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 = 0.0002) 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. Garnuni 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.

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References


[5] Farsi D, Movahedi M, Hafezimoghadam P, Abbasi S, Shahlae A, Rahimi-Movaghar V. Acute pain management with intravenous 0.10 mg/kg vs. 0.15 mg/kg morphine
Table 1
Summary of sub-dissociative ketamine studies administered to adult patients in the emergency department

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Patients (no.)</th>
<th>Treatment(s)</th>
<th>Outcome</th>
<th>Safety</th>
</tr>
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<tbody>
<tr>
<td>Ahern et al [7]</td>
<td>Prospective observational study</td>
<td>32</td>
<td>• 15 mg ketamine + 0.5 mg hydromorphone IV &lt;br&gt; • If at 15 or 30 min the patient said they would like more pain medication, an additional 1 mg of hydromorphone IV was administered</td>
<td>• At 5 min the mean reduction in pain score was 6.0 ± 3.2 on a 10-point verbal NRS &lt;br&gt; • 93% had clinically significant decrease in pain (≥ 2 points decrease on the NRS) &lt;br&gt; • 14 patients declined additional analgesia at both 15 and 30 min &lt;br&gt; • 90% of patients stated they would have the combination with ketamine again</td>
<td>• No hallucinations or agitation reported &lt;br&gt; • No tachycardia, hypertension, dysrhythmia, hypoxia were observed &lt;br&gt; • 80% of patients reported some dissociative effects (dizziness, fatigue, mood changes, headache) &lt;br&gt; • 73% of patients reported the side effects as weak or modest &lt;br&gt; • Less N/V with ketamine (0% vs 35%; P &lt; .05) &lt;br&gt; • Less drowsiness with ketamine at 1 h through 24 h (P &lt; .05) &lt;br&gt; • Mean peak respiratory flow rate improved more with ketamine(P &lt; .05)</td>
</tr>
<tr>
<td>Gurnani et al [17]</td>
<td>Randomized control trial</td>
<td>40</td>
<td>• Ketamine 0.25 mg/kg IV followed by ketamine 1.67 μg/kg - 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</td>
<td>• Pain score (on a 10-point VAS) was lower after 15 min through 24 h (P &lt; .05) &lt;br&gt; • Patients required less supplemental doses of 3 mg IV morphine (0 vs 18 people; P &lt; .001)</td>
<td>• No difference in percentage of patients with adverse effects with ketamine vs morphine (58% vs 57%) &lt;br&gt; • 3, 0, 0, and 0 patients in the ketamine group (n = 24) vs 0, 3, 2 and 1 in the morphine group (n = 21) experienced hallucinations, dysphoria, headache, drowsiness, and decreased oxygen saturation &lt;br&gt; • No dissociation or emergency reactions were detected &lt;br&gt; • Similar RASS scores with ketamine vs morphine &lt;br&gt; • No dangerous adverse events &lt;br&gt; • 1 patient experienced “brief mild dysphoria”</td>
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<tr>
<td>Miller et al [19]</td>
<td>Randomized, double-blinded, superiority controlled trial</td>
<td>45</td>
<td>• Ketamine 0.3 mg/kg total body weight IV (maximum dose of 25 mg) &lt;br&gt; • Morphine 0.1 mg/kg total body weight IV (maximum dose of 8 mg) &lt;br&gt; • Both morphine and ketamine were infused over 5 min in a total of 10 mL normal saline &lt;br&gt; • A second identical dose could be administered 20 min after the first infusion was complete &lt;br&gt; • If a third dose was needed, data collection was stopped and the patient got pain medication the prescriber ordered</td>
<td>• Ketamine may have comparable analgesic effects to morphine &lt;br&gt; • Maximum decrease in pain from baseline on a NRS was similar between ketamine and morphine (4.9 vs 5) &lt;br&gt; • Maximum decrease in pain was seen at 5 min for the ketamine group and 100 min for the morphine group &lt;br&gt; • 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)</td>
<td>• No difference in percentage of patients with adverse effects with ketamine vs morphine (58% vs 57%) &lt;br&gt; • 3, 0, 0, and 0 patients in the ketamine group (n = 24) vs 0, 3, 2 and 1 in the morphine group (n = 21) experienced hallucinations, dysphoria, headache, drowsiness, and decreased oxygen saturation &lt;br&gt; • No dissociation or emergency reactions were detected &lt;br&gt; • Similar RASS scores with ketamine vs morphine &lt;br&gt; • No dangerous adverse events &lt;br&gt; • 1 patient experienced “brief mild dysphoria”</td>
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<td>Lester et al [22]</td>
<td>Retrospective case series</td>
<td>34</td>
<td>• Ketamine was administered at doses less than 0.6 mg/kg IV or IM &lt;br&gt; • 80% of patients either used chronic pain medication or illicit drugs</td>
<td>• 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 patients with adverse effects with ketamine vs morphine (58% vs 57%) &lt;br&gt; • 3, 0, 0, and 0 patients in the ketamine group (n = 24) vs 0, 3, 2 and 1 in the morphine group (n = 21) experienced hallucinations, dysphoria, headache, drowsiness, and decreased oxygen saturation &lt;br&gt; • No dissociation or emergency reactions were detected &lt;br&gt; • Similar RASS scores with ketamine vs morphine &lt;br&gt; • No dangerous adverse events &lt;br&gt; • 1 patient experienced “brief mild dysphoria”</td>
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<td>Richards et al [23]</td>
<td>Prospective observational study</td>
<td>24</td>
<td>• 75% of the patients received opioid analgesics before ketamine with no improvement in their pain score after 30 min</td>
<td>• Pain decreased (on a 10 point VAS) from 8.9 ± 2.1 to 3.9 ± 3.4 (P &lt; .0001) &lt;br&gt; • 67% of the patients prefer to be given ketamine again &lt;br&gt; • 96% of physicians would use ketamine again</td>
<td>• No emergency reactions</td>
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<td>Beaudoin et al [24]</td>
<td>Randomized, double-blinded, controlled trial</td>
<td>60</td>
<td>• 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 &lt;br&gt; • 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</td>
<td>• 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 = .01) &lt;br&gt; • 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 = .04; 0.3 mg/kg ketamine vs placebo P = .01) &lt;br&gt; • 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; P &lt; .04)</td>
<td>• 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 &lt; .01) &lt;br&gt; • One patient developed hypotension and another developed transient respiratory depression (oxygen saturation &lt;92%) with a dose of rescue analgesia in the placebo group &lt;br&gt; • 3 patients in the 0.3 mg/kg ketamine group developed tachycardia which lasted &lt;30 min &lt;br&gt; • 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 &lt;br&gt; • No dangerous adverse effects, tachycardia, hypotension, dysphoria, nausea, vomiting, dream-like state, hallucinations, or emergence reactions &lt;br&gt; • One patient complained of tinnitus and uneasiness during the infusion and one of dizziness</td>
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<tr>
<td>Goltser et al [25]</td>
<td>Retrospective case series</td>
<td>14</td>
<td>• Ketamine 0.2 to 0.4 mg/kg IV diluted in 50 to 100 mL normal saline piggyback administered over 10 min</td>
<td>• No patients required rescue analgesia within one hour of ketamine administration &lt;br&gt; • Pain improved for 8 of 14 patients on a NRS (the remaining patients could not be assessed due to no documentation of the NRS)</td>
<td>• No hallucinations or agitation reported &lt;br&gt; • No tachycardia, hypertension, dysrhythmia, hypoxia were observed &lt;br&gt; • 80% of patients reported some dissociative effects (dizziness, fatigue, mood changes, headache) &lt;br&gt; • 73% of patients reported the side effects as weak or modest &lt;br&gt; • Less N/V with ketamine (0% vs 35%; P &lt; .05) &lt;br&gt; • Less drowsiness with ketamine at 1 h through 24 h (P &lt; .05) &lt;br&gt; • Mean peak respiratory flow rate improved more with ketamine(P &lt; .05)</td>
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</table>
| 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 patients with adverse effects with ketamine vs morphine (58% vs 57%) <br> • 3, 0, 0, and 0 patients in the ketamine group (n = 24) vs 0, 3, 2 and 1 in the morphine group (n = 21) experienced hallucinations, dysphoria, headache, drowsiness, and decreased oxygen saturation <br> • No dissociation or emergency reactions were detected <br> • Similar RASS scores with ketamine vs morphine <br> • No dangerous adverse events <br> • 1 patient experienced “brief mild dysphoria” | • No subjects experienced deep sedation, or severe side effects which required intervention or transfer to a...


