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Brief Research Report

Low-Dose Ketamine Infusion for Emergency Department Patients with Severe Pain

Terence L. Ahern MD,* Andrew A. Herring MD,*,† Steve Miller MD,* and Bradley W. Frazee MD*,†

*Departments of Emergency Medicine, Alameda Health System, Highland Hospital, Oakland; †Emergency Medicine, University of California, San Francisco, California, USA

Reprint requests to: Terence Ahern, MD, Department of Emergency Medicine, Alameda Health System, Highland Hospital, 1411 East 31st Street, Oakland, CA 94602-1018, USA. Tel: 510-437-8497; Fax: 510-437-8322; E-mail: terryahern@gmail.com.

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Abstract

Objective. Use of low-dose ketamine infusions in the emergency department (ED) has not previously been described, despite routine use in perioperative and other settings. Our hypothesis was that a low-dose ketamine bolus followed by continuous infusion would 1) provide clinically significant and sustained pain relief; 2) be well tolerated; and 3) be feasible in the ED.

Methods. We prospectively administered 15 mg intravenous ketamine followed immediately by continuous ketamine infusion at 20 mg/h for 1 hour. Optional morphine (4 mg) was offered at 20, 40, and 60 minutes. Pain intensity, vitals signs, level of sedation, and adverse reactions were assessed for 120 minutes.

Results. A total of 38 patients were included with a median initial numerical rating scale (NRS) pain score of 9. At 10 minutes, the median reduction in pain score was 4, with 7 patients reporting a score of 0. At 60 and 120 minutes, 25 and 26 patients, respectively, reported clinically significant pain reduction (decrease NRS score > 3). Heart rate, blood pressure, respiratory rate, and oxygen saturation remained stable. Mild or moderate side effects including dizziness, fatigue, and headache were common. Patient satisfaction was high; 85% reported they would have this medication again for similar pain.

Conclusion. A low-dose ketamine infusion protocol provided significant pain relief with mostly mild side effects and no severe adverse events

Key Words. Ketamine; Intravenous Infusions; Acute Pain; Analgesia; Emergency Service

Introduction

Ketamine has been used extensively in the emergency department (ED) for procedural sedation and rapid sequence intubation. Recent research has demonstrated that low (subdissociative) dose (0.1–0.3 mg/kg) ketamine is safe and improves pain management when combined with opioid analgesics [1–6]. However, when given as a single bolus, the analgesic effect of ketamine is short lived, with peak effect in the first several minutes after administration and a typical duration of 10–15 minutes [7,8]. For this reason, in the perioperative, palliative care and chronic pain settings, where prolonged analgesia is required, infusions of low-dose ketamine (9–30 mg/h) are commonly used [9–16]. Acute long bone fractures, hemodynamically unstable trauma

victims, intractable cancer pain failing opioid therapy, and opioid dependent patients with various forms of acute pain are all common problems encountered in the ED that might benefit from ketamine infusions. Yet, despite widespread use elsewhere, ketamine infusions remain uncommon in the ED and have never been formally studied.

The objective of this study was to describe the analgesic effect, side effects, and patient acceptance of a low-dose ketamine protocol, comprised of an initial intravenous (IV) bolus followed by infusion, in a diverse cohort of ED patients with acute severe pain. In our protocol, 15 mg IV ketamine was administered as a bolus followed immediately by a 20 mg ketamine infusion administered over 1 hour. Our hypothesis was that a low-dose ketamine bolus followed by continuous infusion would provide clinically significant and sustained pain relief without meaningful side effects or adverse events.

Methods

We performed a prospective, nonrandomized, nonblinded trial of adult ED patients with severe pain at a single urban teaching hospital. The Human Investigational Review Board of Alameda County Health System approved the study protocol and written consent forms. Convenience sampling was used, based on the availability of research assistants (RAs). RAs, and three trained ED physicians, identified potential study subjects based on triage pain scores. Inclusion criteria for enrollment were: age 18 years or older; complaint of moderate to severe pain (five or higher on a numerical rating scale [NRS]); and the ability to provide written informed consent in English or Spanish. Exclusion criteria were: refusal or inability to consent; evidence of traumatic brain injury; poorly controlled hypertension not attributable to pain; known history of ischemic heart disease; unexplained tachycardia; severe psychiatric disorders; pregnancy; in custody of law enforcement; intoxication with alcohol or other drugs; and weight less than 40 kg. Patients were not excluded if they had received pain medications prior to enrollment.

We took steps to monitor and reduce bias in selecting our convenience sample. There were often several potentially eligible patients in the ED at any one time, but because of the requirements for very frequent bedside monitoring and data collection by RAs, only one patient at a time, per RA, could be enrolled. At the beginning of each shift, RAs created a list of candidate patients currently in the ED, based on eligibility criteria. The list was presented to one of three participating attending physicians, who prioritized which patients to approach first for enrollment. All participating physicians had extensive experience with low-dose ketamine given as a bolus over the prior 2 years and were motivated to explore the utility and safety of ketamine infusions. There were several reasons that attending physicians might deem some patients not suitable for the ketamine study. These included: if discharge was anticipated in $<$ 2 hours; procedural sedation anticipated within the 2 hour protocol; the patient's pain was already controlled (NRS $<$ 5); and other reasons which the research staff were required to document. For all candidate patients not enrolled, RAs recorded the reason on a data sheet, along with basic demographic information, chief complaint, exclusion criteria that were found, or if they refused enrollment.

Following enrollment and consent, subjects were placed on continuous pulse oximetry and cardiac monitoring. At time 0, subjects received 15 mg of ketamine IV push and immediately afterward, the IV infusion of 20 mg ketamine in 250 cc normal saline was started. The infusion was delivered over 60 minutes. At 20, 40, and 60 minutes, the RA asked the subject "Would you like any more pain medicine?" If the response was "Yes," the RA notified the ED provider and an additional 4 mg morphine IV was administered. No additional pain medication was offered between 61 and 120 minutes. After 120 minutes, analgesics could be given at the discretion of the ED provider.

Pain intensity was assessed by the RA at 0, 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, and 120 minutes using a 10-point verbal NRS. At the same time points, vitals signs, including blood pressure, heart rate (HR), and oxygen saturation were recorded and level of sedation (minimal, moderate, or deep) was assessed using the standard American Society of Anesthesiologists (ASA) definition of levels of sedation/analgesia [17]. At 60 minutes, side effects were assessed using the side effects rating scale for dissociative anesthetics (SERSDA) [18]. The SERSDA is used to query patients on a variety of symptoms and rate each as weak, modest, bothersome, or very bothersome. In addition, any subjective experiences offered by the patient during the study were recorded. At the conclusion of the observation period, patients were asked "Would you have this medication again for similar pain?" Adverse events were defined as the following: a rapid, unexplained rise in mean systolic blood pressure (SBP in mm Hg) or HR (in beats per minute) greater than 20 mm Hg or beats per minute (bpm), respectively; acute development of chest pain, shortness of breath, or headache; hypoxia (defined at an oxygen saturation $<$ 92% or a decrease in oxygen saturation $>$ 5% from initial values) or supplemental oxygen requirement; acute onset of agitation or hallucinations requiring sedation or medical doctor (MD) intervention.

The primary outcome was the change in NRS pain score during the 2-hour study protocol. Secondary outcomes included the number of patients experiencing significant pain relief (decrease in NRS score greater than or equal to three points), additional morphine requirement, and change in level of sedation and vital signs, incidence of side effects using the SERSDA, adverse events, and patient satisfaction.

We report descriptive statistics and 95% confidence intervals (CI) where appropriate. Statistical analysis was done using Microsoft Excel for Mac 2011 (Microsoft Corporation, Redmond, WA).

Results

Forty patients were enrolled between June of 2013 and February of 2014. Mean age was 43 and types of painful conditions were diverse. Two patients (Table 1) were withdrawn from the analysis because of incomplete data or major deviations from study protocol, leaving 38 patients with complete data in the analysis.

Median pain scores and changes over time are presented in Figure 1. At 10 minutes, the median NRS pain score was 6, with seven patients (18%) reporting a score of 0 (complete pain resolution); the median reduction was 3 points and 22 patients (57%) had a clinically significant decrease of 3 or more points. At 30 minutes, the median NRS pain score was 4, the median reduction was 5 and 15 subjects (40%) had reached their lowest recorded score. At 60 minutes, when the infusion ended, the median NRS pain score was 5, 25 patients (65%) had a clinically significant decrease in NRS score and the median score had increased from its nadir in only nine patients. At 120 minutes (60 minutes after the infusion ended and the last optional dose of morphine), the median NRS pain score was still four and 26 patients (68%) had a clinical significance decrease in NRS score.

A total of 22 patients (58%) received pain medication prior to enrollment in the study; most were administered 0.5–2 mg IV hydromorphone or an equipotent dose of IV morphine. At 20, 40, and 60 minutes, 16 patients (42%), 19 (50%), and 11 (28%), respectively, requested supplemental morphine. Twelve patients, nearly one-third the cohort, refused all three offers of supplemental morphine. Among these 12 patients, median NRS pain scores were noticeably lower (Figure 1—dashed line). In addition, the percentage of patients experiencing a clinically significant decrease of 3 or more points on the NRS scale was noticeably higher in this group. At 10, 60, and 120 minutes, the percentage of patients reaching this outcome in the ketamine alone group vs ketamine and optional morphine group was 75% to 36%, 100% to 53%, and 83% to 61%, respectively.

With few exceptions, the subject's HR, blood pressure, and oxygen saturation remained stable during and after the ketamine infusion and did not exhibit a clinically significant change from baseline levels. At times zero, 10 and 30 minutes, the respective mean SBPs and HRs were 133 (95% CI 126–140) and 89 (95% CI 84–94), 141 (95% CI 131–148) and 92 (95% CI 87–97), and 134 (95% CI 127–141) and 90 (95% CI 85–95). At 10 minutes, three subjects experienced an asymptomatic increase in SBP of greater than 20 mm Hg; in two cases, it returned to baseline spontaneously within 10 minutes. There were no other events meeting our definition of an adverse event.

Level of sedation was assessed 12 times over 2 hours in each subject, for a total of 456 observations. In 436 observations, sedation was rated as minimal, defined as normal response to verbal stimuli. In 20 observations, moderate sedation was found, defined as purposeful response to verbal or light tactile stimulation. No subject experienced deep sedation, required MD intervention or transfer to a higher acuity ED bed for monitoring. We did not detect a delay in diagnosis or critical intervention or change in disposition that was due to the low-dose ketamine infusion. Ultimately, 18 subjects (47%) were discharged home and the rest were admitted. Median time to discharge from the end of the study protocol was approximately 2 hours.

Sixty minutes following treatment with ketamine, 33 (86%) patients reported experiencing some dissociative spectrum side effects on the SERSDA (Table 1). While 20 patients (53%) reported only weak or modest side effects, 13 (34%) rated one or more side effects as "very bothersome." The most commonly reported side effects were dizziness (22 patients), fatigue (23), nausea (16), and feelings of unreality (15). No patient reported hallucinations or became agitated. When queried afterward, 32 patients (84%) responded they would have ketamine again. Despite evidently profound pain relief achieved in the group receiving ketamine alone (Figure 1—dashed line), their satisfaction scores were similar to those of subjects who requested additional morphine.

We analyzed patients identified as study candidates but not enrolled by the attending physician for evidence of selection bias. The most common reasons cited were discharge anticipated in < 2 hours and pain already controlled. Among predefined exclusion criteria, language barrier and altered level of consciousness or intoxication were the most common reasons. We found no pattern to suggest subjective bias in the selection of patients.

Discussion

We found a low-dose ketamine bolus followed by infusion provided clinically significant and lasting pain relief up to 1 hour after the infusion ended. Moreover, we observed inconsistent but profound, pain relief (NRS 0) in a subset (18%) of patients. A significant proportion of patients (34%) reported psychomimetic side effects that were very bothersome, however, overall patient satisfaction was high (84% patients responded that they would have ketamine again). We observed no severe adverse events. Although, the generalizability of our results are limited by the lack of a control arm; the reduction in pain scores we observed was similar to that typically observed with IV opioids [19].

Despite multiple studies demonstrating consistent analgesic and opioid sparing benefits in perioperative settings, there are no studies to date of low-dose ketamine

Table 1 Analgesic and side effect of low-dose ketamine bolus and 1-hour infusion by chief complaint and use of rescue morphine

Age	Sex	Chief Complaint	Pain Intensity (Numerical Rating Score)			Total Rescue Morphine (mg)*	Side Effects Rating Scale for Dissociative Anesthetic	Would have Medicine Again†
			Initial	10 min	60 min		Bothersome or Very Bothersome	
Ketamine + Morphine								
21	M	Abdominal pain	8	8	5	12	Dizziness, Nausea	Yes
40	M	Abdominal pain	7	5	1	12	Fatigue	Yes
48	F	Abdominal pain	9	7	7	8		Yes
32	M	Abdominal pain	9	2	0	4	Fatigue, Dizziness, Nausea, Generalized discomfort	Yes
33	F	Abdominal pain	9	8	6	8		Yes
46	M	Abdominal pain	10	10	10	12		Yes
47	M	Abdominal pain	10	8	5	4		Yes
40	M	Abdominal pain	9	0	1	4		Yes
43	M	Abdominal pain	9	4	6	4		Yes
48	F	Abscess	10	9	10	8	Fatigue, Dizziness, Mood changes, Generalized discomfort	No
53	M	Abscess	8	0	0	4		Yes
44	M	Abscess	10	8	8	12		No
59	M	Cellulitis	7	5	4	4		Yes
30	F	Chest pain	6	3	5	8	Dizziness, Headache	No
52	F	Chest pain	10	5	7	4	Headache	Yes
27	M	Decubitus ulcers	9	8	7	8	Dizziness	Yes
32	M	Decubitus ulcers	8	7	6	8	Generalized discomfort	Yes
40	F	Fibromyalgia	10	5	7	12		Yes
21	M	Fracture	8	6	7	8		Yes
21	M	Flank pain	9	0	7	12	Nausea	Yes
56	M	Flank pain	8	7	5	4		Yes
51	F	Flank pain	9	5	2	4		Yes
52	M	Joint pain	9	8	7	8	Fatigue, Dizziness, Nausea, Feelings of unreality, Mood changes	Yes
27	F	Sickle cell crisis	10	7	6	4	Headache, Generalized discomfort	Yes
55	F	Sickle cell crisis	6	4	4	12	Nausea	Yes
43	F	Sickle cell crisis	6	6	6	12	Dizziness, Nausea	No
Ketamine alone								
32	M	Abdominal pain	9	6	5	0		Yes
31	M	Abdominal pain	8	5	2	0	Changes in vision	Yes
64	M	Abdominal pain	9	7	4	0		No
52	M	Abscess	9	0	0	0		Yes
56	F	Back pain	9	6	0	0		Yes
45	M	Burn	6	0	0	0	Nausea	Yes
51	M	Chest pain	8	0	0	0	Fatigue, Dizziness, Headache, Feelings of unreality, Mood changes	No
66	F	Chest pain	9	0	0	0	Feelings of unreality, Changes in hearing, Changes in vision	Yes
63	M	Cancer	9	3	0	0	Dizziness, Feelings of unreality	Yes
30	F	Flank pain	7	3	1	0		Yes
25	F	Headache	9	4	0	0		Yes
64	F	Hip fracture	10	3	3	0		Yes

Min indicates minutes after initial injection study analgesics.

* Ketamine bolus 15 mg bolus IV followed by 20 mg/h IV infusion begun at time zero. Morphine 4 mg IV was offered at 20, 40, and 60 minutes to patients regardless of reported pain score.

† Patients were asked "Would have this medication again for similar pain?"

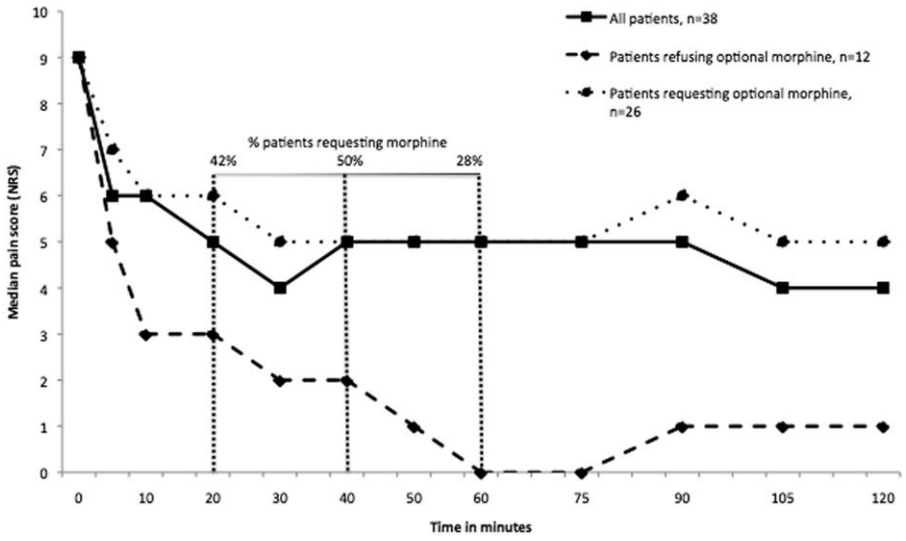

Figure 1 Median pain scores, as assessed on a 10-point NRS, during the 120-minute study protocol. Subjects received a 15 mg IV ketamine bolus at time 0, followed immediately by a 20 mg IV ketamine infusion over 60 minutes. Separate trend lines show median pain score in subjects that refused morphine and those that requested morphine. The percentage of patients requesting optional 4 mg IV morphine at 20, 40, and 60 minutes is shown at top of dashed vertical line.

infusions in the ED [12,14–16]. Ketamine bolus doses ranging from 0.2 to 0.5 mg/kg IV or intramuscular (IM) followed by similarly dosed infusions have consistently resulted in less opioid use and improved pain scores with side effects similar to those in control groups. The largest of these studies, by Remerand et al., also found that the ketamine infusion group had improved rehabilitation and decreased postoperative pain 5 months after surgery, suggesting that ketamine may promote a long lasting antihyperalgesic state [12]. Our data support the prima facie assumption that ketamine's effects of on acute pain should be similar in the emergency and perioperative settings.

Ketamine administered as a single 15 mg IV bolus produces rapid and profound analgesia in an average sized adult, but the effect is short lived. This is distinct from the more gradual onset and sustained analgesic effect of opioids [20–31]. We found that the majority of subjects in our study experienced significant pain relief at 10 minutes, reflecting the predictably strong analgesic effect of a 15 mg ketamine bolus. However, the median NRS scores did not decline as much over a similar time interval as in our previous ketamine study in which the ketamine bolus was delivered in combination with hydromorphone [1]. This finding underscores the point that low-dose ketamine and opioids likely act synergistically. But unlike the previous study where many patients experienced a rebound in pain 10 minutes after the bolus, in this study, median pain scores remained generally low throughout the 1-hour infusion period. Furthermore, the analgesic effect of ketamine seemed to be sustained after the infusion ended, with a median NRS of 4 1 hour later, despite no rescue analgesia being allowed (See Figure 1).

While a majority of subjects requested morphine at some point, there were 12 (31%) who did not; this subgroup of patients also experienced the most profound pain relief (Figure 1—dashed line). This finding raises the intriguing idea that there are ketamine responders. A similar phenomenon is thought to occur with opioids [32]. Unfortunately, our responder subgroup had no clear unifying characteristics (Table 1—ketamine alone). Interestingly, the reported satisfaction scores did not differ between responders and other subjects. Larger studies are needed to further elucidate the observed heterogeneity in patient response to ketamine.

We found that mild to moderate, self-limited psychomimetic side effects were common. However, no side effects changed management or required intervention. Moreover, nearly 85% of patients reported they would have ketamine again for similar pain. This suggests that patients were willing to accept side effects when their pain was so well controlled, or that side effects, although rated as bothersome while occurring, in retrospect were viewed as not unpleasant. Concerns over adverse psychomimetic affects, particularly emergence phenomena, have traditionally limited widespread use of low-dose ketamine in adult ED patients [7,33,34]. Our results confirm those of prior studies of low-dose ketamine infusions [12,14–16] showing that such events are extremely rare.

Adoption of low-dose ketamine infusions might also meet resistance because of concerns about unexpected deep sedation. Ketamine is categorized as an anesthetic on many hospital formularies. Our low-dose ketamine bolus and infusion protocol resulted in only minimal sedation in over 99% of observations. Minimal sedation requires no specialized monitoring equipment or training. Moderate sedation, defined as "purposeful response to verbal or tactile stimulation" by ASA guidelines, occurred transiently in eight subjects, accounting for 20 of 480 total observations [17]. None of these subjects experienced hypoxia or other vital signs changes, required supplemental oxygen, or required nurse or physician intervention. Thus, we did not find the distinction between minimal and moderate sedation to be clinically important. Furthermore, it is important to mention that moderate sedation is common with opioids, in which case it may be accompanied by respiratory depression and hypotension. Our results support the contention that no special monitoring is required for low-dose ketamine bolus and infusion in adults.

Our study has a number of limitations. To approximate usual ED practice, our ketamine infusion protocol differed in a number of ways from previous perioperative studies. For example, we did not exclude subjects from our study that had received opioids prior to the ketamine infusion, (although opioids were not allowed during the first 20 minutes of the infusion), which may have confounded data regarding the analgesic effect of the ketamine bolus. Our infusion was relatively brief (1 hour) and over half of subjects (57%) were discharged home after the study. We were required to have a relatively short observation period, which limited the assessment of any lasting pain relief associated with ketamine. As patient controlled analgesia is rarely used in EDs, subjects were simply asked at set intervals if additional pain medication was desired, but this provided less robust data on opioid sparing than is available from perioperative studies.

There was no comparison group and RA's who were aware of the study objective collected data. In addition, the effect of RAs at the bedside throughout the study protocol is difficult to predict. Their physical, comforting presence may have been antinocioceptive for some subjects, whereas the RAs frequently asking subjects to rate pain may have been pronocioceptive. Convenience sampling is another limitation; the study population is not truly unselected, although the causes of pain were fairly diverse. While side effects were an important outcome, our study design does not allow us to definitely ascribe side effects to either ketamine or morphine. Lastly, the SERSDA scale has rarely been used in ED research; it may have proven too sensitive to minor side effects and comparison to other ED studies may be difficult [18].

Based on the results of this study, prior research [1,35] and 2 years of anecdotal experience in our ED, we suggest the following: low-dose ketamine given as an IV bolus (0.1–0.3 mg/kg, or 5–15 mg in most patients) is not only feasible and can be used routinely in the ED, but when combined with opioids, provides optimal pain relief. Opioid doses should generally be reduced. To minimize psychomimetic side effects from ketamine, the initial bolus can be given over 5–10 minutes. Also, patients should be warned in advance that they might experience a sensation unlike that of other pain medications and be assured that, although strange, the sensation may not be unpleasant, and resolves within minutes. In addition, we recommend selective use of NSAIDs, acetaminophen, gabapentin, and antiemetics as clinically indicated, with care to avoid over-sedation. This multimodal approach to pain management targets multiple pain receptors at once in the hope of achieving better acute analgesia as well as decreasing downstream chronic pain and hypersensitivity syndromes.

The decision to start a low-dose ketamine infusion should be based on several factors: chief complaint, level of pain, anticipated length of ED stay, response to opioids and initial ketamine bolus, degree of opioid tolerance, and other harder to define subjective factors. Ideal patient selection is a challenge and there is no prior literature from the ED setting to guide treatment. Based on this study, we believe there is promise in the use of low-dose ketamine bolus plus infusion in patients with undifferentiated abdominal pain, trauma, musculoskeletal pain, sickle cell pain, cancer pain, and in those with known opioid tolerance. Ketamine should be used with caution in patients with known cardiovascular disease, chest pain, or shortness of breath, although we did include such patients in our cohort.

In conclusion, our results suggest that low-dose ketamine infusions have a role in the ED pain management armamentarium. Our analgesic efficacy and feasibility data provide a basis for a future large comparative trial with opioids.

References

1 Ahern T, Herring A, Stone M, Frazee B. 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.

2 Galinski M, Dolveck F, Combes X, et al. Management of severe acute pain in emergency settings: Ketamine reduces morphine consumption. Am J Emerg Med 2007;25(4):385–90.

3 Jennings PA, Cameron P, Bernard S, 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):497–50.

4 Jennings P, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: A systematic review. Acta Anaesthesiol Scand 2011;55(6):638–43.

5 Johansson P, Kongstad P, Johansson A. The effect of combined treatment with morphine sulfate and

low-dose ketamine in the pre-hospital setting. Scand J Trauma Resusc Emerg Med 2009;17:61.

6 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.

7 Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: A review of current techniques and outcomes. Pain 1999;82(2):111–25.

8 Weinbraum AA. Non-opioid IV adjuvants in the perioperative period: Pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacol Res 2012;65(4):411–29.

9 De Pinto M, Jalacic J, Edwards WT. Very-low-dose ketamine for the management of pain and sedation in the ICU. J Opioid Manag 2008;4(1):54–6.

10 Finkel LC, Pestieau SR, Quezado ZM. Ketamine as an adjuvant for treatment of cancer pain in children and adolescents. J Pain 2007;8(6):515–21.

11 Mercadante S. Ketamine in cancer pain: An update. Palliat Med 1996;10(3):225–30.

12 Remerand F, Le Tendre E, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: A prospective, randomized, controlled, double-blinded trial. Anesth Analg 2009;109: 1963–71.

13 Stoddard FJ, Sheridan RL, Saxe GN, et al. Treatment of pain in acutely burned children. J Burn Care Rehabil 2002;23(2):135–56.

14 Suppa E, Valente A, Catarci S, Zanfini BA, Draisci G. A study of low dose S-ketamine infusion as "preventative" pain treatment for cesarean section with spinal anesthesia: Benefits and side effects. Minerva Anestesiol 2012;78:774–81.

15 Urban M, Ya J, Wukovitz B, Lipnitsky JY. Ketamine as an adjunct to postoperative pain management in opiate tolerant patients after spinal fusions: A prospective randomized trial. HSS J 2008;4:62–5.

16 Zeinaly MB, Zeinaly A, Aghdashi MM, et al. Evaluation of the analgesic and side effects of low dose ketamine infusion for postoperative pain management after abdominal hysterectomy. Am J Sci Res 2012;51:117–21.

17 American Society of Anesthesiologists. Practive guidelines for sedation and analesia by non-anesthesiologists: An updated report by the American Society of Anesthesiologist Task Force on sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004–17.

18 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. J Pain 1994;61(2):347.

19 O'Connor AB, Zwemer FL, Hays DP, Feng C. Intravenous opioid dosing and outcomes in emergency patients: A prospective cohort analysis. Am J Emerg Med 2010;28(9):1041–50.

20 Haas DA, Harger DG. Ketamine: A review of its pharmacologic properties and use in ambulatory anesthesia. Anesth Prog 1992;39(3):61–8.

21 Reich DL, Silvay G. Ketamine: An update on the first twenty-five years of clinical experience. Can J of Anesth 1989;36(2):186–97.

22 Sadove MS, Shulman M, Hatano S, Fevold N. Analgesic effects of ketamine administered in subdissociative doses. Anesth Analg 1971;50(3):452–7.

23 Childers WE, Jr., Baudy RB. N-methyl-D-aspartate antagonists and neuropathic pain: The search for relief. J Med Chem 2007;50(11):2557–62.

24 Corchs F, Mercante JP, Guendler VZ, et al. Sensitivity to aversive stimulation, posttraumatic symptoms and migraines: What do they have in common? Med Hypotheses 2011;77:534–5.

25 Dickenson AH. NMDA receptor antagonists: Interactions with opioids. Acta Anaesthesiol Scand 1997;41:112–5.

26 Fishman SM. Listening to Pain: A physician's Guide to Improving Pain Management Through Better Communication. New York: Oxford University Press; 2012.

27 Koppert W, Dern SK, Sittl R, et al. A new model of electrically evoked pain and hyperalgesia in human skin: The effects of intravenous alfentanil, S +-ketamine, and lidocaine. Anesthesiology 2001;95(2):395.

28 Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: Physiological pathways and pharmacological modalities. Can J Anesth 2001;48(10):1000–10.

29 Bell, RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006;1:CD004603.

30 Bilgin H, Ozcan B, Bilgin T, et al. The influence of timing of systemic ketamine administration on

postoperative morphine comsumption. J Clin Anesth 2005;17:592–597.

31 Ahmadi O, Isfahani MN, Feizi AJ. Comparing low-dose intravenous ketamine-midazolam with intravenous morphine with respect to pain control in patients with closed limb fracture. Res Med Sci 2014;19(6):502–8.

32 Smith HS. Variations in opiate responsiveness. Pain Physician 2008;11:237–48.

33 Rowland LM. Subanesthetic ketamine: How it alters physiology and behavior in humans. Aviat Space Environ Med 2005;76:C52.

34 Carr DB, Goudas LC, Denman WT, et al. Safety and efficacy of intranasal ketamine in a mixed population with chronic pain. J Pain 2004;110(3):762–4.

35 Herring A, Ahern T, Stone M, Frazee B. Emerging applications of low-dose ketamine for pain management in the emergency department. Am J Emerg Med 2013;31(2):416–9.