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Low dose ketamine use in the emergency department, a new direction in pain management

A Pourmand [a,*], M Mazer-Amirshahi [b], C Royall [a], R Alhawas [a], R Shesser [a]

[a] Emergency Medicine Department, George Washington University, Washington DC, United States
[b] Emergency Medicine Department, MedStar Washington Hospital Center, Washington DC, United States

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ABSTRACT

There is a need for alternative non-opioid analgesics for the treatment of acute, chronic, and refractory pain in the emergency department (ED). Ketamine is a fast acting N-methyl-D-aspartate (NMDA) receptor antagonist that provides safe and effective analgesia. The use of low dose ketamine (LDK) (<1 mg/kg) provides sub-dissociative levels of analgesia and has been studied as an alternative and/or adjunct to opioid analgesics. We reviewed 11 studies using LDK either alone or in combination with opioid analgesics in the ED. Ketamine was shown to be efficacious at treating a variety of painful conditions. It has a favorable adverse effect profile when given at sub-dissociative doses. Studies have also compared LDK to opioids in the ED. Although ketamine's analgesic effects were not shown to be superior, they were comparable to opioids. LDK has the benefit of causing less respiratory depression. It likely has less wide spread potential for abuse. Nursing protocols for the administration of LDK have been studied. We believe that LDK has the potential to be a safe and effective alternative and/or adjunct to opioid analgesics in the ED. Additional studies are needed to expand upon and determine the optimal use of LDK in the ED.

1. Introduction

The US is amidst of an epidemic of opioid misuse, abuse, and diversion [1-3]. In the past decade, a 300% increase in opioid analgesic prescribing has been accompanied by a three-fold increase in drug overdose deaths and a two-fold increase in emergency departments (ED) visits for opioid misuse and abuse [4,5]. Opioid analgesics are commonly administered and prescribed from the ED; however, the ED's contribution to the current epidemic remains unclear [6]. In addition, patients are commonly treated with opioid analgesics for a variety of conditions in the outpatient setting and may be tolerant, making pain management in the ED more challenging. The use of high doses of opioid analgesics has been associated with life-threatening adverse effects, secondary to respiratory depression [7,8]. In an effort to curb opioid misuse and abuse, as well as to promote safe and rational opioid prescribing, there has been a renewed interest in alternative non-opioid analgesics.

Low dose ketamine (LDK) has emerged as a safe and effective non-opioid alternative for patients with chronic or refractory as well as acute pain. Ketamine is a distinct pharmacologic agent with a unique mechanism of action and adverse effect profile. It is not simply an "opioid substitute". LDK can be used in the ED in a variety of clinical situations. It can be used for patients who need analgesia prior to an awake procedure. LDK can also be used in the setting of an acute exacerbation of pain in patients that are at high-risk of adverse effects from opioids and when other non-opioid therapies (such as non-steroidal anti-inflammatory drugs) have failed. Ketamine may also be useful to treat acute pain in the setting of hemodynamic instability [9]. Some particularly challenging groups are patients presenting with acute exacerbations of nonmalignant chronic painful conditions such as sickle cell anemia [10], dento-facial pain syndromes [11], headaches [12], axial skeletal pain [13,14], and gastroparesis. Patients with malignant and non-malignant chronic pain are often on high-dose opioid analgesics at baseline, making their pain difficult to manage in the ED. Ketamine infusion may be of utility in opioid-tolerant patients with acute intractable exacerbations of chronic pain by a proposed mechanism of re-sensitizing to their opioid regimen [15]. In recent years, there has been a renewed interest in and study of ketamine in the ED. This review will focus on the use of LDK for the acute treatment of pain, with a focus on its utilization in the ED setting.

2. Ketamine mechanism of action and pharmacokinetics

Ketamine is a well-known *N*-methyl-D-aspartate (NMDA) receptor antagonist. One of the normal functions of the NMDA receptor is to potentiate painful stimuli, which may lead to a "hyperalgesia" or "central

* Corresponding author at: Department of Emergency Medicine, George Washington University, Medical Center, 2120 L St. NW, Washington DC 20037, United States.
E-mail address: apourmand@mfa.gwu.edu (A. Pourmand).

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sensitization". Ketamine's analgesic effect has been attributed, in part, to its ability to block this sensitization [16]. Ketamine is a non-competitive NMDA receptor antagonist with a, "slow off rate" causing a prolonged tonic blockade of the receptor contributing to long lasting analgesic effects [17]. Ketamine also has direct effects on the delta opioid receptor and acts to augment opioid mu-receptor function [17]. The way by which ketamine augments opioid receptor function has been attributed to downstream effects involving the extracellular signal-regulated kinase 1/2 (ERK1/2). Ketamine potentiates opioid induced ERK1/2 phosphorylation, requiring lower opioid doses for equal phosphorylation [18]. Ketamine has also been shown to delay desensitization and improve re-sensitization of opioid receptors resulting in prolonged overall effect of opioid stimulation, which may be useful in patients with opioid-related hyperalgesia [18].

Ketamine has a high first pass metabolism. The oral availability is between 17 and 24% for racemic ketamine and 8–11% for S-ketamine [19]. Intramuscular bioavailability is 90–93%. Ketamine is initially distributed to highly perfused tissues such as the brain, lungs, and heart where it can reach up to 5 times plasma concentrations [20]. Ketamine is metabolized by CYP3A and CYP2B6 through *N*-demethylation to norketamine, which has about one-third of the activity of ketamine [19,20]. The only absolute contraindication to ketamine is for patients who have an allergy to ketamine. Relative contraindications include: moderate to severe hypertension, congestive heart failure, pregnancy, or acute alcohol intoxication [20]. Traditionally, there has been a theoretical concern that ketamine can cause increased intracranial pressure, but recent studies have demonstrated ketamine does not significantly increase intracranial pressure [21,22,23]. Ketamine use has been reported to result in an emergence delirium or emergence reaction. This phenomenon includes alterations in mood and body image, dissociative experiences, vivid dreams and illusions, and delirium. This reaction may be more frequent with larger doses of ketamine, in patients older than 16 years of age, and in female patients [24].

3. Low dose ketamine

Ketamine has been used extensively in the ED at doses above 1 mg/kg for procedural sedation. LDK has gained interest in the ED in recent years. LDK aims to provide analgesia without producing the dissociative effects present at higher doses. For the purpose of this review, we focused on the ED use of ketamine for analgesic purposes, at doses below 1 mg/kg, also known as sub-dissociative or LDK. We located and reviewed 11 articles focusing on ketamine use in the ED at doses under 1 mg/kg, administered via intravenous (IV) bolus, IV infusion, or a combination of the two for the treatment of pain. Six studies used bolus doses only, with doses ranging from 0.1 mg to 0.6 mg/kg [25-30]. Three studies used a combination of an IV bolus dose followed by a brief infusion. Bolus doses were between 0.2 mg/kg and 0.25 mg/kg and infusion doses used were between 0.1 mg/kg/h and 0.2 mg/kg/h of continuous infusion [25,31,33]. Three studies used infusions without an initial bolus; infusion doses ranged from 0.2 to 0.4 mg/kg and infusion times ranged from 5 min to 15 min [25,32,34].

The goal of using LDK is to provide analgesia without producing the adverse effects that occur more frequently at higher doses. LDK has been found to be safe and effective as an analgesic with a favorable adverse effect profile. Within the studies reviewed, 1187 patients received LDK. The most common adverse effects were dizziness, nausea, vomiting, and mild neuropsychological reactions such as hallucinations or agitation [25-26,28-34]. Almost all of these adverse effects resolved spontaneously. The majority of studies reported no emergence phenomenon, which is a concern when using ketamine. Two studies labeled adverse reactions as emergence phenomenon [25,29]. One reported 6 of 63 patients experienced emergence phenomenon although there was no description of what was qualified as an emergence reaction [29]. Another study reported only 1 out of 428 patients with emergence phenomenon and again the exact phenomenon was not specifically described [25]. Ahern et al. reported one patient with metastatic cancer who was noted to, "open his eyes widely and scream while pulling at the gurney side rails" after receiving ketamine 15 mg IV and fentanyl 50 mcg IV. He was treated with lorazepam resulting in resolution of his symptoms [30]. Three studies reported no significant changes in heart rate, blood pressure, respiratory rate, and pulse oximetry after the administration of LDK [30,31,33]. One of these studies reported 3 patients who had an increase in systolic blood pressure >20 mmHg at 10 min after ketamine dose, 2 of which returned to baseline systolic blood pressure spontaneously after 10 min [31]. Two additional studies showed no statistically significant change in vital signs [30,33]. Another study examining 530 LDK cases concluded that LDK is feasible and safe for the treatment of a broad range of painful conditions. The reported adverse event rate including psychomimetic or dysphoric reactions, transient hypoxia, emesis was 6% overall and these events were easily identified and dealt with by ED staff. None of the adverse events changed disposition [26].

In most cases, the side effect profile of LDK should not be a deterrent to its use in the ED (Table 1). We recommend that patients who are to administered LDK receive an adequate explanation of potential adverse effects of the medication prior to administration when it is feasible. This explanation should specifically focus on possibility of emergence phenomenon.

4. Types of pain treated with LDK

Many types of pain were addressed in the 11 studies we reviewed. Four studies focused on LDK for orthopedic fractures or dislocations that did not require procedural sedation [25,29,33]. LDK use for awake patients undergoing incision and drainage procedures were also included [22,24]. One study focused specifically on pain from sickle cell crisis. Others included a broad range of moderate to severe pain such as abdominal pain, back pain, chest pain, skin and soft tissue infections and musculoskeletal pain [25,26,28,31,32,34]. For all of these types of pain ketamine was deemed to be safe and effective in the ED [25,26,28,29,31,32,34,35].

5. LDK administration and dosing

In a study by Ahern et al., LDK was given as an IV bolus followed by an infusion. The authors concluded LDK provided clinically significant pain relief during and one hour after the infusion [28]. They noted that LDK given as a bolus produces rapid and profound analgesia that is usually short lived, but when given with an infusion, is longer lasting [31]. At 120 min (60 min after the infusion ended), the median pain score was 4/10. Sixty-eight percent of patients still had a clinically significant reduction in their numeric rating scale (NRS) score. In their study, 84% of patients responded that they would accept ketamine treatment again. However, the authors observed that profound pain relief was inconsistent and suggested there may be a subset of ketamine responding patients [31]. Two additional studies we reviewed examined LDK infusions. One found that 71% of patients with pain, some with chronic pain (10/14), and many who had already received opioids (12/14), who received a LDK infusion had significantly reduced pain scores [32].

Another study compared LDK infusion to saline infusion following a bolus of both ketamine and morphine. Their results showed that continuous ketamine infusion did not significantly decrease morphine requirements in pre-hospital trauma patients, although neither group required a significant amount of opioids following initial bolus. The patients were only followed for a median time of 35 min following initial bolus [33].

In a study by Miller et al., 0.3 mg/kg of ketamine was compared to 0.1 mg/kg of intravenous morphine. They found that ketamine, although not superior, was found to have comparable reductions in pain scores to morphine. A major difference they reported was the onset of maximal effect. LDK's maximum change in numerical rating scale for

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Table 1
Low dose ketamine efficacy studies.

Study	Design	LDK dose	# of patients	Conclusion	Adverse effects
Sin B. et al., 2015 [25]	Review of 4 RCTs using LDK	0.2–0.5 mg/kg IV (some followed by infusion.)	428	2 studies showed a significant reduction in pain scores. 2 studies showed no significant difference.	2 studies showed nausea and vomiting 2 studies showed neuropsychological, none of which required intervention.
Ahern T.L. et al., 2015 [26]	Retrospective case series	Most received 10–15 mg	530	Use of LDK as an analgesic in a diverse ED population appears to be safe and feasible for treatment of many types of pain.	Only 30 (6%) patients met criteria for adverse event.
Herring A.A. et al., 2013 [27]	Describes 3 cases of LDK use in the ED	15 mg IV	3	LDK is a promising analgesic agent for ED use.	NA
Lester L. et al., 2010 [28]	Retrospective case series	0.1–0.6 mg/kg	35	The administration of LDK in the ED may be a safe and effective adjunct for analgesia in some patients.	No significant adverse events were identified in any of the 35 cases.
Majidinejad S. et al., 2014 [29]	Double blind RCT	0.5 mg/kg	126	Administration of LDK results in a significant decrease in the severity of acute pain in patients with fractures of long bones.	6 patients developed emergence phenomenon (emergence phenomenon not defined)
Richards J.R. et al., 2013 [30]	Survey of patients and their treating clinicians regarding LDK for analgesia	Average dose was 22.2 ± 11.2 mg	24	Most were satisfied with LDK and would use it again. Physicians believed that ketamine is underused.	4 patients reported and adverse experience, but there were no emergence reactions.
Ahern T.L. et al., 2015 [31]	Prospective, non randomized, non-blinded trial.	15 mg IV push followed by 20 mg IV infusion over 60 min.	38	A LDK infusion protocol provided significant pain relief.	LDK infusion resulted in mostly mild side effects and no severe adverse events.
Wiel E. et al., 2015 [32]	Prospective, multicenter, randomized, single blind, controlled trial.	0.2 mg/kg IV bolus followed by continuous 0.2 mg/kg/h infusion.	63	Continuous LDK infusion did not significantly decrease morphine requirements in pre-hospital trauma patients.	No significant differences in terms of central neurologic disorders or excessive sedation were found. A higher systolic blood pressure has been shown in the ketamine group without clinical consequences.
Goltser A. et al., 2015 [33]	Case report series	0.2–0.4 mg/kg infusion	14	Ketamine infusion is a potentially enticing alternative to ketamine push for having less incidence of adverse effects of ketamine while maintaining ketamine's proven analgesic efficacy.	Most of the reported side effects were mild, and none of the patients had to stop infusions because of the side effects.
Miller J.P. et al., 2015 [34]	Double blind randomized control trial	0.3 mg/kg IV	45	LDK did not produce a greater reduction in NRS pain scores compared with morphine for acute pain in the ED. However, LDK induced a significant analgesic effect within 5 min and provided a moderate reduction in pain for 2 h.	Vital signs and adverse events were similar between the two groups.
Uprety D. et al., 2014 [35]	Case report	NA	1	LDK can be an option for control when hyperalgesia due to opioids is identified.	NA

Emergency department (ED), low dose ketamine (LDK), numeric rating scale (NRS).

pain was 4.9 (95% CI 5.8-4), which occurred at 5 min following administration whereas morphine's maximum pain scale reduction was 5 (95% CI 6.6-3.5) at 100 min. In general, morphine had a steady reduction in pain over time while LDK showed a rapid decrease in pain followed by increasing pain scores. However, the LDK group had a >50% decrease in pain scores from baseline for 2 h following administration [34]. In a randomized, controlled trial in patients with long bone fractures, LDK 0.5 mg/kg was compared to morphine 0.1 mg/kg. LDK was found to have significant decrease in the severity of acute pain at 10 min after the dose. This study reported that this onset of effect was similar to the morphine group. Pain severity in the LDK group decreased 2.7 ± 1.8, $P < 0.0001$, and in the morphine group 2.4 ± 1.4, $P < 0.0001$.This study noted that adverse events were higher in the ketamine group but concluded that these complications should not preclude the use of ketamine as all effects resolved spontaneously without therapeutic intervention [29]. Both of these studies concurred that ketamine, although not superior to morphine, provides similar and significant pain reduction with a reasonably safe adverse effect profile [29,34].

Ketamine has been specifically studied as an adjuvant to opioids in patients with difficult to treat painful conditions such as sickle cell crisis and in patients who may be tolerant to opioids [28,30,35]. Richards et al., looked at patient and physician satisfaction with LDK in these often opioid tolerant patients. They showed that overall patient satisfaction was 55% and physician satisfaction was 72%. Reasonably, 67% of the patients reported they would prefer LDK again and 96% of physicians would use LDK again. This study also reported a significant reduction in pain with LDK use from 8.9 ± 2.1 to 3.9 ± 3.4 $P < 0.0001$ [30]. Lester et al., reported use of LDK in 34 patients. The authors concluded that LDK might provide a safe and effective analgesic adjunct particularly in patients with high opioid tolerance [28].

6. Nursing and monitoring considerations for LDK administration

One of the major challenges limiting the use of LDK in many ED's is the level of familiarity and comfort, not only of the physicians, but also the nursing team. This has been due to multiple factors. The “the standard practice” of treating patients in pain in the ED is with opioids. There may be a lack of experience using ketamine outside of the operating room and beyond procedural sedation [36]. Several nursing protocols have been published in various states and institutions. Some of these protocols have suggested that ketamine should be administered under the supervision of a pain specialist or an anesthesiologist. Many others are less restrictive [37,38,39,40]. Existing protocols also provide monitoring parameters and duration advise for the administration of LDK. They can serve as a basis for new ED based-nursing protocols. In 2012, the Texas Board of Nursing (BON) issued a statement regarding the use of IV LDK for pain management [37]. They stated that it had been shown to be safe, but should be administered under the orders of a pain specialist or an anesthesiologist. They also outlined on their website a series of 6 yes/no questions that nurses can use as a tool to assess the safety of LDK if uncertainty is present. The Nebraska BON [38] and the New York State BON issued guidelines in 2013 [39]. The

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Wyoming BON issued guidelines regarding appropriate candidates for LDK, but did not limit it to orders of an anesthesiologist [40]. The American College of Emergency Physicians (ACEP) and Emergency Nurses Association issued a Clinical Policy in Annals of Emergency Medicine in 2014 regarding "Procedural Sedation and Analgesia in the ED", supporting the delivery of sedation and analgesia medications including ketamine by an ED nurse under the supervision of an emergency physician [41].

Many protocols and guidelines annotate the potential adverse effects of and cautions regarding to ketamine administration. They agree on the need to monitor hemodynamic and mental status of the patients. Monitoring parameters include pulse oximetry, blood pressure, telemetry, and mental status [37,28,39,40]. One article argues that monitoring parameters should not differ from the parameters of opioids, which is "the standard practice" [42]. It should be considered that opioids can cause more respiratory depression than LDK [43]. Notwithstanding, it is important that ED nurses and physicians who administer LDK are cognizant of and follow institutional guidelines regarding the use of this medication.

7. Conclusion

Low dose ketamine has been shown to be safe and effective for the treatment of a wide variety of painful conditions in the ED. Although LDK is not superior to opioids in reduction of pain scores, it does have comparable pain reduction. It may have the benefit of less respiratory depression, compared with high dose of IV opioids. Ketamine has less potential for addiction or epidemic overuse. In addition, it is effective for the management of pain exacerbations in opioid tolerant patients. Emergence phenomenon is unusual when low doses are used and when reported, it is mild and transient. Additional studies are needed to expand upon and determine the optimal use of ketamine in the ED.

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