table 1: Baseline characteristics of studied patients

Variables	Placebo	Ketamine	p
	(n = 40)	(n = 40)	
	Mean ± SD		
Age (year)	31.75 ± 8.2	31.42 ± 10.3	0.899
NRS (number)	9.1 ± 2.6	8.5 ± 3.1	0.034
SBP (mmHg)	119.5 ± 25.12	111.6 ± 18.1	0.011
HR (beat/min)	83.9 ± 14.2	81.6 ± 20.2	0.119
O2 sat (%)	98.8 ± 24.2	98.5 ± 15.2	0.112

NRS, numeric rating scale; SBP, systolic blood pressure; HR, heart rate; GCS, Glasgow coma scale

request for a supplemental medication (minutes after the first morphine injection), although clinically apparent, was not statistically significant between the groups (K: 60.83 ± 39.18 vs. P: 37.41 ± 23.95; p = 0.059).

Secondary outcomes

The data concerning the mean NRS by time for both groups are presented in figure 2. The difference in the mean NRS at 30 min (K: 5.08 vs. P: 6.2; p = 0.027), 60 min (K: 3.28 vs. P: 4.6; p = 0.003), and 120 min (K: 2.38 vs. P: 2.8; p = 0.047) was significantly lower in the ketamine than the placebo group. There was no significant difference between the two groups at other checkpoints. Based on the Kruskal-Wallis test, the mean NRS changes from 0 to 180 min was significant in both groups (K, p = 0.000; P, p = 0.000). The mean NRS reduced in both groups with time. The differences in the reduced mean NRS within the different time intervals were not significant between the two groups (table 2).

The mean SBP at 10 min (K: 111.62 vs. P: 119.5; p = 0.002) and 30 min (K: 112.75 vs. P: 117; p = 0.027) was significantly lower in the ketamine group than the placebo. This difference was not significant at 60 min between the two groups (p = 0.512) (table 3). According to the ANOVA results, the changes in the mean SBP from 0 to 180 min was significant in the placebo group (p = 0.038) but not in the ketamine group (p = 0.944). The mean SBP decreased in the placebo and increased in the ketamine group with time. The differences in HR at

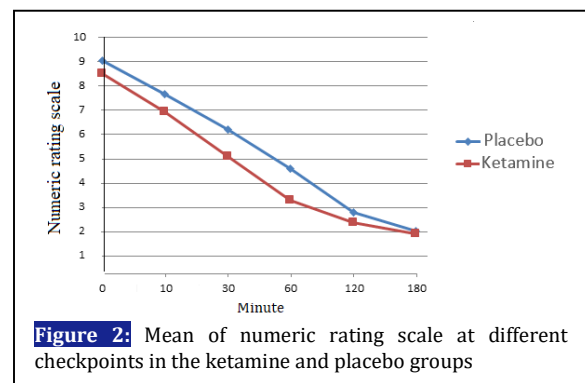
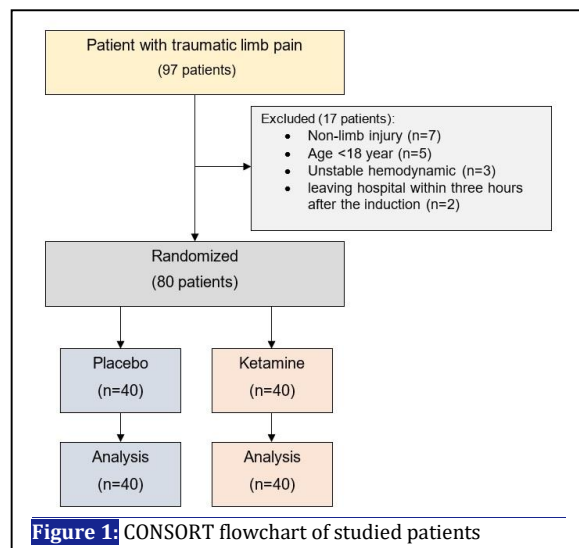


Table 2: Mean numeric rating scale changes within the different time intervals

Time interval (minutes)	Ketamine (n = 40)	Placebo (n = 40)	p-value
0-10	-1.38 ± 1.35	-1.55 ± 1.93	0.917
0-30	-2.85 ± 1.77	-3.42 ± 2.20	0.315
0-60	-4.45 ± 1.98	-5.22 ± 1.90	0.057
0-120	-6.25 ± 1.70	-6.12 ± 1.91	0.864
0-180	-7.02 ± 1.57	-6.6 ± 1.67	0.174

Table 3: Mean heart rate (HR), systolic blood pressure (SBP), and oxygen saturation (O2sat) at different checkpoints in the ketamine and placebo groups

Variable	Groups	Checkpoints			p-value
		10 min	30 min	60 min	
Systolic blood pressure	Ketamine	111.62 ± 11.11	112.75 ± 8.91	113.5 ± 8.63	0.944
	Placebo	119.5 ± 10.61	117 ± 7.91	112.12 ± 9.99	0.038
	p-value	0.002	0.027	0.512	-
Heart rate	Ketamine	81.35 ± 5.52	80.58 ± 5.46	78.62 ± 4.23	0.002
	Placebo	80.58 ± 6.59	78 ± 6.41	76.08 ± 7.66	0.000
	p-value	0.57	0.057	0.069	-
O2 saturation	Ketamine	98.78 ± 0.83	98.62 ± 0.7	98.62 ± 0.86	0.921
	Placebo	98.42 ± 0.95	98.32 ± 1.07	98.35 ± 0.94	0.462
	p-value	0.086	0.327	0.278	-

10 min ($p = 0.57$), 30 min ($p = 0.057$), and 60 min ($p = 0.069$) were not significant between the two groups (table 4). According to the ANOVA results, the changes in the mean HR from 0 to 180 min was significant in both placebo ($p = 0.000$) and ketamine groups ($p = 0.002$). The mean HR reduced in both groups with time. The between-group differences were not significant in terms of O2sat at 10 min ($p = 0.086$), 30 min ($p = 0.327$), and 60 min ($p = 0.278$) (table 3). According to the Kruskal-Wallis test results, changes in the mean O2sat from 0 to 180 minute was not significant in both placebo ($p = 0.462$) and ketamine groups ($p = 0.921$).

Totally, 16 adverse side effects due to the drugs were observed in 13 patients in both groups. Among them, 7 complications were in the placebo group (vomiting: 4, sneezing: 1, and coughing: 2) and 9 in the ketamine group (vomiting: 5, sneezing: 2, and coughing: 1). These complications occurred in 7 cases (17.5%) in placebo and 6 cases (18%) in ketamine group. There was no significant difference in the incidence of side effects between the two groups ($p = 0.769$). The most frequent side effect of the medication was vomiting, seen in 9 out of 16 cases (56.25%).

DISCUSSION

Considering the results, it seems that low-dose IN ketamine administration could reduce the need for opiates in patients in acute pain resulting from limb injury, and its use in ED would be rational.

Previous studies strongly supported the effectiveness of low-dose ketamine administration via various routes in reducing pain (16-21). In an

observational study, Yeaman et al. investigated the effect of IN ketamine on pain reduction in acute limb injuries in children aged 3–13 years with moderate-to-severe degrees of pain. They reported that the median pain score decreased from 74.5 to 30 mm in 30 min. In 24 patients, the median pain score was 25 mm after continuing measurement until 60 min. The rate of satisfaction of anti-nociception was 83%, and 8 patients (33%) received a supplemental opioid analgesic. In total, 28 cases with side effects were reported; however, all of them were mildly severe (14). Shimonovich et al. also conducted a survey to assess the efficacy of IN ketamine compared with IV and intramuscular (IM) morphine for acute traumatic pain management in the ED. They found that IN ketamine provided clinically-comparable results to those of IV morphine with regard to time to onset as well as maximal pain reduction. They concluded that IN ketamine has efficacy and safety comparable to IV and IM morphine (22).

Increased BP is among the known side effects of ketamine (12, 23-25). In the current study, the mean BP at all the mentioned time intervals was higher in the placebo than the ketamine group. However, the BP increased in the ketamine and decreased in the placebo group with time, and it was statistically significant in the placebo group. On the other hand, the modest BP reduction in the placebo group can be attributed to the effects of using morphine and subsequent pain relief (7). Given the use of low-dose ketamine, IN administration, and simultaneous use of IV morphine, it seems that the BP raising effect of

ketamine was lessened. There was no significant between-group difference regarding HR with time; however, HR changes with time was significant in each group. Increased HR is among the definitive side effects of ketamine (17-19). Lower HR in the ketamine group than the placebo may be due to the use of low-dose ketamine and IN administration route.

Previous studies reported low-dose ketamine as almost a safe treatment with very few complications (14, 16, 17, 26). There was no significant between-group difference regarding O₂sat with time. O₂sat drop following ketamine administration is a rare phenomenon. This is because ketamine does not reduce respiratory drive and preserves airway reflexes; incidence of laryngospasm typically occurs following boluses of ketamine intravenously (7, 18, 23-25).

Previous studies reported the effectiveness of low-dose ketamine in reducing the number of requests for supplemental analgesics (14, 16, 20). The number of analgesic demand was significantly higher among the patients receiving placebo. The initial NRS was higher in patients requesting a supplemental analgesic. Although this difference was statistically significant, it was clinically insignificant (0.54-unit difference between the two groups). On average, analgesic demands were made sooner in the placebo than the ketamine group; however, this between-group difference was not significant. The lower number of analgesic demands by the patients in the ketamine group can be attributed to the additional effect of IN administration of low-dose ketamine. The difference in the number of patients developing complications was not significant between the two groups, and no serious complication was observed in them.

Limitations

Although the pain score of the patients in the ketamine group was lower than that in the placebo group, we failed in showing the analgesic effectiveness of IN ketamine plus injectable opiates due to (i) lower pain score in the ketamine group

patients at baseline, and (ii) insignificant difference in pain reduction at the different time intervals between the two groups. To weaken the effect of between-group mismatch in the pain score at baseline, in addition to comparing the mean pain scores at different times in the two groups, their difference in pain reduction at different time intervals was also compared. However, it did not contribute to the absolute reliability of the results.

CONCLUSIONS

It is likely that IN administration of low-dose ketamine plus IV administration of morphine sulfate could reduce the further request for an opioid. Administration of this combination does not result in any hemodynamic instability or more complications than administration of IV morphine alone. Given the effect of IN ketamine on the reduction of the required opioid dose, supplementation of analgesics with it is recommended as a rational choice.

ACKNOWLEDGEMENTS

The research team wishes to thank the ED staff who participated in the management of the cases.

AUTHORS' CONTRIBUTION

AM and HN contributed to designing the study; AS and AA analyzed and interpreted the data. HN and AS prepared the draft manuscript; AM and AA revised it critically for important intellectual content. All the authors approved the final version and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

FUNDING

This study was financially supported by Army University of Medical Sciences, Tehran, Iran.

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