Evaluation of analgesic effects of ketamine through sub-dissociative dosing in the ED☆

To the Editor,

Effectively managing pain is known to be problematic in the emergency department (ED) with up to 43% of patients with oligoanalgesia [1–3]. Opioids alone are commonly inadequate at controlling acute and acute on chronic pain in the ED [4–6]. Furthermore, using higher doses or more potent opioids may be challenging in some patients because of the risk of adverse effects such as somnolence, respiratory and hemodynamic depression, nausea, and vomiting [7–12].

An alternative approach may be to use the analgesic properties of ketamine (Ketalar; JHP Pharmaceuticals, LLC, Rochester, Michigan) at subdissociative doses (intravenous doses less than 1 mg/kg), which have been shown to induce analgesia, reduce hyperalgesia, and decrease the amount of morphine with minimal oxygen desaturation and respiratory depression [7,13–17]. Clinically, analgesia onset is approximately 1 and 3 minutes for intravenous and intramuscular administration, respectively, with an elimination half-life of approximately 10 to 15 minutes [15]. In addition, ketamine can be administered via intranasal route, and it has been shown to decrease pain (from 6.4 to 4.4 and from 6.6 to 4.1; $P < 0.05$) after 1 hour and for a duration of 2 to 3 hours [18,19].

A PubMed, Cochrane Library, and International Pharmaceutical Abstracts (1973 to present) search was performed using the primary key words of "ketamine" and "emergency department." Articles were included if ketamine was administered to adult patients in the ED for analgesia. Eleven original published articles were included and are presented in Table 1.

Most of the studies evaluating ketamine as an analgesic in the emergency setting used it as adjunctive therapy in addition to an opioid [7,16,17,20–26]. A few observational studies and one randomized controlled trial (RCT) evaluated the use of low-dose ketamine alone [19,27–29]. Miller et al [19] showed similar maximum decreases in pain scores with administration of morphine vs ketamine, but noted they occurred at different times (100 vs 5 minutes after administration). Yeaman et al [27] concluded that ketamine use alone produced suboptimal results (56% of patients had a clinically significant decrease in pain) and that it should be used with other analgesics.

A variety of doses were used in studies evaluating low-dose ketamine for analgesia, primarily 0.1 to 1 mg/kg of ketamine. There is a lack of RCTs evaluating the effectiveness of intranasal ketamine as an analgesic; the most common dosing regimen was 0.5 mg/kg [27–29].

There are conflicting results regarding adverse effects with sub-dissociative doses of ketamine. A study by Jennings et al. [20] (N = 135) found 5.7% of patients receiving intravenous ketamine experienced an emergence phenomenon and 11.4% experienced disorientation in the prehospital setting; this may be due to higher ketamine doses (10 to 120 mg or 0.14-1.7 mg/kg in a 70-kg patient). Galinski et al. [16] treated patients experiencing severe pain in mobile intensive care units in a double-blind RCT and found a statistically significant ($P = 0.002$) increase in neuropsychological adverse effects (36% vs 3%) with administration of 0.2 mg/kg intravenous ketamine compared to morphine including hallucinations, dizziness, diplopia, and dysphoria. Gurnani et al. [17] showed less overall nausea, whereas Johansson et al. [21] showed more overall nausea in the morphine only group vs the ketamine plus morphine group. In an RCT by Weinbroum [10], intravenous ketamine (0.25 mg/kg, n = 131) plus morphine (0.015 mg/kg) vs morphine alone (0.030 mg/kg, n = 114) resulted in less postoperative nausea and vomiting (26.3% vs 6.9%; $P < 0.001$); the decreased incidence of nausea may be due to the smaller cumulative dose of morphine required with ketamine to obtain adequate pain relief (2.52 ± 0.56 vs 1.35 ± 0.56 mg/kg morphine; $P < .001$). In a large retrospective study evaluating low-dose ketamine (0.1 to 0.3 mg/kg, intravenously or intramuscularly) administered in the ED for analgesia (n = 530), only 6% of patients developed a mild adverse event, which rarely altered the patient's clinical course [30]. Low-dose ketamine use for analgesia in the emergency setting has generally been shown to be well tolerated [7,17,19,21,22,24–31]. The differences in adverse effects associated with ketamine administration may be due to interstudy variability in the study populations, the dosing strategies used, or random error due to the small study populations.

Ketamine administration without concomitant opioid administration may be an appropriate alternative in those patients complaining of moderate to severe acute pain who have a contraindication to opioid therapy [23]. In patients without a contraindication to opioid therapy but who require high doses of opioids without adequate pain relief, the addition of a single intravenous dose of 0.2 mg/kg of ketamine may be appropriate to facilitate adequate pain control and decrease the overall opioid analgesic requirement [16]. Large RCTs are needed to fully elucidate the benefit and effectiveness of low-dose ketamine administration for analgesia in the ED.

Acknowledgment

The authors would like to acknowledge Faheem Guirgis, MD, who graciously provided an emergency medicine perspective for this review article.

Heidi Riha, BS, Pharm.D.[1]
University of Florida College of Pharmacy, 580 West 8th Street
Box T-5, Jacksonville, FL 32209
E-mail address: coy@ufl.edu

Patrick Aaronson, Pharm.D.
Emergency Medicine, Department of Pharmacy UF Health–Jacksonville
655 West 8th Street, Box C-89, Jacksonville, FL 32209
Corresponding author at: Tel.: +1 904 244 4157; fax: +904 244 4272
E-mail address: aaronson@poison.ufl.edu

Andrew Schmidt, DO, MPH[2]
Department of Emergency Medicine, University of Florida Health Jacksonville, FL
Emergency Medicine/University of Florida, 655 West 8th Street
Box C-89, Jacksonville, FL 32209
E-mail address: andrew.Schmidt@jax.ufl.edu

[1] Tel.: +1 904 244 9590; fax: +1 904 244 9591
[2] Tel.: +1 904 244 4986; fax: +1 904 244 5885

http://dx.doi.org//10.1016/j.ajem.2015.03.045

References

[1] Albrecht E, Taffe P, Yersin B, Schoettker P, Decosterd I, Hugli O. Undertreatment of acute pain (oligoanalgesia) and medical practice variation in prehospital analgesia of adult trauma patients: a 10 yr retrospective study. Br J Anaesth 2013;110(1):96–106.
[2] Todd KH, Ducharme J, Choiniere M, Crandall CS, Fosnocht DE, Homel P, et al. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. J Pain 2007;8(6):460–6.
[3] Cordell WH, Keene KK, Giles BK, Jones JB, Jones JH, Brizendine EJ. The high prevalence of pain in emergency medical care. Am J Emerg Med 2002;20(3):165–9.
[4] Bijur PE, Kenny MK, Gallagher EJ. Intravenous morphine at 0.1 mg/kg is not effective for controlling severe acute pain in the majority of patients. Ann Emerg Med 2005; 46(4):362–7.
[5] Farsi D, Movahedi M, Hafezimoghadam P, Abbasi S, Shahlaee A, Rahimi-Movaghar V. Acute pain management with intravenous 0.10 mg/kg vs. 0.15 mg/kg morphine

☆ Explanation of lead authors credentials.We believe Heidi Riha, BS, PharmD Candidate 2015, has the qualifications and contributions to the paper to establish herself as the lead author. She received her Bachelor of Science in Biochemistry and is currently on her last year of the Doctor of Pharmacy program. Per ICMJE guidelines, Heidi Riha has substantial contribution, conception, acquisition, analysis, and interpretation of the data for this review article.

Table 1
Summary of sub-dissociative ketamine studies administered to adult patients in the emergency department

Reference	Design	Patients (no.)	Treatment(s)	Outcome	Safety
Ahern et al [7]	Prospective observational study	32	• 15 mg ketamine + 0.5 mg hydromorphone IV • If at 15 or 30 min the patient said they would like more pain medication, an additional 1 mg of hydromorphone IV was administered	• At 5 min the mean reduction in pain score was 6.0 ± 3.2 on a 10-point verbal NRS • 93% had clinically significant decrease in pain (≥2 points decrease on the NRS) • 14 patients declined additional analgesia at both 15 and 30 min • 90% of patients stated they would have the combination with ketamine again	• No hallucinations or agitation reported • No tachycardia, hypertension, dysrhythmia, hypoxia were observed • 80% of patients reported some dissociative effects (dizziness, fatigue, mood changes, headache) • 73% of patients reported the side effects as weak or modest
Gurnani et al [17]	Randomized control trial	40	• Ketamine 0.25 mg/kg IV followed by ketamine 1.67 μg kg^{-1} min^{-1} SQ continuous infusion x 24 h + saline Q4H IV x 24 h OR • Morphine 0.1 mg/kg IV followed by morphine 0.1 mg/kg IV Q4H x 24 h + saline SQ continuous infusion x 24 h	• Pain score (on a 10-point VAS) was lower after 15 min through 24 h ($P < .05$) • Patients required less supplemental doses of 3 mg IV morphine (0 vs 18 people; $P < .001$)	• Less N/V with ketamine (0% vs 35%; $P < .05$) • Less drowsiness with ketamine at 1 h through 24 h ($P < .05$) • Mean peak expiratory flow rate improved more with ketamine($P < .05$)
Miller et al [19]	Randomized, double-blinded, superiority controlled trial	45	• Ketamine 0.3 mg/kg total body weight IV (maximum dose of 25 mg) • Morphine 0.1 mg/kg total body weight IV (maximum dose of 8 mg) • Both morphine and ketamine were infused over 5 min in a total of 10 mL normal saline • A second identical dose could be administered 20 min after the first infusion was complete • If a third dose was needed, data collection was stopped and the patient got pain medication the prescriber ordered	• Ketamine may have comparable analgesic effects to morphine • Maximum decrease in pain from baseline on a NRS was similar between ketamine and morphine (4.9 vs 5) • Maximum decrease in pain was seen at 5 min for the ketamine group and 100 min for the morphine group • There was no difference between the number of second and third doses administered in the ketamine group vs the morphine group (54% vs 38%; $P = .37$ and 25% vs 14%; $P = .47$)	• No difference in percentage of patients with adverse effects with ketamine vs morphine (58% vs 57%) • 3, 4, 0, 0, and 0 patients in the ketamine group (n = 24) vs 0, 0, 3, 2 and 1 in the morphine group (n = 21) experienced hallucinations, dysphoria, headache, drowsiness, and decreased oxygen saturation • No dissociation or emergency reactions were detected • Similar RASS scores with ketamine vs morphine
Lester et al [22]	Retrospective case series	34	• Ketamine was administered at doses less than 0.6 mg/kg IV or IM • 80% of patients either used chronic pain medication or illicit drugs	• Median dose: 10 mg (Range: 5–35 mg) • Mean dose: 15.7 mg • 91% had opioids administered before or concomitant with ketamine • 54% of patients had ≥3 point decrease in pain score (on a 10-point VAS) • 23% of patients had insufficient data in the record to assess benefit in pain score	• No dangerous adverse events • 1 patient experienced "brief mild dysphoria"
Richards et al [23]	Prospective observational study	24	• 75% of the patients received opioid analgesics before ketamine with no improvement in their pain score after 30 min • Ketamine (average dose 22.2 ± 11.2 mg) IV or IM + 2 repeated doses (average dose 12.5 ± 3.5 mg) IV or IM or an average total dose of 0.67 mg/kg in a 70-kg patient	• Pain decreased (on a 10 point VAS) from 8.9 ± 2.1 to 3.9 ± 3.4 ($P < .0001$) • 67% of the patients prefer to be given ketamine again • 96% of physicians would use ketamine again	• No emergence reactions
Beaudoin et al [24]	Randomized, double-blinded, controlled trial	60	• Morphine 0.1 mg/kg IV (max dose of 10 mg) + either ketamine 0.15 mg/kg IV or ketamine 0.3 mg/kg IV or placebo IV • Morphine 0.05 to 0.1 mg/kg IV every hour was used for rescue analgesia as needed to target at least a 50% decrease in patient discomfort or per patient request	• Reduction in pain intensity (on a NRS of 0 to 10) over 2 h was higher with concomitant ketamine administration vs placebo (7.0 with 0.15 mg/kg ketamine vs 7.8 with 0.3 mg/kg ketamine vs 4.0 with placebo; 0.15 mg/kg ketamine vs placebo $P = .04$; 0.3 mg/kg ketamine vs placebo $P = 0.01$) • Greater % of patients with concomitant ketamine experienced ≥33% reduction in pain-intensity (50% vs 70% vs 25%; 0.15 mg/kg ketamine vs placebo $P = .19$; 0.3 mg/kg ketamine vs placebo $P = .01$) • Time-to-event to first receipt of rescue analgesia was longer with 0.3 mg/kg ketamine vs placebo (HR: 0.31; 95% CI: 0.10 to 0.96; $\boldsymbol{P} < .04$)	• A higher proportion of patients given 0.3 mg/kg ketamine experienced dizziness or lightheadedness at 30 min compared to 0.15 mg/kg ketamine and placebo (45% vs 0% vs 10%; $P < .01$) • One patient developed hypotension and another developed transient respiratory depression (oxygen saturation <92%) with a dose of rescue analgesia in the placebo group • 3 patients in the 0.3 mg/kg ketamine group developed tachycardia which lasted <30 min • 0 patients in placebo vs 2 patients in the 0.15 mg/kg ketamine vs 3 patients in the 0.30 mg/kg ketamine group experienced dysphoria or confusion
Goltser et al [25]	Retrospective case series	14	• Ketamine 0.2 to 0.4 mg/kg IV diluted in 50 to 100 mL normal saline piggyback administered over 10 min • 12 of 14 patients received opioids in the emergency department before the low dose ketamine infusion	• No patients required rescue analgesia within one hour of ketamine administration • Pain improved for 8 of 14 patients on a NRS (the remaining patients could not be assessed due to no documentation of the NRS)	• No dangerous adverse effects, tachycardia, hypertension, dysphoria, nausea, vomiting, dream-like state, hallucinations, or emergence reactions • One patient complained of tinnitus and uneasiness during the infusion and one of dizziness
Ahern et al [26]	Convenience sampling	38	• Ketamine 15 mg IV push followed by a 20 mg/h infusion (infusion was in 250 mL normal saline)	• At 10 min, 60 min (the end of the infusion), and 120 min (60 min after the end of the infusion) 57%, 65%, and 68% of	• No subjects experienced deep sedation, or severe side effects which required intervention or transfer to a

Table 1 *(continued)*

Reference	Design	Patients (no.)	Treatment(s)	Outcome	Safety
			• Morphine 4 mg IV was administered at 20, 40, and 60 min if the patient needed it • No other pain medication was given between 60 and 120 min	patients had a clinically meaningful decrease of 3 or more points on the NRS • 58% of patients had received pain medication prior to study enrollment • At 20, 40, and 60 min, 42%, 50%, and 28% of patients requested supplemental morphine • 31% of patients requested no supplemental morphine	higher acuity ED bed for monitoring • 86% of patients experienced some dissociative spectrum side effects • 53% and 34% of the patients reported the side effects as "weak or modest" and "very bothersome" • 58%, 61%, 42%, and 39% patients reported dizziness, fatigue, nausea, and feelings of unreality
Yeaman et al [27]	Prospective observational study	72	• Ketamine 0.7 mg/kg IN (during the first 6 mo of the study) OR 1.0 mg/kg IN (during the second 6 mo of the study) initial dose followed by a 0.5 mg/kg IN supplementary dose if there was no reduction in pain after 15 min	• Median pain score (on a 100 mm VAS) decreased by 24 mm (IQR: 2–45) at 30 min ($P < .001$) • 55% patients (CI: 44.0-66.7) had a reduction in VAS ≥20 mm • After 60 min, 19.4% of patients received an alternative form of analgesia	• No hallucinatory or emergence reactions • 31.9% reported dizziness • Unwanted sedation reported by 41.2% at 60 min • Adverse reactions common but mild
Andolfatto et al [29]	Prospective observational study	40	• Ketamine 0.5 mg/kg IN + a single additional ketamine 0.25 mg/kg IN dose if VAS after 10 min was ≥50 mm (on a 100-mm VAS pain scale)	• VAS were statistically decreased at 15, 30, and 60 min ($P < .001$)	• All adverse reactions were transient and did not require treatment
Ahern et al [30]	Retrospective case-series	530	• Ketamine 5 to 20 mg IV (93% of patients) or 10 to 25 mg IM (equivalent doses to 0.1 to 0.3 mg/kg in the average size adult) • Used alone or in combinations with other pain relieving drugs • There were no absolute contraindications for ketamine and administration was ultimately left up to provider preference	• N/A	• No significant change in SBP or heart rate from triage (141 and 93 vs 138 and 86) • 6% met criteria for adverse event within 1 hour of ketamine administration • 1.5% (n = 7) developed hypoxia (4 of these people received concomitant 1-2 mg of hydromorphone) • 1% (n = 5) developed emesis • 3.5% (n = 18) experienced psychomimetic or dysphoric reactions (mild in nature and rarely altered a patients clinical course)

Abbreviations: CI, confidence interval; HR, hazard ratio; IM, intramuscular; IN, intranasal; IQR, interquartile range; IV, intravenous; NRS, numerical rating scale; N/V, nausea and vomiting; OR, odds ratio; Q4H, every 4 h; SBP, systolic blood pressure; SQ, subcutaneous; VAS, visual analog scale.

sulfate in limb traumatized patients: a randomized double-blinded placebo-controlled trial. Ulus Travma Acil Cerrahi Derg 2013;19(5):398–404.

[6] Patanwala AE, Jarzyna DL, Miller MD, Erstad BL. Comparison of opioid requirements and analgesic response in opioid-tolerant versus opioid-naïve patients after total knee arthroplasty. Pharmacotherapy 2008;28(12):1453–60.

[7] Ahern TL, Herring AA, Stone MB, Frazee BW. Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. Am J Emerg Med 2013;31(5):847–51.

[8] Yanagihara Y, Ohtani M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, et al. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. Biopharm Drug Dispos 2003;24(1):37–43.

[9] Neri CM, Pestieau SR, Darbari DS. Low-dose ketamine as a potential adjuvant therapy for painful vaso-occlusive crises in sickle cell disease. Paediatr Anaesth 2013;23(8):684–9.

[10] Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg 2003;96(3):789–95.

[11] Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician 2008;11(2 Suppl.):S105–20.

[12] Chang AK, Bijur PE, Napolitano A, Lupow J, Gallagher EJ. Two milligrams i.v. hydromorphone is efficacious for treating pain but is associated with oxygen desaturation. J Opioid Manag 2009;5(2):75–80.

[13] Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 2011;57(5):449–61.

[14] Carstensen M, Møller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth 2010;104(4):401–6.

[15] Sinner B, Graf BM. Ketamine. Handb Exp Pharmacol 2008;182:313–33.

[16] Galinski M, Dolveck F, Combes X, Limoges V, Smaïl N, Pommier V, et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. Am J Emerg Med 2007;25(4):385–90.

[17] Gurnani A, Sharma PK, Rautela RS, Bhattacharya A. Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. Anaesth Intensive Care 1996;24(1):32–6.

[18] Huge V, Lauchart M, Magerl W, Schelling G, Beyer A, Thieme D, et al. Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. Eur J Pain 2010;14(4):387–94.

[19] Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. Am J Emerg Med 2015;33(3):402–8.

[20] Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, et al. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: a randomized controlled trial. Ann Emerg Med 2012;59(6):497–503.

[21] Johansson P, Kongstad P, Johansson A. The effect of combined treatment with morphine sulphate and low-dose ketamine in a prehospital setting. Scand J Trauma Resusc Emerg Med 2009;17:61–6.

[22] Lester L, Braude DA, Niles C, Crandall CS. Low-dose ketamine for analgesia in the ED: a retrospective case series. Am J Emerg Med 2010;28(7):820–7.

[23] Richards JR, Rockford RE. Low-dose ketamine analgesia: patient and physician experience in the ED. Am J Emerg Med 2013;31(2):390–4.

[24] Beaudoin FL, Lin C, Guan W, Merchant RC. 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. Acad Emerg Med 2014;21(11):1193–202.

[25] Goltser A, Soleyman-Zomalan E, Kresch F, Motov S. Short (low-dose) ketamine infusion for managing acute pain in the ED: case-report series. Am J Emerg Med 2014 [Epub ahead of print].

[26] Ahern TL, Herring AA, Miller S, Frazee BW. Low-dose ketamine infusion for emergency department patients with severe pain. Pain Med 2015 [Epub ahead of print].

[27] Yeaman F, Meek R, Egerton-Warburton D, Rosengarten P, Graudins A. Sub-dissociative-dose intranasal ketamine for moderate to severe pain in adult emergency department patients. Emerg Med Australas 2014;26(3):237–42.

[28] Johansson J, Sjöberg J, Nordgren M, Sandström E, Sjöberg F, Zetterström H. Prehospital analgesia using nasal administration of *S*-ketamine—a case series. Scand J Trauma Resusc Emerg Med 2013;21:38–42.

[29] Andolfatto G, Willman E, Joo D, Miller P, Wong WB, Koehn M, et al. Intranasal ketamine for analgesia in the emergency department: a prospective observational series. Acad Emerg Med 2013;20(10):1050–4.

[30] Ahern TL, Herring AA, Anderson ES, Madia VA, Fahimi J, Frazee BW. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. Am J Emerg Med 2015;33(2):197–201.

[31] Sin B, Ternas T, Motov SM. The use of subdissociative-dose ketamine for acute pain in the emergency department. Acad Emerg Med 2015;22(3):251–7.