Original Contributions

The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED

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Abstract

Objectives: The objective of this study is to describe the clinical use and safety profile of low-dose ketamine (LDK) (0.1-0.3 mg/kg) for pain management in the emergency department (ED).

Methods: This was a retrospective case series of consecutive patients given LDK for pain at a single urban ED between 2012 and 2013. Using a standardized data abstraction form, 2 physicians reviewed patient records to determine demographics, indication, dose, route, disposition, and occurrence of adverse events. Adverse events were categorized as minor (emesis, psychomimetic or dysphoric reaction, and transient hypoxia) and serious (apnea, laryngospasm, hypertensive emergency, and cardiac arrest). Additional parameters measured were heart rate and systolic blood pressure.

Results: Five hundred thirty patients received LDK in the ED over a 2-year period. Indications for LDK were diverse. Median patient age was 41 years, 55% were women, and 63% were discharged. Route of administration was intravenous in 93% and intramuscular in 7%. Most patients (92%) received a dose of 10 to 15 mg. Comorbid diseases included hypertension (26%), psychiatric disorder (12%), obstructive airway disease (11%), and coronary artery disease (4%). There was no significant change in heart rate or systolic blood pressure. Thirty patients (6%) met our criteria for adverse events. Eighteen patients (3.5%) experienced psychomimetic or dysphoric reactions. Seven patients (1.5%) developed transient hypoxia. Five patients (1%) had emesis. There were no cases of serious adverse events. Agreement between abstractors was almost perfect.

Conclusion: Use of LDK as an analgesic in a diverse ED patient population appears to be safe and feasible for the treatment of many types of pain.

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1. Introduction

The Institute of Medicine report, Relieving pain in America: a blueprint for transforming prevention, care, education, and research, highlighted inadequate emergency department (ED) treatment of pain as a major public health concern [1]. However, strategies to successfully manage acute pain in a safe and expeditious manner are the source of considerable debate, and there is wide variation in clinical practice [2]. Current pharmacologic strategies in the ED rely heavily on monotherapy with opioids; but adverse events such as sedation, bradypnea, hypotension, and tolerance limit their utility in many patients [3-8]. In addition, the epidemic of opioid pain medication misuse has become a nationally recognized problem, and emergency physicians have been tasked with carefully assessing opioid administration and prescriptions [9]. More than ever, emergency physicians are considering alternative, complimentary medications, such as ketamine, that can be combined with traditional drugs such as opioids and nonsteroidal antiinflammatory drugs, to achieve multimodal analgesia in the acute setting.

Ketamine has been used extensively in the ED for procedural sedation and rapid sequence intubation. An alternative, off-label, use of ketamine is for pain control, using subanesthetic dosing—typically 0.1 to 0.3 mg/kg. Research conducted over the last 15 years has demonstrated that such low-dose ketamine (LDK) is safe, effective, and improves pain management when combined with opioid analgesics [10-13]. Low-dose ketamine has been shown to potentiate the analgesic effect of opioids, have opioid-sparing effects, and to attenuate development of centralized chronic pain states [14-20]. For these reasons, LDK for analgesia has been widely adopted in the anesthesia, surgical, and...
palliative care settings for the treatment of postoperative and chronic cancer-related pain.

Emergency medicine has been slower to incorporate LDK for analgesia into routine practice, likely due to lack of familiarity with this indication as well as concerns over adverse effects, particularly emergence phenomena. But a small yet growing body of evidence has emerged over the last 10 years documenting the successful use of LDK in the ED and prehospital environment [12,21–25]. These studies consistently show that the safety and side effect profile of LDK is similar to that of opioids and that LDK causes few significant psychomimetic reactions. In response, some institutions have begun to routinely incorporate LDK into acute pain management as a complimentary and rescue analgesic. Two years ago, in collaboration with emergency physicians, nursing, and pharmacy staff, we developed an ED-specific LDK protocol to facilitate use for a broad array of painful conditions in our department.

The aim of this study is to document the clinical use, safety, and side effect profile of LDK for pain management in the ED.

2. Methods

2.1. Setting

This retrospective, consecutive case series was conducted in a single ED at an urban trauma center. We obtained a database, derived from our electronic medical record (EMR) (Wellsoft Corporation, Sumerset, NJ), of all patients receiving ketamine in our ED during a 2-year period from January 2012 to December 2013. This 2-year timeframe coincided with an increase in popularity and awareness of ketamine on the part of ED providers after the creation of an ED-specific LDK protocol in 2012. With broad inclusion criteria, the protocol proposed LDK as an agent for analgesia in patients with many types of acute or chronic pain, either alone or in combination with additional pain relieving drugs. The protocol recommended doses of 5 to 20 mg intravenous (IV) or 10 to 25 mg intramuscular (IM). There were no absolute contraindications except for known allergy to ketamine. Relative contraindications included age younger than 18 years, uncontrolled seizure activity, severe signs of elevated intracranial pressure, renal and/or liver failure, and women who are pregnant or breastfeeding. Patients were not specifically excluded for having abnormal vital signs (ie, hypertension, tachycardia, or hypoxia), and the ultimate decision whether to order LDK was left up to provider preference.

Our ED uses computerized drug storage units (Pyxis Corporation, San Diego, CA) and EMRs that permit accurate tracking of department drug ordering and administration, including dosage and route of administration. To facilitate ease of use and cut down on unnecessary waste, our pharmacy began stocking preloaded syringes of 15 mg ketamine for IV administration, which were kept in the drug storage units. Our hospital’s institutional review board approved this retrospective review.

2.2. Study population

We extracted data from electronic systems to include all ED patients for whom ketamine was ordered during the study period. The data included medical record number, arrival date, age, sex, disposition, and chief complaint. Chief complaints were categorized into 7 broad groups of indications for LDK before chart review. The groups included musculoskeletal pain, abdominal pain, chest pain, skin and soft tissue infections, headache, back pain, and other. For the purposes of this study, we defined LDK as a dose less than or equal to 20 mg IV or 25 mg IM or roughly 0.1 to 0.3 mg/kg in the average size adult.

2.3. Data abstraction

After a formal training period and data abstraction pilot trial, a standardized data abstraction form was used to review patient records independently by 2 authors. We abstracted ketamine dose (milligram), route of administration (IV or IM) and systolic blood pressure (SBP), and heart rate (HR) at 2 time points: at triage and within 1 hour of LDK administration.

Detailed review of the clinical chart was done to ascertain the presence or absence of specific, predefined adverse events with one hour of LDK administration including cardiac arrest, apnea (respiratory rate <10 breaths per minute or need for jaw thrust and/or bag valve mask ventilation), hypoxia (oxygen saturation, <90% on room air or >5% decreased in oxygen saturation from baseline value if >90% at triage), hypertensive emergency (SBP >180 and the acute onset of chest pain, shortness of breath, or severe headache), laryngospasm, emesis, psychomimetic reaction (agitation, hallucinations, or unusual behavior recorded by provider), and other (nurse or physician documentation of specific problem related to LDK administration). Lastly, comorbidities including a history of hypertension, coronary artery disease (CAD), psychiatric illness (schizophrenia, bipolar, and depression requiring medication), and chronic obstructive pulmonary disease (COPD) or asthma were recorded. If not documented in the medical record, each of these adverse events and comorbidities was assumed to be absent.

Frequent meetings were held between abstractors and study coordinators to answer questions, resolve disputes, and review identified adverse events. A random sample of 10% of charts reviewed was duplicated to assess interrater reliability.

2.4. Data analysis

We report descriptive statistics and 95% confidence intervals (CIs), where appropriate. Interrater reliability was ascertained through the Cohen $k$ statistic for route of administration and absence or presence of any adverse events and the Spearman rank correlation for dose of administration. Statistical analysis was done using Stata version 11 (StataCorp, College Station, TX).

3. Results

We found almost perfect agreement between the 2 abstractors: $k = 0.98$ for route of administration, $k = 0.90$ for presence of adverse reaction, and $r = 0.99$ for dose of administration.

The initial database included 683 patients who received ketamine in our ED over the study period. We excluded all cases of ketamine administration that did not meet our definition of LDK ($\geq 20$ mg IV or 25 mg IM). Using this definition, 153 cases were excluded from the analysis. The excluded cases primarily comprised ketamine used for conscious sedation and rapid sequence intubation.

This series ultimately included 530 consecutive ED LDK administrations, of which 294 (55.5%) were female. The median age was 40 years, and the distribution of patients was fairly even between the second to fifth decades of life (Table 1). Indications for LDK were diverse, and many of the patients had substantial underlying illness including hypertension (26%), psychiatric disorder (12%), COPD (11%), and CAD (4%). Ultimately, near two-thirds (63%) were discharged home from the ED.

Low-dose ketamine was administered IV in the vast majority of cases (93%) and IM in the remaining cases. Most patient (92%) received a single dose of either 10 or 15 mg, although the dose range was 5 to 25 mg IV/IM. There was no significant change in SBP and HR within 1 hour of LDK administration, as compared with triage values. Mean triage SBP and HR was 141 (99% CI, 138–144) and 93 (99% CI, 91–95), whereas SBP and HR within 1 hour of LDK administration were 138 (99% CI, 135–141) and 86 (99% CI, 84–88), respectively.

Of 530 LDK cases, only 30 (6%) met our criteria for an adverse event. Each event is specifically detailed in Table 2. There were 7 patients (1.3%)}
Concerns over adverse psychomimetic affects, particularly emergence phenomena, have traditionally limited widespread use of LDK in adult ED patients [28]. Our results confirm those of prior smaller studies of LDK showing that psychomimetic reactions are mostly mild in nature and rarely alter a patient's clinical course [10,12,21–24,29]. In our cohort, 18 patients (3.5%) had documented psychomimetic or dysphoric reactions within 1 hour of LDK administration. Although 3 patients required lorazepam for sedation during the episode, most reactions were mild and improved without intervention or with reassurance from ED staff.

It is now apparent that mild dysphoric effects of LDK occasional occur with doses lower than what is traditionally considered the dissociative range (1–2 mg/kg IV), at which actual emergence phenomenon can occur. The rate of such reactions in recent prospective studies ranges from 16% to 26% [21,22,30]. It is important to note that the negative reactions are universally short lived and differ substantially from emergence phenomenon. Our rate of mild dysphoric events is much lower than described in previous prospective studies; but this is likely due to the inherent limitations of retrospective chart review, reliance on the medical records for documentation of events, and the sensitivity of screening instruments for such events used in prospective studies. Nonetheless, we suspect that some patients reported the effects as negative experiences primarily because they were taken by surprise. Based upon our (the investigators) growing experience with LDK, we believe that advising patients about the possibility of psychomimetic effects reduces the likelihood that the effect will be perceived as negative if it occurs. In addition, a prior prospective trial on LDK showed that the same patient who reports very bothersome dissociative effects might report high satisfaction at discharge [21]. It seems prudent that providers who administer LDK should routinely coach patients just before administration, reassuring them that any dysphoric reaction will be short lived and create as calm an environment as possible.

Other types of adverse events were infrequent. Seven patients (1.5%) experienced transient oxygen desaturation within 1 hour of ketamine administration. Of these patients, 4 were given concomitant opioids with LDK, and all but 1 patient responded quickly with 2 to 4 L nasal cannula oxygen. One patient required 2 hours of bilevel positive airway pressure (bipap) support; but she had been hypoxic at triage, required oxygen support via non-rebreather facemask and bipap before LDK, and was already admitted for a COPD exacerbation. According to provider’s documentation, the indication for LDK in this case was to treat chest pain but, perhaps, more importantly, to facilitate therapy for hypoxia by way of providing anxiolysis and bronchodilation. Overall, the rate of hypoxia is substantially less than reported in prior prospective research on opioid-based pain protocols in the ED [31]. For example, in the widely cited “1 + 1” hydromorphone titration protocol study, Chang et al [31] found a 5% rate of hypoxia in patients receiving hydromorphone. In addition, their study excluded patients with baseline oxygen saturation less than 95%. However, a direct comparison with our heterogeneous cohort is not possible because some patients may have been given LDK in spite of their hypoxia.

Similarly, we found a lower rate of emesis in our cohort than what was reported in patients receiving hydromorphone in the study of Chang et al [31] (1% vs 7%, respectively). Furthermore, most of our emesis cases were in patients who had experienced nausea and/or vomiting before receiving LDK (reference, Table 2 for details), whereas such patients would have been excluded from the reporting of emesis in the study of Chang et al [31].

We observed no significant change in blood pressure or HR within 1 hour of administering LDK as compared with triage values. Patients who were tachycardic, hypertensive, or hypoxic at triage remained so after receiving LDK. This is not surprising given the well-established favorable hemodynamic profile of ketamine [32]. Although these findings suggest that LDK may be safe in patients who have abnormal vital signs, there is much uncertainty in this patient population given the limitations of retrospective data. Furthermore, our LDK protocol does not explicitly exclude patients with abnormal vital signs and allows for...
Table 2
All 30 adverse events that occurred within 1 hour of LDK bolus, among 530 patients

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Age</th>
<th>Sex</th>
<th>Disposition</th>
<th>Indication</th>
<th>Dose</th>
<th>Route</th>
<th>Comorbidities</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>LDK given for chronic pelvic pain. Hypoxia noted during LDK administration requiring non-rebreather facemask, which resolved within 1 h. Patient had been given 2 mg hydromorphone 45 minutes before LDK.</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>M</td>
<td>Admit</td>
<td>Abdominal pain</td>
<td>10</td>
<td>IV</td>
<td>Hypertension</td>
<td>LDK given for abdominal pain. Placed on 2-L nasal cannula after LDK, although no desaturation was noted.</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>M</td>
<td>Admit</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td>Depress, Hypertension, CAD</td>
<td>LDK given for abdominal pain secondary to diabetic ketoacidosis. 45 min prior received 2 mg hydromorphone. SpO2 dropped to 88%, transient 2-L NC applied.</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>M</td>
<td>Admit</td>
<td>Abscess</td>
<td>20</td>
<td>IV</td>
<td></td>
<td>LDK given for abscess drainage. 1 h after administration noted to have SpO2 of 88% when asleep, which improved with elevation head of bed. Patient may have had undiagnosed obstructive sleep apnea.</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>M</td>
<td>Home</td>
<td>Cancer</td>
<td>15</td>
<td>IV</td>
<td>Hypertension, COPD</td>
<td>LDK and 2 mg hydromorphone given for back pain related to metastatic lesion. SpO2 dropped to 88%, transient 2-L NC applied.</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>F</td>
<td>Admit</td>
<td>COPD</td>
<td>15</td>
<td>IV</td>
<td>Hypertension, COPD</td>
<td>Patient was admitted for COPD. SpO2 95% on 2-L NC before LDK but dropped to 80% with increased work of breathing and lethargy obstructive lung disease noted by MD afterward. Placed on bipap for next 2 h then improved. LDK and 1 mg hydromorphone given for head laceration repair. SpO2 dropped to 90%, transient 2-L NC applied.</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>M</td>
<td>Admit</td>
<td>Trauma</td>
<td>20</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>M</td>
<td>Admit</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>LDK and 8 mg ondansetron given for nausea and vomiting in setting of pyelonephritis. Patient had 2 small episodes of emesis afterward but stated “it’s due to not eating.”</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>LDK, 25 mg benedryl and 4 mg ondansetron given for nausea and vomiting in setting of gastroparesis. Patient had large emesis 45 min afterward, improved with 10 mg metoclopramide.</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>M</td>
<td>Home</td>
<td>Back pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>LDK, 30 mg ketorolac and 10 mg dexamethasone given for cauda equina syndrome. Patient had small emesis 15 min afterward while lying flat for electrocardiogram. LDK given for chronic abdominal pain and hyperemesis syndrome. Patient complained of continued nausea and vomiting after LDK.</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>F</td>
<td>Home</td>
<td>Chronic pain</td>
<td>15</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>F</td>
<td>Home</td>
<td>Chronic pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>LDK and 1 mg hydromorphone given for humerus fracture. Patient had large emesis 10 min afterward, improved with 4 mg ondansetron.</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>M</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>10</td>
<td>IV</td>
<td></td>
<td>After LDK and 2 mg hydromorphone, patient reported, “I feel dizzy.”</td>
</tr>
</tbody>
</table>

55 F Home Abdominal pain 5 IV After LDK and 400 mg ibuprofen, patient reported, “I feel dizzy.”

39 F Home Abdominal pain 15 IV COPD After LDK and 1 mg hydromorphone, patient stated her pain is improved, but the medicine made her feel “like I’m going to die.”

67 F Home Abdominal pain 15 IV Hypertension After LDK, noted that “she does not want ketamine again for pain; that it made her hallucinate.”

33 F Home Abdominal pain 15 IV CAD, COPD After LDK and 4 mg morphine, patient reported “pain gone” but “I feel crazy.” Given 1 mg lorazepam.

43 F Home Abdominal pain 15 IV After LDK and 4 mg morphine, patient noted by nurse to become unresponsive to verbal stimuli. Awakened with sternal rub and began crying. Vital signs normal except for HR of 110. Given 1 mg lorazepam.

22 F Admit Abdominal pain 20 IV After LDK, patient reported “I feel dizzy, but the pain is gone.” Later noted by RN to patting the wall with hand repeatedly with eyes closed. She remained alert and oriented but no explanation offered.

55 F Admit Abcess 10 IV LDK and 25 μg fentanyl given for abscess drainage. Noted to become anxious and was crying because she “didn’t like the effect of the drug.”

42 F Home Back pain 10 IV Hypertension LDK and 2 mg hydromorphone given for back pain. Noted to be very anxious for 10 min afterward.

40 F Home Back pain 15 IV After LDK, patient became highly anxious and was crying. Reported “I feel like a zombie.” Improved with reassurance by nurse.

57 M Admit Cancer 15 IV After LDK and 50 μg fentanyl, patient noted to have enlarged eyes and be screaming in pain while pulling at side rails. Required 2 mg lorazepam and was calmed by MD

65 F Admit Chest pain 15 IV COPD After LDK, noted to be anxious and disoriented by nurse. Patient stated “If this is what people feel like on drugs, then I don’t want them.” Feelings resolved spontaneously within 10 min.

36 M Home Chest pain 15 IV Hypertension, coronary Patient did not like feeling of LDK immediately, and the bolus was stopped before completion.

38 F Home Chest pain 10 IV Hypertension Received LDK for asthma exacerbation. Afterward, noted to be more calm and stated “I feel like I’m flying,” then “I’m going to sleep.”

54 F Home Chest pain 15 IV Hypertension During LDK administration, noted to have “a bad dream-like state,” and “felt like she was going to die in her dream.”

44 M Home Hematoma 15 IV Hypertension After LDK noted, “I feel weird. I feel funny... What is wrong with me?” Symptoms resolved without intervention.

43 F Home Sickle cell pain 15 IV Depression, hypertension After LDK, patient became nauseated and flushed feeling. Improved with 25 mg phenergan.

Abbreviations: M, male; F, female; SpO2, oxygen saturation as measured by pulse oximetry; NC, nasal cannula; MD, doctor of medicine; RN, registered nurse.

a No patient experienced cardiac arrest, apnea, hypertensive emergency, or laryngospasm.

b Significant comorbidities abstracted included history of hypertension, psychiatric illness (depression, bipolar, and schizophrenia), CAD, and COPD.

c Hypoxia was defined as oxygen saturation as measured by pulse oximetry less than 90% or decrease in oxygen saturation more than 5% from triage vital signs.

d Psychomimetic/dysphoric side effects were defined as hallucinations, agitation, unusual behavior, or registered nurse/doctor of medicine documentation of a specific problem related to ketamine.
provider preference, so we cannot account for individual practice patterns and must assume some avoided LDK in these situations.

The favorable safety profile of LDK is especially notable given the wide age distribution and prevalence of comorbidities in our cohort (Table 1). To date, prior studies of LDK had rigorous inclusion and exclusion criteria and represented a tightly controlled cohort of patients. We believe that our cohort represents a typical diverse, urban ED population, where many patients have chronic medical and psychiatric disease, substance abuse, and lack of social support. In spite of this, our findings are consistent with those of a prior small retrospective study in a similar setting [25] and recent prospective data [21,22,24,30], showing that LDK is feasible, generally well tolerated, and very safe in the ED.

This study has the usual limitations inherent in a retrospective review. Quality of the data was dependent on that of the medical record, particularly nursing documentation. To mitigate this, we focused on data that were objective and not prone to interpretation or abstractor bias using a standardized abstraction protocol based upon accepted guidelines for chart review methodology [33]. Our EMRs include extensive documentation from nursing and physicians, so it is unlikely that we missed any major adverse events (ie, cardiac arrest, apnea, hypoxia, laryngospasm, and hypertensive emergency). Despite this, it is likely our data underestimate minor adverse events, such as emesis or transient psychomimetic and dysphoric events.

Although emergency physicians should be encouraged by the safety of LDK in this large and diverse cohort of ED patients, we emphasize that data from prospective, randomized blinded trials are needed to definitively determine the efficacy, safety, and side effect profile of LDK compared with standard opioid analgesics and other opioid adjuncts.

5. Conclusion

Use of LDK alone or in combination with other pain medications as a primary or rescue analgesic in a diverse ED patient population appears to be safe and feasible for the treatment of many types of pain. Minor psychomimetic side effects were observed but easily addressed by ED personnel and did not alter disposition. Other side effects, including emesis and hypoxia, appear to be equally or less common than reported with opioids. Prospective randomized trials are needed to determine the efficacy and further elucidate the safety and side effect profile of LDK.

References