Intranasal Ketamine for Analgesia in the Emergency Department: A Prospective Observational Series

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Abstract

**Objectives:** The objective was to examine the feasibility, effectiveness, and adverse effect profile of intranasal ketamine for analgesia in emergency department (ED) patients.

**Methods:** This was a prospective observational study examining a convenience sample of patients aged older than 6 years experiencing moderate or severe pain, defined as a visual analog scale (VAS) score of 50 mm or greater. Patients received 0.5 to 0.75 mg/kg intranasal ketamine. Pain scores were recorded on a standard 100-mm VAS by trained investigators at baseline, then every 5 minutes for 30 minutes, and then every 10 minutes for an additional 30 minutes. The primary outcome was the number and proportion of patients experiencing clinically significant reductions in VAS pain scores, defined as VAS reductions of 13 mm or more, within 30 minutes. Secondary outcomes included the median reduction in VAS, the median time required to achieve a 13 mm reduction in VAS, vital sign changes, and adverse events. Continuous data are reported with medians and interquartile ranges (IQRs). The Wilcoxon signed-ranks test was used to assess changes in VAS scores. Adverse effects are reported with proportions and 95% confidence intervals (CIs).

**Results:** Forty patients were enrolled with a median age of 47 years (IQR = 36 to 57 years; range = 11 to 79 years) for primarily orthopedic injuries. A reduction in VAS of 13 mm or more within 30 minutes was achieved in 35 patients (88%). The median change in VAS at 30 minutes was 34 mm (44%). Median time required to achieve a 13 mm VAS reduction was 9.5 minutes (IQR = 5 to 13 minutes; range = 5 to 25 minutes). No serious adverse effects occurred. Minor adverse effects included dizziness (21 patients, 53%; 95% CI = 38% to 67%), feeling of unreality (14 patients, 35%; 95% CI = 22% to 50%), nausea (four patients, 10%; 95% CI = 4% to 23%), mood change (three patients, 8%; 95% CI = 3% to 20%), and changes in hearing (one patient, 3%; 95% CI = 0% to 13%). All adverse effects were transient and none required intervention. There were no changes in vital signs requiring clinical intervention.

**Conclusions:** Intranasal ketamine reduced VAS pain scores to a clinically significant degree in 88% of ED patients in this series. Adverse effects were minor and transient. Intranasal ketamine may have a role in the provision of effective, expeditious analgesia to ED patients.

T he provision of analgesia is a frequent and integral component of care in the emergency department (ED) setting, yet adequate and timely analgesia is often challenging due to scarcity of available health care providers, stretcher space, and monitoring availability in overcrowded EDs. This study...
examines the use of intranasal ketamine as an analgesic option that does not require physiologic monitoring, stretcher space, or specialized skills for its delivery. Ketamine is a N-methyl-D-aspartate receptor antagonist that acts as an analgesic through central and peripheral mechanisms distinct from those of opioids and has been shown to be effective in a variety of settings.\textsuperscript{3} When administered intranasally, ketamine has a bioavailability of 45% and blood levels correspond well to analgesic effect.\textsuperscript{2} Reports on the use of intranasal ketamine for analgesia include the prehospital, outpatient surgery, and battlefield settings;\textsuperscript{3} however, there is a paucity of data regarding the feasibility and effectiveness of intranasal ketamine use in the ED setting.

**METHODS**

**Study Design**

This was a prospective observational study of intranasal ketamine for pain in the ED. This study was approved by the University of British Columbia Clinical Research Ethics Board (#H12-01953) and registered with ClinicalTrials.gov (NCT01686009).

**Study Setting and Population**

The study facility is a 250-bed community teaching hospital and Level 3 trauma center with an annual ED census of 55,000 visits, of which 80% are by adults. Seven staff emergency physicians (EPs) (study EPs) were trained by the primary investigator (GA) and performed patient enrollments, medication delivery, and study data collection.

A convenience sample of patients was enrolled between October 2012 and January 2013. Enrollment occurred at various times when one of the study EPs was available for recruitment and data collection as his or her sole responsibility. Patients aged greater than 6 years experiencing moderate to severe pain as defined by a 100-mm visual analog scale (VAS) score of 50 mm or greater were eligible. Exclusion criteria included pregnancy, schizophrenia, systolic blood pressure greater than 180 mm Hg, need for immediate intravenous (IV) access as judged by the study EP, nasal occlusion, or Glasgow Coma Scale score less than 15.

**Study Protocol**

After being triaged, each patient was approached by one of the study EPs for written informed consent. Baseline pain score was then determined using a standard 100-mm VAS anchored with “no pain” at 0 mm and “worst pain imaginable” at 100 mm. The use of a 100-mm VAS has been validated in previous studies regarding ED analgesia, and it has been shown that the minimum clinically significant change in pain severity is 13 mm.\textsuperscript{4} A patient was eligible for the study protocol if the baseline VAS was 50 mm or greater. The study EP then determined the patient’s body weight and baseline vital signs before administering intranasal ketamine according to a preprepared weight-based dosing schedule. Each patient received an initial dose of 0.5 mg/kg intranasal ketamine; this dose was based on previous studies regarding postoperative pain.\textsuperscript{5} The patient could receive a single repeat dose of 0.25 mg/kg intranasal ketamine if the VAS recorded 10 minutes after the initial drug administration remained 50 mm or greater. This time was chosen empirically as a reasonable time frame for clinical reassessment of analgesic effect.

The study EP recorded pain scores, vital signs, and adverse effects every 5 minutes for the first 30 minutes, then every 10 minutes for an additional 30 minutes. If a patient received supplemental analgesia, left the ED for imaging, or was discharged home, then data collection for the study was stopped.

Adverse effects recorded were based on the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA)\textsuperscript{6} and included fatigue, dizziness, nausea, headache, feeling of unreality, changes in hearing, mood change, general discomfort, and hallucinations. Patients graded the severity of adverse effects on a five-point scale, with “0” representing the absence of any adverse effects and “4” representing an effect severity the patient rated as bothersome. Adverse effects were considered serious if they resulted in clinical intervention or removal from the study protocol. After 30 minutes patients were asked to rate the severity of nasal irritation on a 1 to 10 ordinal scale anchored with “1 = none” and “10 = very severe,” as well as their overall satisfaction with the pain relief provided with ketamine; “1 = not satisfied” and “10 = very satisfied.” Patients were then contacted by phone 24 and 72 hours after ED discharge and queried for any adverse effects using the SERSDA elements. Two investigators not involved in enrollments or data collection conducted these telephone interviews.

All study data were recorded on data sheets separate from the clinical record and were entered in Microsoft Excel (Version 14.1.4, Microsoft, Redmond, WA) for tabulation and analysis by a single research assistant, who was uninvolved in patient recruitment or data collection.

**Outcome Measures**

The primary outcome was the number and proportion of patients experiencing at least 13-mm reductions in VAS within 30 minutes. Secondary outcomes included the median reduction in VAS, the median time required to achieve 13-mm reductions in VAS, vital sign changes, and adverse events.

**Data Analysis**

Continuous data are described with medians and interquartile ranges (IQRs). Categorical data are represented with proportions and 95% confidence intervals (CIs). For the primary outcome, changes in VAS scores were assessed using the Wilcoxon signed-ranks test. A \( p < 0.05 \) was considered statistically significant. Sample size calculation was not included, as this pilot study will be used to design future comparative studies of intranasal ketamine.

**RESULTS**

Patient characteristics are shown in Table 1, and patient recruitment and inclusion for analysis is illustrated in Figure 1. Main results are displayed in Table 2. The reductions in VAS scores were statistically significant at all time points \( (p < 0.001) \).
Adverse events are described in Table 3. All adverse effects were transient and did not require treatment. There were no changes in vital signs requiring intervention or removal from the study protocol. Phone follow-up at 24 and 72 hours was accomplished in 18 patients (45%). Three patients were not contacted because of admission to hospital for reasons unrelated to the study, and 19 patients could not be contacted. Two patients reported mild nausea at 24 and 72 hours after the study protocol. Both were also using opioid analgesics for orthopedic injuries. One patient reported mild dizziness at 24 hours only.

**DISCUSSION**

The provision of timely analgesia is challenging for many EDs because of limited numbers of health care providers, limited time for staff to commit to each patient, lack of free stretchers, and the lack of availability of physiologic monitoring spaces. IV opioid analgesia is widely used as a primary method of attaining analgesia, but is limited by the requirement for specialized skills, invasiveness, requirement for stretcher space, and the need for respiratory monitoring. Oral analgesics are often indicated for mild to moderate pain, but their utility is limited due to slow absorption and due to fasting requirements in injured or vomiting patients.

The intranasal route is known to provide excellent absorption through the nasal mucosa and has several advantages over IV or intramuscular administration including shorter time to administration, minimal training or specialized skill requirement, and elimination of
the use of opioid analgesia raises the concern of respiratory depression, particularly when used in nonmonitored settings. Respiratory depression and concerns of oversedation have been cited by physicians as primary justifications for withholding opioid analgesia. Ketamine possesses an improved cardiorespiratory profile compared to opioids, and its use in subdissociative doses may obviate the need for the physiologic monitoring that is obligatory when using opioids. This characteristic leads to the potential for intranasal ketamine to be used as a rapidly acting analgesic for use in unmonitored settings such as the ED waiting room. This would be an important advantage for many EDs, which often suffer from overcrowding and the resultant challenges in providing adequate analgesia.

**LIMITATIONS**

Intranasal ketamine was not compared in a randomized fashion to other analgesics or to placebo, and the investigators and patients were not blinded to the drug being used. Patients were enrolled as a convenience sample at the discretion of the study EPs; thus there existed the potential for bias in patient selection. Less common adverse effects may not have been detected due to the small sample size.

**CONCLUSIONS**

Intranasal ketamine appears to provide rapid, well-tolerated, and clinically significant analgesia in ED patients.

The authors thank Dr. Hazel Park for her assistance in data collection.

**References**

1. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-n-aspartic acid receptor activation.

### Table 2

**Main Results in Patients Receiving Intranasal Ketamine**

<table>
<thead>
<tr>
<th>Results</th>
<th>Subjects (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects achieving 13-mm-or-more reductions in VAS pain score within 30 minutes*</td>
<td>35 (88) [74–95]</td>
</tr>
<tr>
<td>Time required to achieve 13-mm reductions in VAS pain score, minutes (n = 35)</td>
<td>9.5 (5–13) [5–25]</td>
</tr>
<tr>
<td>Patient-reported satisfaction (1 to 10 scale)</td>
<td>7 (5–9) [1–10]</td>
</tr>
<tr>
<td>Patient-reported nasal irritation (1 to 10 scale)</td>
<td>2 (1–4) [1–10]</td>
</tr>
<tr>
<td>Dosing</td>
<td>Time</td>
</tr>
<tr>
<td>Subjects receiving one dose (0.5 mg/kg total) of intranasal ketamine, No. (%)</td>
<td>17 (43)</td>
</tr>
<tr>
<td>Subjects receiving two doses (0.75 mg/kg total) of intranasal ketamine, No. (%)</td>
<td>23 (57)</td>
</tr>
</tbody>
</table>

### Table 3

**Patient-reported Minor Adverse Effects in Subjects Receiving Intranasal Ketamine (n = 40)**

<table>
<thead>
<tr>
<th>Incidence of Adverse Effects†</th>
<th>Patient-reported Severity Score of 0 to 2</th>
<th>Patient-reported Severity Score of 3 or 4‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>15 (38) [24 – 53]</td>
<td>6 (15) [7 – 29]</td>
</tr>
<tr>
<td>Feeling of unreality</td>
<td>10 (25) [14 – 40]</td>
<td>4 (10) [4 – 23]</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (8) [3 – 20]</td>
<td>1 (3) [0 – 13]</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (10) [4 – 23]</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Changes in hearing</td>
<td>1 (3) [0 – 13]</td>
<td>0</td>
</tr>
<tr>
<td>Mood change</td>
<td>3 (8) [3 – 20]</td>
<td>0</td>
</tr>
<tr>
<td>General discomfort</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are reported as number (%) [95% CI].

*No serious adverse effects occurred.
†Fourteen subjects experienced more than one adverse effect.
‡Scale was 0–4.

The need for IV equipment or stretcher space. Demands on nursing staff are reduced, and the risk of needle-stick injuries is eliminated. Carr et al. showed that intranasal ketamine resulted in detectable blood levels after 2 minutes, with a maximum concentration apparent at 30 minutes. Huge et al. showed that intranasal ketamine reduced pain for at least 3 hours. Both of these studies judged intranasal ketamine to be effective, with adverse events being minor and transient. In this series no serious adverse events occurred and minor adverse effects occurred with an incidence similar to that found with the use of IV opiates.

Experience with intranasal fentanyl has shown that efficacious analgesia is achieved with a shorter time to administration compared to IV morphine. However, the use of opioid analgesia raises the concern of