

# Slow Infusion of Low-dose Ketamine Reduces Bothersome Side Effects Compared to Intravenous Push: A Double-blind, Double-dummy, Randomized Controlled Trial

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## ABSTRACT

**Objective:** We compared the analgesic efficacy and incidence of side effects when low-dose (0.3 mg/kg) ketamine (LDK) is administered as a **slow infusion (SI)** over 15 minutes versus an intravenous **push (IVP)** over 1 minute.

**Methods:** This was a prospective, randomized, double-blind, double-dummy, placebo-controlled trial of adult ED patients presenting with moderate to severe pain (numerical rating scale [NRS] score  $\geq 5$ ). Patients received **0.3 mg/kg** ketamine administered either as a **SI** or a **IVP**. Our primary outcome was the proportion of patients experiencing any **psychoperceptual** side effect **over 60 minutes**. A secondary outcome was incidence of moderate or greater psychoperceptual side effects. Additional outcomes included reduction in pain NRS scores at 60 minutes and percent maximum summed pain intensity difference (%SPID).

**Results:** Fifty-nine participants completed the study. A total of 86.2% of the IVP arm and 70.0% of the SI arm experienced any side effect (difference = 16.2%, 95% confidence interval [CI] = -5.4 to 37.8). We found a large reduction in moderate or greater psychoperceptual side effects with SI administration—**75.9%** reported moderate or greater side effects versus **43.4%** in the SI arm (difference = 32.5%, 95% CI = 7.9 to 57.1). Additionally, the IVP arm experienced more **hallucinations** (n = 8, **27.6%**) than the SI arm (SI n = 2, **6.7%**, difference = 20.9%, 95% CI = 1.8 to 43.4). We found no significant differences in analgesic efficacy. At 60 minutes, the mean %SPID values in the IVP and SI arms were 39.9 and 33.5%, respectively, with a difference of 6.5% (95% CI = -5.8 to 18.7).

**Conclusion:** **Most** patients who are administered LDK **experience** a **psychoperceptual side effect** **regardless** of administration via SI or IVP. However, patients receiving LDK as a SI reported significantly fewer moderate or greater psychoperceptual side effects and hallucinations with equivalent analgesia.

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The American College of Emergency Physicians recommends opioid-sparing multimodal analgesia including the intravenous (IV) ketamine for acute pain in the emergency department (ED).<sup>1</sup> However, since ketamine is lipophilic and rapidly crosses the blood–brain barrier, even low-dose ketamine (LDK), IV doses of 0.3 mg/kg or less, may produce dysphoria and hallucinations. This may make some emergency providers hesitant to administer ketamine.<sup>2</sup> One recent study demonstrated that slow infusion (SI) of LDK over 15 minutes resulted in less “feeling of unreality” than LDK administered by IV push (IVP) over 5 minutes.<sup>3</sup> These findings suggested a new way to administer LDK to obtain similar analgesia while limiting side effects. We sought to evaluate if these findings remained consistent at a different clinical site.

## METHODS

### Study Design and Setting

This randomized, double-blind, double-dummy, placebo-controlled trial was conducted at an urban, safety-net ED that cares for ~80,000 patients per year. The study was approved by the institutional review board and registered on ClinicalTrials.gov (NCT02916927).

### Selection of Participants

A convenience sample of participants was enrolled between September 2016 and May 2017. Enrollment occurred on weekdays from 10 AM to 5 PM. Trained, volunteer research assistants (RAs) screened patients  $\geq 18$  years old with pain numeric rating scale (NRS) score  $\geq 5$  and obtained informed consent. Exclusion criteria included: known pregnancy, breastfeeding, unstable vital signs (systolic blood pressure [sBP]  $< 90$ , sBP  $> 180$ , heart rate [HR]  $< 50$ , HR  $> 150$ , respiratory rate [RR]  $< 10$ , RR  $> 30$ ), arrhythmias on cardiac monitoring, altered mental status, opioid administration in the preceding hour, history of head or ocular trauma, allergy to ketamine, and presence of known intracranial mass.

### Interventions

After study enrollment, participants were placed on cardiac and pulse-oximetry monitoring. In the ketamine IVP arm, the ED clinical pharmacist prepared 0.3 mg/kg ketamine in a masked 10-mL syringe and a placebo 100-mL minibag of normal saline (NS). The

participant received the ketamine IVP over 1 minute and concurrently had the placebo minibag administered over 15 minutes. In the ketamine SI arm, the ED clinical pharmacist prepared 0.3 mg/kg ketamine in a 100-mL NS minibag (identical to the IVP arm's placebo) and a placebo 10-mL syringe of NS. The participant received the placebo IVP over 1 minute and concurrently had the ketamine minibag administered over 15 minutes. Infusion pumps were used for minibags.

The randomization list was generated using [www.randomization.com](http://www.randomization.com), and the list was kept in a closed folder in the hospital pharmacy (located outside of the ED). The pharmacist was the only study member who knew the randomization allocation, and the pharmacist was not involved in direct patient care or data collection. The participant, nurse, provider, and RAs were blinded to the randomization allocation. The data analysis was blinded and the key was unlocked after data analysis was complete.

### Measurements

The RAs collected the participants' pain NRS score (0–10); vital signs; additional opioid pain medications; and side effects at 0, 5, 10, 15, 20, 30, 45, and 60 minutes on a standardized data collection form. Side effects were assessed using the “Side Effects Rating Scale for Dissociative Anesthetics.”<sup>4</sup> SERSDA is a nine-component scale (fatigue, headaches, dizziness, feelings of unreality, generalized discomfort, changes in hearing, changes in mood, hallucinations, and changes in vision) that measures the severity of each component from “0” (no side effects), “1” (weak), “2” (moderate), and “3” (“bothersome”) to “4” (very bothersome). While this scale is not validated, it was chosen because it is consistently used in studies of ketamine's side effects.<sup>3–6</sup>

### Outcomes

The primary outcome was the proportion of patients experiencing a composite SERSDA score  $\geq 1$  at any time point during the 60-minute study period. The secondary outcomes were proportion of patients experiencing any moderate or greater side effect (SERSDA component score  $\geq 2$ ), change in pain NRS score between 0 and 60 minutes, and percent maximum summed pain intensity difference (%SPID) at 60 minutes. The SPID evaluates analgesia over time by incorporating the pain intensity difference (PID) at each time point. The PID equals the

baseline pain NRS score minus the pain NRS score at time<sub>x</sub>, and the SPID is the sum of the PID at each time point weighted by the time since the prior measurement. It is reported as a %SPID, and a difference of  $\geq 33\%$  is considered clinically significant.<sup>7</sup>

### Data Analysis

For this superiority trial, we estimated that a sample size of 28 patients per group would provide 80% power to detect an absolute 40% difference in proportion of participants experiencing any side effects (60% vs. 20%) at the two-sided  $\alpha < 0.05$  level. Prior research demonstrated significant heterogeneity in the proportion of patients experiencing side effects (3%–100%).<sup>2,5,6,8,9</sup> The sample size was inflated to 62 patients to account for missing data and attrition.

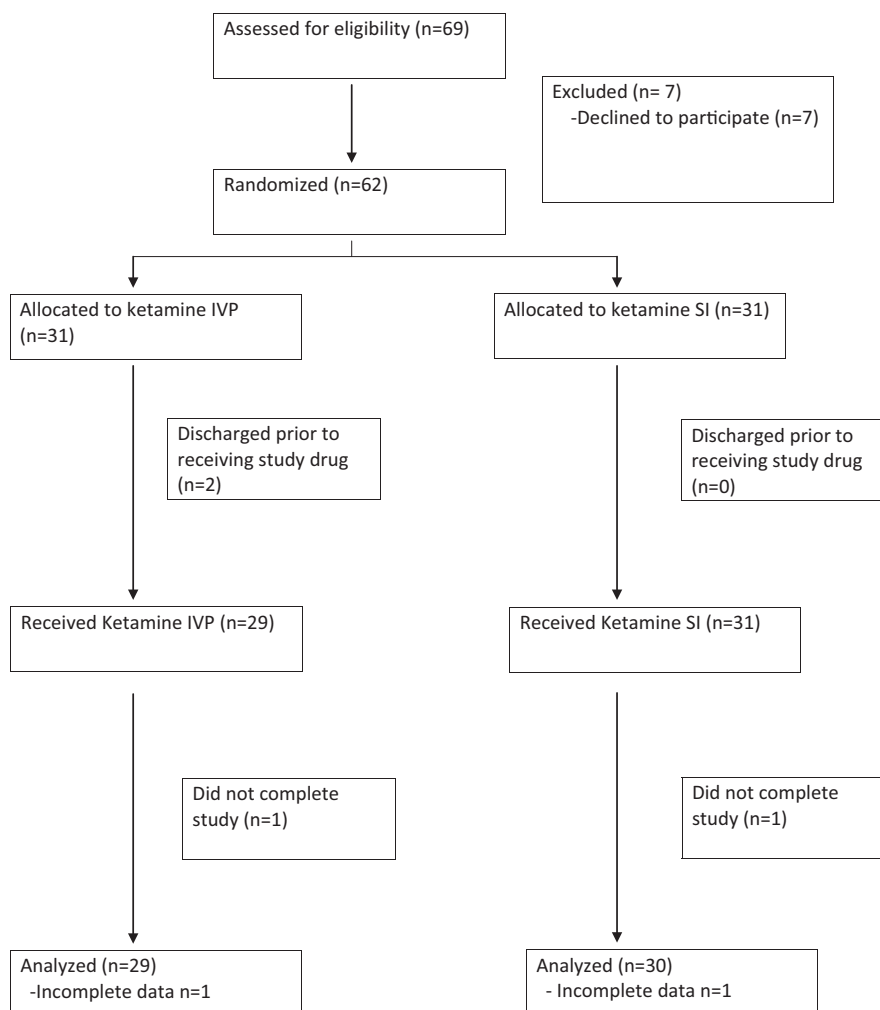
Patient characteristics and study outcomes were reported as means, standard deviation, medians,

interquartile ranges, and percentages as appropriate. The difference in proportions was evaluated with two-sample tests of proportions. We used Student's *t*-test for normally distributed continuous data and Mann-Whitney rank-sum for skewed continuous data. All analyses were performed in STATA 12 (2011, Stata Statistical Software, StataCorp LP).

Two sensitivity analyses prior to unmasking the data evaluated missing data's influence on the results. First, patients in the SI arm were assumed to have maximum SERSDA and pain scores while patients in the IVP arm were assumed to have no side effects or pain. Second, patients in the SI arm were assumed to have no side effects or pain and participants in the IVP were assumed to have maximum side effects and pain.

### RESULTS

Sixty-two patients underwent randomization and 59 completed the study (Figure 1). Baseline characteristics



**Figure 1.** Flow diagram of study participants. IVP = intravenous push; SI = slow infusion.

were similar between the two groups (Data Supplement S1, Table S1, available as supporting information in the online version of this paper, which is available at <http://onlinelibrary.wiley.com/doi/10.1111/acem.13428/full>). Eighty-six percent of the IVP arm and 70% of the SI arm experienced any side effect (difference = 16.2%, 95% confidence interval [CI] = -5.4 to 37.8; Table 1). More patients in the IVP arm experienced unreality (IVP  $n = 17$ , 59%; SI  $n = 10$ , 33%) and hallucinations (IVP  $n = 8$ , 28%; SI  $n = 2$ , 7%; Table 1). Most side effects occurred within the first 20 minutes of the study (Data Supplement S1, Figure S1).

Patients receiving ketamine IVP arm reported more moderate or greater side effects (SERSDA component  $\geq 2$ ) than the SI arm, 76% versus 43% (difference = 32.5%, 95% CI = 7.9 to 57.1; Table 1). This difference was driven by feelings of unreality (IVP 52% vs. SI 10%;  $p = 0.01$ ) and hallucinations (IVP 28% vs. SI 7%;  $p = 0.03$ ). At 60 minutes, median pain scores were similar between the arms (IVP 4.5 [2–7.5] and SI 6 [4–7],  $p = 0.94$ ; Data Supplement S1, Figure S2). Both arms achieved %SPID  $\geq 33\%$ , indicating good pain relief (IVP 40% and SI 34%; difference = 6.1% 95% CI = -5.7 to 18.7). Three patients in the IVP arm and one in the SI arm received additional pain medication. Both arms' vital signs were similar throughout the study (Data Supplement S1, Table S2). There were no observed incidences of

apnea in either group. The sensitivity analyses did not alter the outcomes (Data Supplement S1, Tables S3 and S4).

## DISCUSSION

In this double-blind, double-dummy, randomized, placebo-controlled trial of ketamine SI versus ketamine IVP, we found no statistical difference in the proportion of patients experiencing any side effect. However, a higher proportion participants in the IVP arm experienced moderate or greater side effects than in the SI arm—a number needed to harm of 3.

Similar to Motov et al.,<sup>3</sup> unreality was more common in the IVP group, and in addition, this study found that hallucinations were more frequent and side effects were more intense in the IVP arm. These data are consistent with the pharmacokinetics of ketamine: when it is rapidly administered, it crosses the blood–brain barrier causing rapid accumulation at active sites in the brain, and this peak concentration in the brain is the likely cause of the more intense side effects noted in the IVP arm.<sup>10</sup>

Our study suggests that both ketamine SI and ketamine IVP achieve excellent analgesia for ED patients with moderate to severe pain at 60 minutes but side effects are common. We did find that IVP rapidly produces a stronger but transient analgesic effect versus SI (Data Supplement S1, Figure S2).

**Table 1**  
Frequency and Proportion of Participants Experiencing Any Side Effects and Any Side Effect Stronger Than “Weak” by Study Arm Over 60 Minutes

	Any SERSDA Adverse Effect > 0			Any SERSDA Adverse Effect > 1		
	Study Arm			Study Arm		
	IVP (29)*	SI (30)*	p-value†	IVP (29)*	SI (30)*	p-value†
Fatigue	8 (27.6)	6 (20.0)	0.68	6 (22.2)	5 (17.2)	0.65
Dizziness	16 (55.1)	13 (43.3)	0.90	5 (17.2)	3 (10.0)	0.43
Headache	7 (24.1)	5 (16.7)	0.70	5 (17.2)	3 (10.0)	0.43
Unreality	17 (58.6)	10 (33.3)	0.05	15 (51.7)	6 (20.0)	0.01
Hearing	3 (10.3)	2 (6.7)	0.62	3 (10.3)	2 (6.7)	0.62
Vision	4 (13.8)	1 (3.3)	0.15	3 (10.3)	1 (3.3)	0.29
Mood	10 (34.5)	4 (13.3)	0.06	7 (24.1)	4 (13.3)	0.29
Discomfort	8 (27.6)	5 (16.7)	0.32	6 (20.7)	2 (6.7)	0.12
Hallucination	8 (27.6)	2 (6.7)	0.03	8 (27.6)	2 (6.7)	0.03
Overall	25 (86.2)	21 (70.0)	0.14	22 (75.9)	13 (43.3)	0.01

Bonferroni correction for nine individual SERSDA components  $p = 0.006$ .

IVP = IV push over 1 minute; SERSDA = Side Effect Rating Scale for Dissociative Anesthetics (0 = none, 1 = weak, 2 = moderate, 3 = bothersome, 4 = very bothersome); SI = slow infusion over 15 minutes.

\*Frequency (%).

†Two-sample test of proportions.

## LIMITATIONS

We enrolled a convenience sample because a clinical pharmacist was required to make blinded study medications, which may result in a selection bias. Based on previous data, we assumed that the proportion of patients experiencing side effects for the power calculation was lower than what was observed in this trial. Therefore, this study cannot detect a smaller but still clinically significant difference between the arms. There is no validated score for studying ketamine side effects, but SERSDA is the most used score. This study occurred at a single site, which limits its external validity. While all study members and participants were blinded and the study drugs were masked, there could be unintentional unmasking based on observation of the patient's reaction to the administered drug. Two patients did not complete the trial. One patient in the IVP arm went to radiology for the 45- and 60-minute time points. One patient in the SI arm halted the study after <5 minutes (calculated infused dose 4 mg) because of feeling of unreality and the patient's pain NRS score had decreased to zero.

## CONCLUSION

In conclusion, we found that low-dose ketamine is administered as slow infusion over 15 minutes has a similar rate of patient report of any side effect, but a significantly reduced report of moderate or greater side effects, particularly hallucinations and feelings of unreality compared to low-dose ketamine intravenous push. Our data suggest that administration of low-dose ketamine for analgesia as an slow infusion may be an effective strategy to reduce the severity side effects for ED patients with moderate to severe pain.

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## References

1. Optimizing the treatment of acute pain in the emergency department. *Ann Emerg Med* 2017;70:446–8.

2. Richards JR, Rockford RE. Low-dose ketamine analgesia: patient and physician experience in the ED. *Am J Emerg Med* 2013;31:390–4.
3. Motov S, Mai M, Pushkar I, et al. 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. *Am J Emerg Med* 2017;35:1095–100.
4. Eide PK, Jørum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994;58:347–54.
5. Ahern TL, Herring AA, Stone MB, Frazee BW. Effective analgesia with low-dose ketamine and reduced dose hydro-morphine in ED patients with severe pain. *Am J Emerg Med* 2013;31:847–51.
6. Ahern TL, Herring AA, Miller S, Frazee BW. Low-dose ketamine infusion for emergency department patients with severe pain. *Pain Med* 2015;16:1402–9.
7. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage* 2003;25:406–11.
8. Eide K, Stubhaug A, Oye I, Breivik H. Continuous subcutaneous administration of the N-methyl-D-aspartic acid (NMDA) receptor antagonist ketamine in the treatment of post-herpetic neuralgia. *Pain* 1995;61:221–8.
9. Gurnani A, Sharma P, Rautela R, Bhattacharya A. Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. *Anaesth Intens Care* 1996;24:32–6.
10. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clin Pharmacokinet* 2016;55:1059–77.

## Supporting Information

The following supporting information is available in the online version of this paper available at <http://onlinelibrary.wiley.com/doi/10.1111/acem.13428/full>  
**Data Supplement S1. Appendix.**