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CME

Low-dose Ketamine Improves Pain Relief in Patients Receiving Intravenous Opioids for Acute Pain in the Emergency Department: Results of a Randomized, Double-blind, Clinical Trial

Francesca L. Beaudoin, MD, MS, Charlie Lin, Wentao Guan, MS, and Roland C. Merchant, MD, MPH, ScD

Abstract

Objectives: Low-dose ketamine has been used perioperatively for pain control and may be a useful adjunct to intravenous (IV) opioids in the control of acute pain in the emergency department (ED). The aim of this study was to determine the effectiveness of low-dose ketamine as an adjunct to morphine versus standard care with morphine alone for the treatment of acute moderate to severe pain among ED patients.

Methods: A double-blind, randomized, placebo-controlled trial with three study groups was conducted at a large, urban academic ED over a 10-month period. Eligible patients were 18 to 65 years old with acute moderate to severe pain (score of at least 5 out of 10 on the numerical pain rating scale [NRS] and pain duration < 7 days) who were deemed by their treating physician to require IV opioids. The three study groups were: 1) morphine and normal saline placebo (standard care group), 2) morphine and 0.15 mg/kg ketamine (group 1), or 3) morphine and 0.3 mg/kg ketamine (group 2). Participants were assessed at 30, 60, and 120 minutes after study medication administration and received rescue analgesia as needed to target a 50% reduction in pain. The primary outcome measure of pain relief, or pain intensity reduction, was derived using the NRS and calculated as the summed pain-intensity (SPID) difference over 2 hours. The amount and timing of rescue opioid analgesia was evaluated as a secondary outcome. The occurrence of adverse events was also measured.

Results: Sixty patients were enrolled (n = 20 in each group). There were no differences between study groups with respect to age, sex, race/ethnicity, preenrollment analgesia, or baseline NRS. Over the 2-hour poststudy medication administration period, the SPIDs were higher (greater pain relief) for the ketamine study groups than the control group (standard care 4.0, interquartile range [IQR] = 1.8 to 6.5; group 1 7.0, IQR = 4.3 to 10.8; and group 2 7.8, IQR = 4.8 to 12.8; $p < 0.02$). The SPIDs for the ketamine groups were similar ($p < 0.46$). When compared to standard care, group 2 sustained the reduction in pain intensity up to 2 hours, whereas group 1 was similar to standard care by 2 hours. Similar numbers of patients received rescue analgesia: standard care group, seven of 20, 35%; group 1, four of 20, 20%; and group 2, four of 20, 20% ($p = 0.48$). Among those receiving rescue analgesia, those in the standard care group received analgesia sooner than either low-dose ketamine group, on average. More participants in the low-dose ketamine groups reported dysphoria and dizziness.

Conclusions: Low-dose ketamine is a viable analgesic adjunct to morphine for the treatment of moderate to severe acute pain. Dosing of 0.3 mg/kg is possibly more effective than 0.15 mg/kg, but may be associated with minor adverse events. Future studies should evaluate additional outcomes, optimum dosing, and use in specific populations.

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Intravenous (IV) opioids are the mainstay of treatment for severe acute pain in the emergency department (ED). Although opioids can provide rapid and effective pain relief, dosages needed to produce adequate analgesia can also result in adverse effects such as oversedation and respiratory depression.[1] In addition, morphine dosed at the frequently recommended 0.1 mg/kg can be ineffective in controlling severe acute pain.[2] Although there are many possible reasons for the lack of analgesic effect of morphine at this dosing, one possible explanation is that some patients experience antinociceptive effects of morphine through activation of *N*-methyl-D-aspartate (NMDA) receptors.[3] NMDA receptors play an important role in the perception of pain, and there is growing interest in these receptors as a pharmacotherapeutic target for adjunctive analgesics.[4] In preclinical studies, inhibition of NMDA receptors has been shown to modulate opioid receptor activation and improve opioid effectiveness.[5]

Ketamine, a potent NMDA receptor antagonist, has demonstrated effectiveness as an adjunct to opioids for perioperative pain control, even at low doses. Low-dose ketamine, defined as a "subanesthetic" dose (less than 1 mg/kg), has been shown to improve pain perception and produce an opioid-sparing effect when given perioperatively.[6] In the ED, ketamine has made a resurgence as an agent for procedural sedation,[7] but its use as an analgesic adjunct has remained limited. Several small observational or open-label studies have demonstrated either morphine-sparing effects or reductions in pain severity when low-dose ketamine is employed for pain in the prehospital or ED setting.[8–12] However, lack of randomized controlled clinical trials examining the effectiveness of low-dose ketamine in the ED may partly explain why it has not been incorporated into regular clinical practice. In addition, guidance is needed regarding the optimum dose for ketamine as an adjunct analgesic; studied doses have ranged from 0.05 to 1 mg/kg, and various methods and routes of administration have been employed (single bolus, repeat dosing, or continuous infusion; IV, intramuscular, intranasal, or intrathecal).[6]

The aim of this double-blind, randomized, placebo-controlled trial was to determine the comparative effectiveness of low doses of ketamine as an adjunct to morphine versus standard care (morphine alone) for the treatment of acute severe pain among patients presenting to the ED. The primary outcome of effectiveness was measured by reductions in patient-perceived pain intensity and pain relief. The amount and timing of administered rescue opioid analgesia were also evaluated as outcomes. Exploring the utility of dose options for low-dose ketamine was a secondary aim; we therefore compared two different low doses of ketamine (0.15 and 0.3 mg/kg) to each other and versus morphine plus placebo. Last, we monitored adverse events between administration of morphine alone and ketamine as an adjunct to morphine.

METHODS

Study Design and Setting

This study was a pilot, double-blind, placebo-controlled, randomized clinical trial with three study groups. Prior to recruitment, the study was registered at ClinicalTrials.gov. All participants provided written informed consent, and the study protocol was approved by Rhode Island Hospital's institutional review board.

Study Setting and Population

The study was conducted at the Rhode Island Hospital ED, a large, urban, medical school-affiliated, Level I trauma center and tertiary care referral center with a census of over 100,000 adult ED visits per year. Patients were recruited during scheduled 8-hour time blocks over a 10-month period from December 2012 through September 2013. The 8-hour time blocks occurred Monday through Saturday between 8 a.m. and 12 a.m., the time when the majority of ED patients present for medical care at our ED. Recruitment shifts were scheduled based on research assistant (RA) availability, but overall were evenly distributed over the days of the week and over 8-hour time blocks (8 a.m. to 4 p.m., 12 p.m. to 8 p.m., and 4 p.m. to 12 a.m.).

During enrollment periods, trained RAs identified study-eligible patients by screening the patient electronic medical records and querying providers. After a medical evaluation by the treating emergency physician (EP), potentially study-eligible patients were approached to further determine eligibility, and those meeting inclusion criteria were asked to enroll. Patients were eligible for study inclusion if they were English-speaking, 18 to 65 years old, had moderate to severe acute pain (score of ≥5 out of 10 on the numerical pain rating scale [NRS] with pain duration < 7 days), and had been deemed by their treating EPs to require IV opioid analgesia. Patients who had already received analgesia prior to study enrollment were still study-eligible as long as their NRS scores were ≥5. Patients were excluded if they had neurologic, respiratory, or hemodynamic compromise; had known or suspected allergy to ketamine or morphine, acute psychiatric illnesses, history of stroke, renal impairment (creatinine > 2.0 mg/dL), liver failure, or history of cardiac disease (prior myocardial infarction, angina, cardiac stents, or bypass surgery); were pregnant or breastfeeding; or were unable to provide informed consent.

Study Protocol

After written informed consent was obtained, each participant enrolled in the study was randomly assigned to one of three study groups using a computer-generated block randomization schedule with block sizes of six. Participants received: 1) morphine and 0.9% saline placebo (standard care group), 2) morphine and 0.15 mg/kg ketamine (group 1), or 3) morphine and 0.3 mg/kg ketamine (group 2). In all three groups, patients first received IV morphine 0.1 mg/kg up to a dose of 10 mg, followed by the administration of the study medication (placebo or ketamine). Ten minutes was allowed to elapse between dosing of morphine and the study medication to monitor for adverse reactions; pain was not assessed during this time. Doses of ketamine were chosen based on frequently used doses published in a Cochrane review of low-dose ketamine for postsurgical pain.[6]

Randomization, allocation, and dispensing of medication were overseen by a hospital pharmacist who was not involved with any other aspect of the study. The pharmacy maintained the allocation key until needed for data analysis; participants, providers, RAs, and study investigators were blinded to group allocation. The study medication (0.9% saline placebo or ketamine at concentrations of 1.5 or 3 mg/mL) was mixed and dispensed by the hospital pharmacy. Syringes containing equal volumes of study medication with uniquely labeled identifiers were stored in the ED in a medication dispensing system (Omnicell Inc.) which was accessed by the ED nurses for administration of study medication. Patients received equal volumes of study medication (0.1 mL/kg) or placebo to maintain allocation concealment.

Following administration of morphine (0.1 mg/kg up to 10 mg) and the study medication (placebo or ketamine), the emergency medicine providers caring for the patient prescribed additional rescue analgesia as needed. They were encouraged to wait at least 30 minutes before determining if rescue analgesia was needed. Rescue analgesia was prespecified as a dose of morphine of 0.05 to 0.1 mg/kg, which could be administered as frequently as every hour. Providers were instructed to target analgesia toward a self-reported decrease of at least 50% in patient discomfort or per patient request. Pain severity, the need for rescue analgesia, vital signs, and adverse side effects were assessed by the study RA at regular intervals after administration of the study medication (30 minutes, 1 hour, and 2 hours). Treating nurses and physicians were made aware of the results of these assessments to facilitate the need for rescue analgesia.

Outcome Measures

To assess the primary outcome of pain relief, we used patient-reported pain scores, which were expressed as the summed pain-intensity difference (SPID) over 2 hours. SPID is calculated based on patient-reported pain scores and is a widely used measurement of treatment response to analgesics over a relevant period of time.[13] Trained RAs asked the participants to report their pain scores using an 11-point NRS that ranged from 0 ("no pain") to 10 ("worst pain imaginable"). Baseline NRS scores were measured after randomization assignment but before administration of the study medications. Repeat pain score measurements were taken at 30 minutes, 1 hour, and 2 hours after receipt of study medications. A maximum of 2 hours was chosen to coincide with the anticipated ED length of stay after the administration of study medications.

The SPID was calculated using the pain-intensity difference (PID) at each of these study time points. The PID for a given time point is equal to the baseline NRS minus the subsequent NRS at each study time point. SPID is the summation of the PID at each of the study time points, weighted using the amount of time since the prior assessment, and approximates the area under the curve for PID over time. SPID is advantageous over raw NRS scores in that it takes into account individual differences in baseline pain intensity as well as time. SPID also is usually reported as a percentage of the maximum possible SPID (%SPID). The maximum possible SPID is the value that would be achieved if the patient were pain-free (NRS = 0) for the entire study period. We calculated the proportion of patients who achieved a %SPID of at least 33% and considered these patients to be treatment responders. A %SPID of 33% has been previously established to represent a clinically important measurement in pain outcomes.[14]

The secondary outcomes measured were NRS at each study time point, total patient-perceived pain relief, amount of rescue analgesia received, time to rescue analgesia, and global analgesic effectiveness (a combination score of SPID and rescue analgesia). The total patient-perceived pain relief was calculated using weighted sum of the pain relief scale performed at each study time point. This pain relief scale is a five-point scale that asks participants to rate pain relief as complete = 4, a lot = 3, some = 2, a little = 1, and none = 0; it can be used in conjunction with the NRS to assess a patients response to analgesia. The amount of rescue analgesia received (in milligrams of morphine equivalents) and the time administered were recorded. Time to rescue analgesia was calculated as the time from administration of the last study medication (placebo or ketamine) to administration of an opioid analgesic. Global analgesic effectiveness was assessed using the Silverman integrated analgesic assessment (SIA) score,[15] which integrates the two outcomes of pain relief (SPID) and rescue analgesia (total amount of opioid analgesia administered in milligrams of morphine equivalents) by assigning participants ranks for both outcomes. The ranks are then converted into percentiles and transformed into a combined score. The highest score indicates the most pain despite the most use of rescue analgesics, whereas the lowest score represents the least pain with the least use of rescue analgesics.

We also assessed for the occurrence of adverse events. We recorded participant-reported dizziness, nausea, vomiting, confusion, dysphoria, visual disturbances, or other complaints at baseline and each study time point. All patients were placed on cardiac telemetry for the duration of the study period and vital signs were recorded at each time point. The presence of tachycardia (heart rate > 100 beats/min.), hypotension (systolic blood pressure [sBP] < 100 mm Hg), hypertension (sBP > 180 mm Hg or diastolic blood pressure [dBP] > 100 mm Hg), and respiratory depression (respiratory rate < 12 breaths/min, oxygen saturation < 92%, or need for supplemental oxygen) were noted. The ED electronic medical records of all participants were further independently reviewed after the study by two of the coinvestigators (FLB, CL) to further assess for adverse events, including naloxone administration, cardiac dysrhythmias, agitation, and confusion.

Data Analysis

The study was designed to test the superiority of adjunctive low-dose ketamine given that the side effect profile of ketamine is not well established for this indication and setting. We estimated that a sample size of 16 participants in each group would provide 80% power to detect a 33% difference in SPID between the treatment groups at the $\alpha < 0.05$ level (two-tailed). This difference was chosen based on prior research consid-

ering 33% SPID to be an accepted measure of a clinically significant improvement in pain.[14] The sample size was inflated by 20% (to 20 patients in each group) to account for missing data, attrition, and protocol violations. The study was not powered to detect a difference in rescue analgesia or adverse events.

A study enrollment flow diagram was prepared in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Figure 1).[16] Patient characteristics and outcome measures were reported as means, standard deviations (SDs), medians, interquartile ranges (IQRs), and percentages, as appropriate. Descriptive and inferential statistical analyses (Kruskal-Wallis, Mann-Whitney rank-sum, or Friedman tests for continuous variables; Fisher's exact or chi-square tests for categorical data) were performed using STATA 11.0. Nonparametric statistical techniques were used for the continuous data, as these data were not normally distributed. An $\alpha = 0.05$ level was used to determine significant differences; this was not adjusted for multiple comparisons.

We anticipated that some patients would be discharged before the 2-hour study endpoint and therefore data would be missing for some participants. Missing data for the 2-hour NRS (used to calculate the primary outcome SPID) were imputed in three different ways: 1) the NRS at the last recorded study time point (1 hour) was carried forward, 2) the average pain score of the participant's respective group (standard care, group 1, or group 2) at the 2-hour point was used, and 3) multivariable linear regression (using study group, demographic, and clinical variables as predictors) was used to predict the 2-hour NRS. Sensitivity analyses were performed to determine the effects of the three imputation methods on study outcomes.

Kaplan-Meier analyses were performed to compare time to rescue analgesia among the three groups. Patients discharged before the end of the study period were censored at the time of discharge. We used Breslow's method to test if the time to rescue analgesia differed among groups, both overall and in pairwise comparisons. Breslow's method was chosen at it gives emphasis to earlier time to rescue analgesia as this was thought to be of greater clinical significance and reflective of the data on visual inspection of the time-to-event curves. Cox proportional hazard modeling was used to estimate hazard ratios and corresponding 95% confidence intervals (CIs) for receipt of rescue analgesia by groups. Hazard ratios were adjusted for clinical and demographic characteristics thought to predict the receipt of analgesia. Likelihood ratio testing was used to determine the final Cox model by comparing nested models ($\alpha = 0.05$); chronic pain, opioid use within the previous 24 hours, and analgesia (in milligrams of morphine equivalents) were included in the final model. Schoenfeld residuals were used to confirm that data satisfied the proportional hazards assumption.

RESULTS

Participant Enrollment and Characteristics

The CONSORT diagram of study enrollment is displayed in Figure 1. Sixty-nine patients underwent randomization; of these, nine were withdrawn from the study prior to receiving the study medications. Of the nine withdrawals, five were discharged by their treating physicians, three participants with orthopedic injuries received regional anesthesia, and one participant left the ED for a procedure in the radiology department. Sixty patients ultimately received the study medications (20 in each group).

Summary demographic and clinical characteristics for patients in all three study groups are presented in Table 1. There were no significant differences among

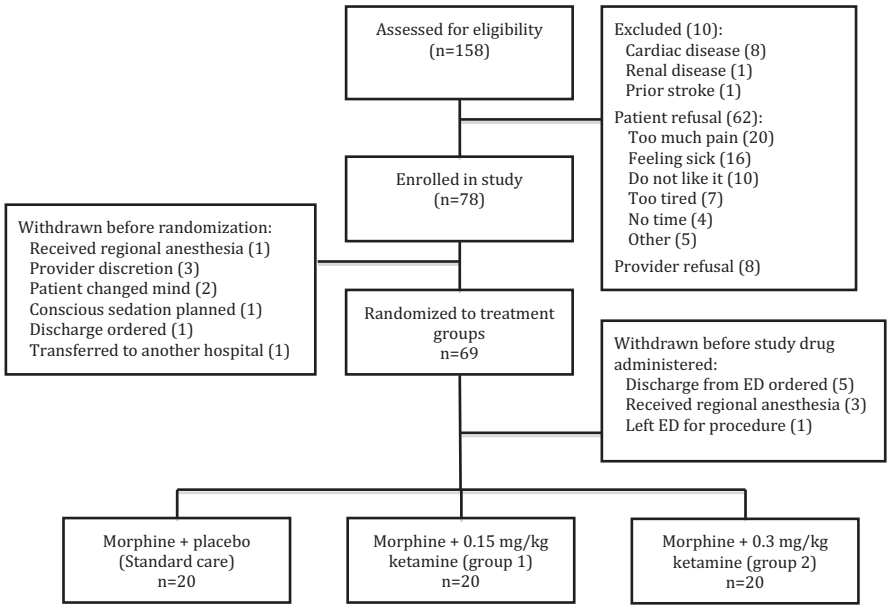

Figure 1. Study enrollment flow diagram.

Table 1
Patient Demographics, Clinical Characteristics, and Baseline Outcome Measurements by Group

Characteristic	Standard Care (*n* = 20)	Group 1 (*n* = 20)	Group 2 (*n* = 20)	p-value
Age (yr)	37.5 (31.5–44.0)	37.5 (25.5–46.0)	32.5 (25.5–41.0)	0.55
Sex				0.18
Male	15 (75)	13 (65)	9 (45)	
Female	5 (25)	7 (35)	11 (55)	
Ethnicity and race				0.34
White	14 (70)	14 (70)	10 (50)	
Black	4 (20)	3 (15)	4 (20)	
Hispanic	0 (0)	3 (15)	3 (15)	
Asian	0 (0)	0 (0)	0 (0)	
Other	2 (10)	0 (0)	3 (15)	
Weight (kg)	80.6 (68.2–95.7)	80.6 (67.4–99.8)	86.3 (68.6–102.1)	0.71
History of chronic pain	3 (15)	6 (30)	5 (25)	0.64
History of opioid use*				
Opioid use in the past month	6 (30)	7 (35)	6 (30)	1.00
Chronic opioid usage	3 (15)	4 (20)	4 (20)	1.00
Opioid use in the past 24 hours	2 (10)	6 (30)	5 (25)	0.27
Discharge diagnosis				
Abdominal pain (nonspecific)	0 (0)	5 (25)	1 (5)	
Back pain/sciatica	1 (5)	4 (20)	1 (5)	
Gastrointestinal†	2 (10)	2 (10)	6 (30)	
Fracture	5 (25)	1 (5)	4 (20)	
Genitourinary infection‡	2 (10)	2 (10)	1 (5)	
Musculoskeletal, other	3 (15)	1 (5)	2 (10)	
Orofacial pain/headache	3 (15)	1 (5)	0 (0)	
Renal colic	1 (5)	2 (10)	3 (15)	
Sickle cell disease	1 (5)	1 (5)	0 (0)	
Skin and soft tissue infection	2 (10)	2 (10)	2 (10)	
Baseline pain and pain relief scores				
NRS	9 (7–10)	9 (8–10)	8 (8–10)	0.68
Pain relief scale				0.66
None	10 (50)	9 (45)	7 (35)	
A little relief	7 (35)	10 (50)	10 (50)	
Some relief	3 (15)	1 (5)	3 (15)	
Preenrollment analgesia				
Proportion receiving	16 (80)	16 (80)	14 (70)	0.80
Amount received (mg)	6.4 (3.0–12.1)	4.3 (3.3–6.7)	4.0 (0.0–7.2)	0.46
Baseline vital signs				
Heart rate (beats/min)	77 (72–86)	79 (71–85)	81 (69–88)	0.89
sBP (mm Hg)	129 (114–142)	127 (121–135)	126 (115–139)	0.95
dBP (mm Hg)	79 (70–84)	77 (73–87)	79 (68–87)	0.93
Oxygen saturation (%)	99 (98–100)	99 (98–100)	99 (98–100)	0.86

Continuous data are presented as median (IQR); categorical data are presented as a number (%). Standard care = morphine + placebo; group 1= morphine + 0.15 mg/kg ketamine; group 2 = morphine + 0.3 mg/kg ketamine.
IQR = interquartile range; dBP = diastolic blood pressure; NRS = numeric rating score; sBP = systolic blood pressure.
*Categories of opioid use not mutually exclusive.
†Gastrointestinal: appendicitis, biliary colic, colitis, cholecystitis, or diverticulitis.
‡Genitourinary: pyelonephritis or pelvic inflammatory disease.

the three treatment groups with respect to selected demographic or clinical characteristics. Prior to receipt of study medications, two patients in group 2 reported nausea and dizziness, compared to one in group 1, and none in the standard care group. No other adverse events were reported prior to receipt of study medications. Median length of stay after study medication administration did not differ significantly between treatment groups (standard care 133.5 minutes, IQR = 98 to 245.5 minutes; group 1 170 minutes, IQR = 88 to 200 minutes; group 2 172.5 minutes, IQR = 120 to 303 minutes; p = 0.27).

Primary and Secondary Outcomes

Primary and secondary effectiveness outcomes are presented in Table 2. Pain scores in each group decreased over time ($p < 0.001$). The median change in pain intensity at each time point was ≥2 across all treatment groups, which also corresponds to clinically meaningful decreases in pain. However, the SPID over the 2-hour study period was greater in the ketamine groups compared to the standard care group. There was no significant difference in SPID between group 1 and group 2. In addition, the proportion of subjects with clinically meaningful total pain relief over 2 hours (i.e., treatment responders of %SPID ≥ 33,) was lowest in the standard care group (*n* = 5, 25%) compared with group 1 (*n* = 10, 50%) and group 2 (*n* = 14, 70%). PID in the standard care group was significantly different from both ketamine groups at the 30-minute study time point, but group 1 was no different than standard care at 1 and 2 hours. Overall, group 2 sustained the same PID over

Table 2
Primary and Secondary Effectiveness Outcomes for the Three Treatment Groups

Variable	Standard Care (n = 20)	Group 1 (n = 20)	Group 2 (n = 20)	p-values			
				Overall	Group 1 vs. Standard	Group 2 vs. Standard	Group 1 vs. Group 2
Pain intensity							
SPID	4.0 (1.8 to 6.5)	7.0 (4.3 to 10.8)	7.8 (4.8 to 12.8)	0.02	0.04	0.01	0.37
%SPID	21% (10 to 37)	39% (22 to 86)	42% (29 to 80)	0.02	0.05	0.01	0.42
Achieved SPID33%	5 (25%)	10 (50%)	14 (70%)	0.02	0.19	0.01	0.33
Pain intensity decrease							
30 minutes	2 (0.5 to 3)	4 (3 to 6.5)	4 (2 to 6)	0.01	0.00	0.02	0.70
1 hour	2 (1 to 3.5)	4 (2.5 to 6)	4 (1.5 to 7)	0.07	0.06	0.04	0.60
2 hours	2 (0.4 to 3)	2.51 (0.7 to 4)	4 (2 to 7)	0.07	0.32	0.02	0.19
Total patient-perceived pain relief	2.5 (1.0 to 4.3)	4.3 (1.3 to 5.5)	4.5 (3.0 to 6.0)	0.06	0.07	0.12	0.86
SIA score	44.3 (–18.0 to 82.0)	–8.2 (–86.1 to 55.7)	–65.6 (–100 to 21.3)	0.01	0.19	0.00	0.14

Continuous data are presented as median (IQR); categorical data are presented as a number (%).
Standard care = morphine + placebo; group 1 = morphine + 0.15 mg/kg ketamine; group 2 = morphine + 0.3 mg/kg ketamine.
SIA = Silverman integrated analgesic assessment; SPID = summed pain-intensity difference; SPID33% = the proportion of subjects achieving an SPID% score of ≥33%, treatment responders.

the study period, whereas group 1 returned to levels similar to the standard care group by 1 and 2 hours. Group 1 and group 2 were not significantly different with respect to any of the study endpoints.

The number of missing values at 2 hours (n = 4) did not differ among study groups. The methods of imputation for the missing 2-hour time points did not change the analytic results for primary and secondary effectiveness outcomes presented in Table 2. For the sake of brevity, the SPID scores presented are the results of imputation by regression modeling.

There were no differences between the standard care group (n = 7, 35%) and the ketamine groups (n = 4, 20% in each) regarding use of rescue analgesia (p=0.48). Among those receiving rescue analgesia, there was no significant difference in the amount administered among the three treatment groups (p < 0.53). The median dose of rescue analgesia was 6.1 mg (in morphine equivalents) in the standard care group, compared to 5.4 mg in group 1 and 4.3 mg in group 2. The median time when rescue analgesia was received in the standard care group (54 minutes, IQR = 36.0 to 94.0 minutes) was similar to both ketamine groups (group 1 119.5 minutes, IQR = 73.5 to 143.5 minutes; group 2 113.0 minutes, IQR = 105.0 to 118.5 minutes; p < 0.18).

The results of Kaplan-Meier time-to-event analysis are displayed in Figure 2; the outcome event was the first receipt of rescue analgesia after study medications were administered. Individuals were censored if they left the ED. The Breslow test demonstrated a pairwise difference between group 2 and the standard care group (p < 0.04), but not between group 1 and the standard care group (p < 0.10). The associated hazard ratios from the adjusted Cox proportional hazard model were 0.29 (95% CI = 0.8 to 0.99) for group 1 versus standard care and 0.31 (95% CI = 0.10 to 0.96) for group 2 versus standard care (p < 0.04).

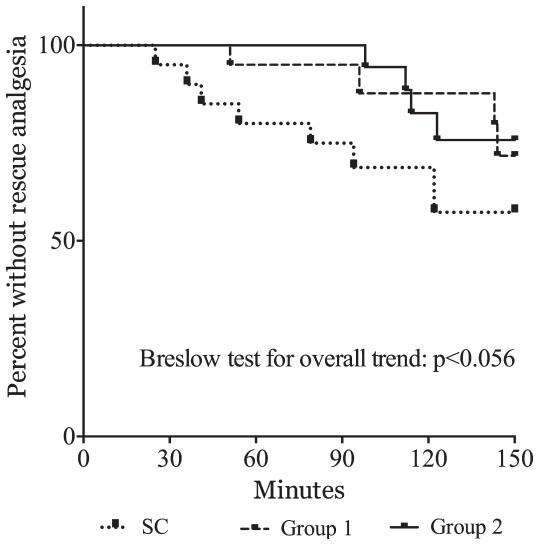

Figure 2. Kaplan-Meier curves comparing time to rescue analgesia among the treatment group.

Global analgesic effectiveness as measured by integrated pain and morphine scores (i.e., SIA scores) are also presented in Table 2. The lowest median scores (most pain relief with least amount of analgesia) occurred in the group 2, followed by group 1, and then the standard care group. When pairwise comparisons were performed, only group 2 and the standard care group were significantly different.

Adverse Events

A higher proportion of patients in group 2 (n = 9, 45%) reported dizziness or lightheadedness at 30 minutes, compared with either group 1 (0%) or the standard care group (n = 2, 10%; p < 0.01). Of the nine participants reporting dizziness in group 2, five had dizziness that

persisted longer than 1 hour. Nausea was reported by an equal number of participants in each group (n = 3, 15%), but two patients in the group 2 vomited within 15 minutes after receiving the study medication. Dysphoria or confusion was reported by none in the standard care group, two participants in group 1, and three (15%) in group 2. One participant in group 1 used the descriptor "scary, felt loss of control," and another stated "I wouldn't want to do this again." Comments from group 2 included "felt unstable" and a "whole body hot flash." One patient in each group commented on an abnormal taste sensation at 30 minutes after receiving the study medications. One patient in the standard care group developed hypotension after a dose of rescue analgesia, and another developed transient respiratory depression (oxygen saturation < 92%) after a dose of rescue analgesia. Three patients in group 2 developed sinus tachycardia (heart rate > 100 beats/min) after administration of the study medication, but this had resolved by the 30-minute mark. No behavioral disturbances or dysrhythmias occurred during the study period and no patients required naloxone.

DISCUSSION

Low-dose ketamine (at doses of 0.15 and 0.3 mg/kg) is a promising alternative to standard care with morphine alone for the control of moderate to severe acute pain in the ED. It confers an advantage over morphine alone with decreased pain intensity over a 2-hour period. At least half the patients in each ketamine groups had clinically significant decreases in pain intensity (i.e., SPID ≥ 33%), compared to only a quarter of patients in the standard care group. In addition, our findings support a previous prehospital study that demonstrated that low-dose ketamine results in an opioid-sparing effect.[17] The standard care group received rescue analgesia earlier (in less than half the time) of either ketamine group. The analysis for time to rescue analgesia only reached statistical significance in group 2, and the lack of significance of the other rescue analgesia outcomes likely reflect the small number of patients who received rescue analgesia and resultant inadequate power to detect a difference in receipt of rescue analgesia.

This investigation's results suggest that 0.3 mg/kg may be more efficacious than 0.15 mg/kg. When compared to standard care, group 2 had more significant effects than group 1 at the 1- and 2-hour study time points. Furthermore, when rescue analgesia and pain outcomes (SPID) were integrated using the SIA score, group 2 again appeared to have superior effects. In other words, once SPID was weighted with rescue analgesia, the difference in SPID between group 1 and the standard care group was attenuated. This may explain why previous findings by Galinski et al.[17] showed only a morphine-sparing effect without a difference in pain intensity when 0.2 mg/kg ketamine was used as an adjunct to 0.1 mg/kg of morphine.[17] Future studies should further investigate the optimum dosing of ketamine for analgesia, the role of repeat dosing or continuous dosing, and alternate routes of administration.

As with any other drug, use of low-dose ketamine for treatment of pain must be balanced against the potential for adverse events. With the acknowledgement that this investigation did not have adequate power to detect a difference in the frequency of adverse events, this preliminary study did not find any serious adverse events that would limit the use of 0.15 to 0.3 mg/kg ketamine in generally healthy adult patients. However, five (two in group 1, three in group 2) participants who received ketamine experienced unpleasant dysphoria, and nearly half of the participants in group 2 experienced dizziness. In addition, two patients in group 2 vomited within 30 minutes, and three patients in group 2 experienced episodes of sinus tachycardia. While all episodes had resolved within 30 minutes, this occurrence may have important implications for the use of low-dose ketamine in populations with medical comorbidities for which tachycardia may be detrimental (e.g., cardiac disease). In comparison, a recent Cochrane review of perioperative low-dose ketamine concluded that its administration reduced postoperative nausea and vomiting and that other adverse events were mild or absent when compared to morphine only.[6] This review supports the safety of low doses of ketamine, but adverse events such as hemodynamic abnormalities and dizziness were not explicitly evaluated. An open-label prehospital study concluded that boluses of adjuvant ketamine (dose range of 10 to 120 mg) were superior to morphine alone, but were associated with a higher rate of mild adverse events such as dysphoria and hypertension.[18]

We do not advocate for the use of low-dose ketamine for all patients with moderate to severe pain in the ED. Rather, it should equip the emergency physician with another tool to treat pain, particularly for pain refractory to opioids. As a criterion for this study, patients had to have ongoing moderate to severe pain at the time of enrollment. As a consequence, patients whose pain was managed adequately with opioid or nonopioid analgesics were excluded from this study. In fact, the majority of patients in this study had already received opioid analgesia prior to enrollment, implying that these patients may have had pain refractory to initial opioids. In addition, we postulate that low-dose ketamine would be useful among patients for whom the use of opioids is problematic, such as severe polytrauma, chronic pain, suspected opioid induced-hyperalgesia, and tolerance to opioids (i.e., sickle cell pain crises).[19,20] These specific subpopulations have challenging issues when it comes to pain management and approaches to assist them are interesting areas of future study.

LIMITATIONS

This study was performed among a small sample of a heterogeneous group of patients at a single study site with diverse conditions requiring emergency medical treatment. We believed that it was of greater clinical utility (i.e., more external validity) to include patients with a variety of acute painful conditions. Because the sample size was small, clinical diagnoses were not distributed evenly among the treatment groups. This could have led to confounding if certain painful conditions were more or less responsive to ketamine or morphine. In general, there is the possibility for residual confound-

ing despite the randomized design given the small sample size. Various factors may affect treatment response, and prediction of treatment response is an interesting future area of study that would help guide clinical practice in choosing the most appropriate patients to administer low doses of ketamine.

Pain was only measured at three time points. Although it was not possible to take continuous measurements of pain, perhaps different information would have been elicited with more frequent assessments. We limited the assessments to 30 minutes, 1 hour, and 2 hours to mimic what might occur in clinical practice and also to avoid response biases that might occur if participants were asked to report their pain too frequently. Additionally, future studies might focus on pain outcomes at points past 2 hours, including after discharge and admission. It would be interesting and relevant to examine whether the administration of low-dose ketamine (even as a single dose) has the ability to affect pain trajectory after disposition from the ED. We also did not take into account the role or effect of other analgesics, such as nonsteroidals, acetaminophen, and other medications that may influence pain (e.g., muscle relaxants). Because the primary aim was to examine low-dose ketamine as an adjunct to opioids and to also examine an opioid-sparing effect, only opioids were evaluated.

Finally, although a standardized approach to rescue analgesia was recommended to treating providers, rescue analgesia ultimately was left up to the discretion of the treating physician. Only 15 of the 60 participants received rescue analgesia, despite the fact that roughly only half of the study participants achieved clinically significant changes in pain. While this may reflect practice at the study institution, other studies have found similar problems when the treating physician is allowed to dose rescue analgesia.[21] It is possible that using a truly standardized approach to rescue analgesia would have led to different study results, but we would not know how low-dose ketamine would have performed in typical clinical practice.

CONCLUSIONS

A low dose of ketamine appears to be a viable analgesic adjunct to morphine for the treatment of moderate to severe acute pain. No serious adverse events occurred in our study, but the emergency care provider should be aware that low doses of ketamine may cause dysphoria and dizziness. Dosing of 0.3 mg/kg may be more effective than 0.15 mg/kg, but may be associated with tachycardia and vomiting. Future studies of low-dose ketamine should evaluate additional outcomes, optimum dosing, and in determining which subpopulations are most ideal for its use.

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