Original Contribution

A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED

Sergey Motov, MDa,⁎, Mo Mai, MD a, Illya Pushkar, MPH a, Antonios Likourezos, MA, MPH a, Jefferson Drapkin, BS a, Matthew Yasavolian, MD a, Jason Brady, PharmD b, Peter Homel, PhD c,d, Christian Fromm, MD a

a Department of Emergency Medicine, Maimonides Medical Center, Brooklyn, NY, USA
b Department of Pharmacy, Maimonides Medical Center, Brooklyn, NY, USA
c Office of Research Administration, Maimonides Medical Center, Brooklyn, NY, USA
d Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA

abstract

Study objective: Compare adverse effects and analgesic efficacy of low-dose ketamine for acute pain in the ED administered either by single intravenous push (IVP) or short infusion (SI).

Methods: Patients 18–65, presenting to ED with acute abdominal, flank, or musculoskeletal pain with initial pain score ≥ 5, were randomized to ketamine 0.3 mg/kg by either IVP or SI with placebo double-dummy. Adverse effects were evaluated by Side Effects Rating Scale for Dissociative Anesthetics (SERSDA) and Richmond Agitation-Sedation Scale (RASS) at 5, 15, 30, 60, 90, and 120 min post-administration; analgesic efficacy was evaluated by Numerical Rating Scale (NRS).

Results: 48 patients enrolled in the study. IVP group had higher overall rates of feeling of unreality on SERSDA scale: 92% versus 54% (difference 37.5%; p = 0.008; 95% CI 9.3–59.5%). At 5 min median severity of feeling of unreality was 3.0 for IVP versus 0.0 (p = 0.001). IVP also showed greater rates of sedation on RASS scale at 5 min: median RASS = −2.0 versus 0.0 (p = 0.01). Decrease in mean pain scores from baseline to 15 min was similar across groups: 5.2 ± 3.53 (95% CI 3.7–6.7) for IVP; 5.75 ± 3.48 (95% CI 4.3–7.2) for SI. There were no statistically significant differences with respect to changes in vital signs and need for rescue medication.

Conclusion: Low-dose ketamine given as a short infusion is associated with significantly lower rates of feeling of unreality and sedation with no difference in analgesic efficacy in comparison to intravenous push.© 2017 Elsevier Inc. All rights reserved.

Keywords: Ketamine, Analgesia, Emergency department, Infusion

1. Introduction

1.1. Background

Ketamine’s role as a safe and effective modality for treating pain in the emergency department (ED) has recently been expanding. Ketamine possesses potent analgesic, amnestic, and anesthetic properties. It is a non-competitive N-methyl-D-aspartate (NMDA) and glutamate receptor antagonist that decreases central sensitization and “wind-up” phenomenon at the level of the spinal cord (dorsal ganglion) and central nervous system and provides anti-hyperalgesia, anti-allodynia, and anti-tolerance. The NMDA receptor blockade leads to decreases in acute pain, opioid tolerance, opioid-induced hyperalgesia, as well as decreases in persistent chronic (allodynia) and neuropathic pain. Ketamine given intravenously in low (sub-dissociative, analgesic) doses (0.1–0.3 mg/kg) provides effective analgesia with minimal effects on hemodynamics, cognition or consciousness.
nausea, vomiting, and dizziness. These adverse effects are apparent in the first several minutes after intravenous push (IVP) administration and are typically short-lived. For that reason, at our institution, we modified our protocol for the administration of LDK from an IVP over 3 to 5 min to a short infusion (SI) over 10 to 15 min in order to mitigate these effects. To date, no trial has directly compared intravenous push dose to short infusion of LDK.

1.3. Goals of this investigation

The goal of our study was to evaluate the rates of adverse effects and the analgesic efficacy of intravenous push (IVP) dose of LDK in comparison to short infusion (SI) for adult patients presenting to the ED with a variety of acute painful conditions. We hypothesized that administration of LDK by SI would be associated with decreased rates of adverse effects and would have similar analgesic efficacy when compared to IVP dose.

2. Methods

2.1. Study design and setting

Our study was a prospective, randomized, double-blind, double-dummy trial comparing safety and analgesic efficacy of intravenous LDK given as a push dose (over 5 min) versus given as a short infusion (over 15 min). The study was conducted at a 711-bed urban community teaching hospital with an annual ED census of >120 000 visits. Patient screening, enrollment, and data collection were performed by study investigators (SM, CF, JD, MM, MY, and IP).

This study was approved by the Maimonides Medical Center Institutional Review Board and registered with ClinicalTrials.gov (NCT02363270). Written and signed informed consent was obtained in accordance with institutional policy. We report this trial in accordance with the Consolidated Standards of Reporting Trials statement [9].

2.2. Selection of participants

Patients considered for enrollment into the study comprised adults aged 18 to 65 years who presented to the ED primarily for management of acute abdominal, flank, back, traumatic chest or musculoskeletal pain with an intensity of 5 or greater on a standard 0–10 Numeric Pain Rating Scale (NRS)5. Patients had to be awake, alert and oriented to person, place, and time, and able to demonstrate understanding of the informed consent process and content. Patients also had to demonstrate ability to verbalize the nature of any adverse effects they might experience as well as to express their severity of pain using the NRS. Exclusion criteria included pregnancy, breast-feeding, altered mental status, allergy to ketamine, weight <46 kg or >115 kg, unstable vital signs (systolic blood pressure <90 or >180 mm Hg, pulse rate <50 or >150 beats/min, and respiration rate <10 or >30 breaths/min), and medical history of acute head or eye injury, seizure, intracranial hypertension, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4 h before) analgesic use. For the purposes of this study, LDK was used without co-administration of any other analgesics, with the exception of rescue medication.

Enrollment of patients occurred between April 2015 and August 2016. Screening and enrollment took place Monday through Friday 8 AM to 8 PM when an ED pharmacist was available for blinded medication preparation. Study investigators approached all potentially qualifying participants after they were evaluated by the treating emergency physician and determined to meet study inclusion criteria. All participants provided written informed consent and Health Insurance Portability and Accountability Act authorization. For non-English speakers, a language appropriate consent form was used and non-investigator, hospital-employed, trained interpreters assisted in acquisition of informed consent.

2.3. Interventions

Participants were allocated to two groups according to a predetermined randomization list that was generated using SPSS 20.0 by the research manager. Participants received intravenous LDK of 0.3 mg/kg by either (1) IVP given over 5 min or (2) mixed in 100 ml normal saline solution and given via SI over 15 min. All participants received a corresponding placebo in order to maintain double-dummy design. Accordingly, all patients randomized to receive LDK via IVP also received 100 ml of normal saline via SI, and all patients randomized to receive LDK via SI also received 10 ml of normal saline via IVP. ED pharmacy investigators maintained the randomization list, prepared the medication, and delivered it in blinded fashion to the treating registered nurse, who administered it to the study participant. The ED pharmacist set up the SI dose on an infusion pump with a 15 min run time and the IVP dose on a syringe pump with a 5 min run time. The two administration routes started simultaneously.

2.4. Methods and measurements

The preparing ED pharmacist, research manager, and statistician were the only ones with knowledge of the study arm to which each participant was randomized. Treating providers, participants, and the data collecting research team were blind to the medication route received. Study investigators consisted of two treating physicians who assisted in screening and supervised the research fellow and research coordinators who enrolled patients, recorded pain scores, vital signs, and adverse effects at baseline, 5, 15, 30, 60, 90, and 120 min. For subjects still desiring pain medication 30 min after study drug administration, investigators offered intravenous morphine at 0.1 mg/kg as a rescue analgesic.

2.5. Outcomes

The main outcomes included: 1) the overall rates as well as the specific severity levels of the side effects which were recorded in accordance with the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA6) [10]. The SERSDA measures the severity of nine adverse effects based on a five point scoring system from “0” (adverse effect absent) to “4” (adverse effect is very bothersome); and 2) severity of agitation and/or sedation in accordance to the nine point Richmond Agitation-Sedation Scale (RASS)7 [11] with scores ranging from “+4” (deeply sedated) to “0” (alert and calm) to “−4” (combative). Secondary outcomes consisted of (1) a standard 11 point NRS score for self-reported pain severity, (2) changes in vital signs, and (3) need for rescue analgesia.

2.6. Data analysis

Research staff recorded all data on data collection sheets (separate from clinical data). These were entered into Microsoft Excel, and then imported into the programs used for statistical analysis. Baseline characteristics of patients in each treatment group were described in terms of mean ± standard deviation for normally distributed variables and frequency (percent) in the case of categorical variables. Student t-tests were used to compare simple group differences in terms of means (e.g., age), while chi square tests were used to look at differences in terms of percent rates (e.g., sex). A generalized linear model with an

---

6 Side Effects Rating Scale for Dissociative Anesthetics.

7 Richmond Agitation-Sedation Scale.
underlying gamma distribution was used for the analysis over time of all ordinal (e.g., SERDSA unreality score) while mixed model regression was used for continuous outcomes (e.g., pain). This analysis allowed for inclusion of all patients regardless of any missing data under the assumption of data being missing at random. Only time points prior to when either the SERSDA or RAS scores had completely resolved to “0” were included for the generalized linear model analysis since otherwise lack of variability did not allow for model effects or test statistics to be estimated.

A bootstrap algorithm based on 1000 randomly selected samples from the data was used to estimate non-parametric 95% confidence limits for the median differences [12]. All statistical analyses were carried out using SAS 9.4 (SAS Inc., Cary, NC). Based on the study of Andolfatto et al. (2013) [13] of intranasal ketamine usage in the ED, we estimated a standard deviation = 1.20 for severity of any adverse event on the SERSDA. Assuming at least a one unit difference between the two administration methods (on a scale from 0 to 4), we further estimated an effect size $d = 0.83$. A sample size of 24 patients per group was calculated to be necessary for 80% power to detect this effect size with alpha = 0.05. No adjustment of the significance level was made to control for multiple comparisons in order to maximize the power of detecting any adverse event.

3. Results

We enrolled 48 subjects (24 in the IVP group and 24 in the SI group) into our study (Fig. 1). The groups were similar in terms of demographic characteristics (Table 1). Mean ages were 42.2, 43.6 years old, respectively with 37.5% and 50.0% males, also respectively. Mean baseline NRS pain scores in the two groups were both >8.0 and not significantly different from each other. The first dropout occurred at 60 min in the IVP group; 21 participants in each group were still observable at 120 min.

3.1. Main outcomes

As shown in Table 2, overall rates of adverse effects as measured on SERSDA scale (i.e., subject presented with the adverse effect at any time

---

7 Patients Refused

- 29% Did not want Ketamine.
- 14% Did not want any pain medication.
- 14% Were in too much pain to consent.
- 14% Requested morphine.
- 14% Tylenol currently controlling pain.
- 14% Refused to participate in the study.

55 Patients Approached

- 48 Patients Enrolled

24 Randomized to Push Group

- 24 Available

24 Randomized to Drip Group

- 24 Available

Subjects available for analysis at 5 minutes

- 24 Available

Subjects available for analysis at 15 minutes

- 24 Available

Subjects available for analysis at 30 minutes

- 24 Available

Subjects available for analysis at 60 minutes

- 23 Available
- 1 missing data

Subjects available for analysis at 90 minutes

- 21 Available
- 3 missing data

Subjects available for analysis at 120 minutes

- 21 Available
- 3 missing data

---

$a$ Subjects were missing data because of either discharge or transfer from the ED.

Fig. 1. Study flow diagram for consented subjects.
point during the study period) were similar between the two groups with the exception of overall feeling of unreality, which was significantly higher in the IVP group: 91.7% for IVP versus 54.2% for SI (percent difference 37.5%; \( p = 0.008 \)). The median SERSDA scores for unreality were likewise significantly higher for the IVP group up to 30 min (\( p = 0.004 \)). Looking more closely at severity of feelings of unreality over time, this difference was most marked at 5 and 15 min, as shown in Fig. 2. At 5 min, the median for feeling unreality score was 3.0 for the IVP group versus 0 for the SI group (median difference = 3; \( p = 0.001 \); 95% CI 1 to 4). In the IVP group, 2 (8%) patients reported no adverse effects (0 score) while 11 (46%) reported the feeling of unreality to be very bothersome (score 4); in contrast, 13 (54%) of the SI groups reported no change while 4 (17%) reported their symptoms as very bothersome. The IVP group was still elevated with regard to the feeling of unreality at 15 min although the difference was no longer significant. The median score was 2 for the IVP group versus 0 for SI (median difference = 2; \( p = 0.14 \); 95% CI -1 to 3).

The IVP group also showed a significantly greater degree of sedation at 5 min (\( p = 0.01 \)) as measured by the Richmond Agitation-Sedation Scale (RASS). As shown in Fig. 3, the median RASS score was −2 for the IVP group versus a median RASS of 0 for the SI group (median difference = −2; 95% CI -2 to −0.5). In the IVP group at 5 min, 13 (54%) showed light to deep sedation (scores ≤−2) and 6 (25%) were alert and calm (score 0). No patients in the SI group had scores ≤−2, while 6 (25%) were drowsy (score −1) and 15 (62%) were alert and calm.

### 3.2. Secondary outcomes

From baseline to 15 min (Fig. 4), both groups showed similar significant decreases in pain scores as measured by NRS. Mean pain decreased by 5.17 ± 3.53 (95% CI 3.67 to 6.66) in the IVP group and by 5.75 ± 3.48 (95% CI 4.28 to 7.22) in the SI group; \( p \)-value for overall difference = 0.026. There were no differences in analgesic efficacy between the treatment groups at any time point in the study (\( p = 0.14 \)). Likewise, there were no statistically significant differences between the groups with respect to the use of rescue morphine analgesia (Table 3) or changes in vital signs.

### 4. Limitations

This was a single center study in which subjects were enrolled as a convenience sample based on availability of members of both the ED research and pharmacy teams. This may have led to selection bias or under-representation of patients who may present to the ED late at night. Our stringent exclusion criteria and sample size of 48 subjects were inadequate to assess variance in safety of the two different administration routes of study medication.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline patient characteristics.</td>
</tr>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>No. of subjects</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Source of pain</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

\[ a \] Mean (standard deviation).  
\[ b \] Frequency (percent).

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates of SERSDA adverse effects encountered in each group at any point throughout the study period</td>
</tr>
<tr>
<td>Adverse effects</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Unreality</td>
</tr>
<tr>
<td>Hearing</td>
</tr>
<tr>
<td>Vision</td>
</tr>
<tr>
<td>Mood change</td>
</tr>
<tr>
<td>Discomfort</td>
</tr>
<tr>
<td>Hallucination</td>
</tr>
</tbody>
</table>

\[ a \] Frequency (percent).
by the high lipophilicity of ketamine which allows for rapid penetration of the blood-brain barrier and immediate saturation of the NMDA/glutamate receptor complex. In contrast, a slow (over 10–15 min) infusion of the same dose of ketamine leads to a steady saturation of the receptors with a decrease in neuropsychiatric side effects.

In order to test this hypothesis, we conceived a novel double-blind, double-dummy randomized clinical trial that directly compares rates of adverse effects of sub-dissociative dose ketamine given via intravenous push to those when given by short infusion. The trial results demonstrate that administration of LDK by SI rather than IVP significantly reduces the two major bothersome adverse effects of feeling of unreality and sedation. These results validate our site’s recent LDK protocol change from IVP to SI administration.

One of the possible barriers to short infusion of low-dose ketamine is a practical one that requires availability of the infusion pump which must be programmed by a nurse. However, modern infusion pumps that are widely available in EDs have the capability of being pre-programmed for commonly used medications, including ketamine, and require only patients’ weights to be entered, which reduces the possibility of drug and dosing pump errors. In addition, these pumps have the advantage of great ease and speed of set-up without delaying provision of analgesia. Based on our experience, formal monitoring of patients receiving low-dose ketamine infusion is not necessary for patient safety. We do formally monitor patients for research purposes, but in our clinical practice we do not routinely monitor patients in our ED when short infusion of low-dose ketamine is being administered.

Our study demonstrated significantly higher rates of feeling of unreality and sedation when LDK was administered as an intravenous push. While these side effects are not dangerous to patients, they are very unpleasant and in some cases exquisitely bothersome which can lead to patients requesting termination of therapy. Therefore it has become our practice to administer low-dose ketamine in pre-programmed infusions. These pumps have the advantage of great ease and speed of set up without any added cost, as infusions up to 15 min in duration are billed the same as intravenous push doses.

In conclusion, intravenous sub-dissociative dose ketamine given as a short infusion significantly decreases rates of feeling of unreality and sedation in the first 15 min of administration without sacrificing analgesic efficacy. These results support more widespread and well-tolerated use of ketamine as an adjunct or alternative to opioid analgesics for treating pain in the emergency department.

Table 3

<table>
<thead>
<tr>
<th>Time of rescue med.</th>
<th>Group</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Push</td>
<td>Drip</td>
</tr>
<tr>
<td>30 min*</td>
<td>1/24</td>
<td>1/24 (4.2%)</td>
</tr>
<tr>
<td>60 min</td>
<td>4/23</td>
<td>2/24 (8.3%)</td>
</tr>
<tr>
<td>90 min</td>
<td>2/22</td>
<td>4/23 (17.4%)</td>
</tr>
<tr>
<td>120 min</td>
<td>1/21</td>
<td>0/21 (0.0%)</td>
</tr>
</tbody>
</table>

* No rescue morphine given before 30 min.

b Frequency (percent).

5. Discussion

Sub-dissociative dose ketamine analgesia in the ED is gaining recognition as a viable adjunct and alternative to opioid analgesics for managing a variety of acute and chronic painful conditions. To date, the high incidence of unpleasant (bothersome) adverse effects associated with ketamine administration has proven to be a significant barrier to the promotion of more widespread and well-tolerated utilization of this analgesic modality. It has remained unclear if the rate of intravenous administration influences the adverse effect profile of LDK. Several clinical trials evaluated the role of short-term (over 10 min) and continuous LDK infusion on frequency of adverse effects and analgesic efficacy. Goltser et al. utilized a short infusion of LDK analgesia in 14 ED patients with acute and chronic painful conditions by administering 0.3 mg/kg over 10 min and demonstrated acceptable pain relief in 11 patients (NRS reduction of >3) and minor side effects in only two patients (dizziness and tinnitus) [14]. Similarly, Ahern et al. prospectively administered 15 mg of intravenous ketamine that was immediately followed by a continuous infusion of 20 mg/h for 1 h to 38 patients with acute pain. At the 10 min mark, 7 patients were pain-free and 25 and 26 patients had significant pain relief (NRS reduction >3) at 60 and 120 min, respectively. However, 87% of patients experienced adverse effects of nausea, fatigue, headache, and feeling of unreality [15]. We postulated that the high observed rates of bothersome adverse effects from LDK administration may be mediated by the rate of initial bolus dose administration.

Multiple studies have demonstrated a clear correlation of low-dose ketamine-induced side effects, particularly feeling of unreality and dizziness, with rapid rates of infusion. This phenomenon can be explained

Additional contributions

John Marshall, MD for his support and guidance; Maryam Zaeem, PharmD, Russell Bardsley, PharmD, and Nechama Rothberger, PharmD for medication administration to study patients, and all the volunteers for their assistance. Authors acknowledge and thank all the ED nurses for their tireless help and support of this project.

Meetings

The study was accepted for oral presentation at the May 2017 Society for Academic Emergency Medicine Conference in Orlando, Florida.

Grant support

None.

Conflicts of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors have no independent disclosures or conflicts of interest.
Author contributions

A. Likourezos and P. Homel had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Motov, Fromm.
Acquisition, analysis, or interpretation of data: All authors.
Statistical analysis: Likourezos, Homel.
Drafting of the manuscript: Drapkin.
Critical revision of the manuscript for important intellectual content: Motov, Homel, Fromm.
Obtained funding: Fromm.
Study supervision: Motov, Fromm.

References