

ORIGINAL RESEARCH

Sub-dissociative-dose intranasal ketamine for moderate to severe pain in adult emergency department patients

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Abstract

Background: There are currently no studies assessing effectiveness of sub-dissociative intranasal (IN) ketamine as the initial analgesic for adult patients in the ED.

Objective: The study aims to examine the effectiveness of sub-dissociative IN ketamine as a primary analgesic agent for adult patients in the ED.

Method: This is a prospective, observational study of adult ED patients presenting with severe pain (≥ 6 on 11-point scale at triage). IN ketamine dose was 0.7 mg/kg, with secondary dose of 0.5 mg/kg at 15 min if pain did not improve. After 6 months, initial dose was increased to 1.0 mg/kg with the same optional secondary dose.

Primary outcomes: The primary outcomes are change in VAS rating at 30 min; percentage of patients reporting clinically significant reduction in VAS (≥ 20 mm) at 30 min; dose resulting in clinically significant pain reduction.

Results: Of the 72 patients available for analysis, median age was 34.5 years and 64% were men. Median initial VAS rating was 76 mm (interquartile

range [IQR]: 65–82). Median total dose of IN ketamine for all patients was 0.98 mg/kg (IQR: 0.75–1.15, range: 0.59–1.57). Median reduction in VAS rating at 30 min was 24 mm (IQR: 2–45). Forty (56%, 95% CI: 44.0–66.7) reported VAS reduction ≥ 20 mm, these patients having had a total median ketamine dose of 0.94 mg/kg (IQR: 0.72–1.04).

Conclusion: IN ketamine, at a dose of about 1 mg/kg, was an effective analgesic agent in 56% of study patients. The place of IN ketamine in analgesic guidelines for adults requires further investigation.

Key words: analgesia, emergency medicine, intranasal, ketamine, pain.

Introduction

Ketamine is commonly used for dissociative anaesthesia and procedural sedation.^{1,2} In sub-dissociative doses, it is a potent analgesic^{1,3} and can be used as adjunctive analgesia with opioids, or when opioids are contraindicated.^{4–6} There is no literature describing the use of ketamine as primary intranasal (IN) analgesia in the

Key findings

- Intranasal ketamine at a dose of about 1 mg/kg was moderately effective in providing pain relief as a single agent to adult patients presenting to the ED with severe pain from various presenting complaints.
- Patients who did not respond to initial dosing of intranasal ketamine did not gain any additional benefit from an additional dose.
- When using intranasal ketamine as an analgesic agent, other agents, such as opioids, should be added in patients who do not respond to initial ketamine dosing.
- Further research regarding the role of intranasal ketamine as an analgesic in the ED would be useful. Particularly, its role in combined analgesic regimens with opioid agents.

adult ED. IN fentanyl is commonly used in the paediatric ED.^{7,8} Pre-hospital services use high-concentration IN fentanyl for analgesia.^{9,10} However, standard concentration fentanyl (50 mcg/mL) is only suitable in patients up to 50 kg.¹¹ This is unlikely to provide adequate doses in most adult patients. Ketamine might be an alternative IN agent in adults where standard concentration fentanyl is impractical. This pilot study assesses the effectiveness of IN ketamine as an analgesic for treatment of moderate to severe pain in adult ED patients.

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Accepted 11 November 2013

Method

Study design, setting

This is a prospective, open-label, observational study in the EDs of Monash Medical Centre (major referral ED, annual census 59 000), Dandenong Hospital (urban district ED, annual census 57 000) and Frankston Hospital (urban district ED, annual census 50 000). The study was approved by Monash Health and Peninsula Health Human Research and Ethics Committees (HREC) and registered as a clinical trial with the Australian and New Zealand Clinical Trials Registry (ACTRN12611001102965). Recruitment took place between February 2012 and February 2013.

Participants

Subjects were 18 years and older; with self-reported pain severity of six or more at triage (0 to 10 numerical rating scale); and with medical recommendations for parenteral analgesia.

So as to not delay analgesia delivery, we received HREC approval for initial verbal consent of ketamine administration. Written consent was obtained after treatment was commenced.

Exclusion criteria are the following: subarachnoid haemorrhage; migraine or myocardial ischaemia; head injury with loss of consciousness; haemodynamic instability; hypertension (>180/100 mmHg); trauma to more than one body region; history of schizophrenia; known or suspected pregnancy; aberrant nasal anatomy or nasal problems affecting IN drug administration; inability to self-report pain severity; history of recreational substance abuse; ketamine allergy; administration of opioids in previous 4 h (prior non-opioid analgesic use was not an exclusion).

Outcome measures

Primary

1. Change in VAS rating 30 min after administration of ketamine. Patients rated pain severity on a standard 100 mm line marked 'no pain' at the left-hand end and 'worst pain ever' at the right-hand

end. Severity ratings were recorded in mm from the left-hand end of the line. Change in mm recorded as positive for movement to the left (less pain) and negative to the right (more pain).

2. Percentage of patients reporting clinically significant reduction in VAS rating (defined as ≥ 20 mm. The minimum clinically significant difference in pain is variously reported as 13–18 mm^{12,13}) at 30 min.
3. Comparison of doses that did and did not result in clinically significant reductions in pain at 30 min.

Secondary

1. Change in VAS and percentage of patients reporting clinically significant reduction in VAS at 60 min.
2. Adjectival description of change ('a lot less', 'a little less', 'the same', 'a little more' or 'a lot more') at 30 and 60 min, and the number improving (a little or a lot less).
3. Self-reported level of sedation at 30 and 60 min ('excessively sedated', 'level of sedation satisfactory' or 'no opinion') and observed (Ramsay Sedation Scale [RSS]):¹⁴ 1 'anxious or restless or both', 2 'Cooperative, orientated and tranquil', 3 'Responding to commands', 4 'Brisk response to stimulus', 5 'sluggish response to stimulus', 6 'no response to stimulus'.
4. Patient satisfaction with analgesic effect ('satisfied', 'not satisfied' or 'no opinion').
5. Need for additional analgesia.
6. Frequency of AEs.

Study procedure

Subjects recorded baseline pain severity rating using VAS were weighed, and an initial IN dose of ketamine was given by nursing staff trained in IN drug delivery. If there was no reduction in pain after 15 min, a supplementary dose was given. VAS pain rating at each time-point was measured on a new page of the case report form. Three ketamine dosing tables were used. These approximated 0.7 mg/kg, for the initial dose in first 6 month study period and 1.0 mg/kg used for the initial dose during the second 6

month study period. A 0.5 mg/kg table was used for supplementary dosing of ketamine throughout the study. Doses were chosen from previous literature, suggesting that between 0.7 and 1.0 mg/kg, IN ketamine provides adequate analgesia with minimal side-effects.^{15,16} Outcome data were recorded 30 min after initial ketamine dosing, and again at 60 min if additional analgesia had not been given.

Study materials

Ketamine preparation used was Ketalar® Solution for injection 100 mg/mL (Hospira, Melbourne, Victoria, Australia). Half the total volume was given per naris, via a mucosal atomiser device (Wolfe Tory Medical, Salt Lake City, UT, USA).

Data analysis

Paper case report forms were completed by the treating ED doctor. Data entry was performed by one investigator (FY) (Microsoft Excel, Microsoft Corporation, Redmond, WA, USA) and analysed using Stata version 8.0 statistical package (Stata Corporation, College Station, TX, USA). Baseline variables (sex, age and pain aetiology) are described as number and percentage or median with interquartile range as appropriate. Pain severity is reported as median with interquartile range and compared using the Mann-Whitney *U*-test. Categorical descriptions of change are reported as number and percentage with 95% confidence intervals (CI), and compared using the χ^2 -test or Fisher's exact test. Levels of satisfaction, sedation and AEs are descriptive.

Sample size calculation was difficult, given the lack of adult research on IN ketamine. Our paediatric study reported that IN ketamine at 1.0 mg/kg produced a mean reduction in VAS rating of 40 mm (SD 25 mm).¹⁶ For this degree of change, a sample size of 10 patients yields a lower 95% confidence limit of 20 mm. This equates with clinical significance for this study. Given the uncertainty around the level of response in adults, the percentage requiring a second dose and the numbers in dosing groups, the aim was

TABLE 1. Diagnostic groups

Diagnostic group	Frequency (%)
Acute musculoskeletal injury	30 (41.7)
Back pain	9 (12.5)
Abdominal pain	12 (16.7)
Wound infections	6 (8.3)
Perineal abscess	6 (8.3)
Renal colic	4 (5.6)
Other	5 (6.9)

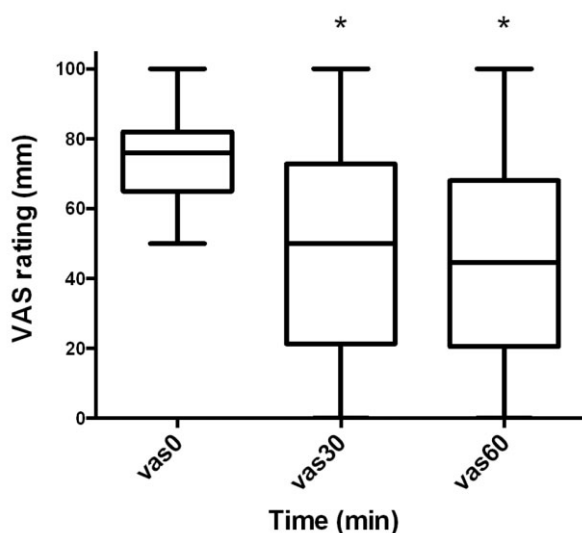


Figure 1. Box and whisker plot of VAS ratings at enrolment ('vas0') and at 30 min ('vas30') and 60 min ('vas60') for all patients following IN ketamine administration (median score with boxes showing IQ range and whiskers showing range of scores at each time-point). * $P < 0.001$ vas30 and vas60 compared with vas0. (Kruskal-Wallis test, Dunn's multiple comparison post-test).

to ensure recruitment of at least double this number during each 6 month period.

Results

Baseline data

Seventy-nine people were recruited to the study. Seven (8.9%) did not have a VAS rating recorded at 30 min. Reasons were: two were given i.v. morphine after 15 min, two declined further participation at 30 min and further recordings were not obtained on three because of excessive ED workload.

Of 72 patients available for analysis, 49 (68.1%), 12 (16.7%) and 11 (15.3%) were recruited at the Monash,

Dandenong and Frankston sites, respectively. Forty-six (63.9%) were men and the median age was 34.5 years (interquartile range [IQR]: 26–52.5). Acute musculoskeletal injury was the most frequent underlying condition (30 of 72, 41.7%) (Table 1). Initial median VAS rating was 76 mm (IQR: 65–82). There were no differences in baseline characteristics between patients recruited at study sites.

Ketamine dose and effectiveness

The median total dose (initial plus supplementary) of IN ketamine received by all patients was 0.98 mg/kg (IQR: 0.75–1.15, range: 0.59–1.57). The median reduction in VAS rating at 30 min was 24 mm (IQR: 2–45). Fifty-

five per cent (95% CI: 44.0–66.7) reported VAS reduction of ≥ 20 mm. The VAS ratings on enrolment and at 30 and 60 min for the whole sample are shown in Figure 1.

Of the 32 patients recruited during the first 6 months of the study, 75.0% of patients received a single median dose of 0.71 mg/kg (IQR: 0.68–0.75), whereas 25.0% received a total median dose of 1.19 mg/kg (IQR: 1.12–1.25), with administration of a median supplementary dose of 0.48 mg/kg (IQR: 0.46–0.50). Forty patients were recruited during the second 6 months. There were 67.5% who received a single median dose of 1.0 mg/kg (IQR: 0.95–1.03), and 32.5% who received a total median dose of 1.51 mg/kg (IQR: 1.43–1.56), with administration of a median supplementary dose of 0.51 mg/kg (IQR: 0.48–0.52) (Fig. 2, Table 2).

A comparison of variables between patients reporting a VAS reduction of ≥ 20 mm and those who did not is shown in Table 3. There was no difference in age, sex, initial VAS rating or diagnosis between the groups. The total median dose in patients who reported a VAS reduction of ≥ 20 mm compared with those who did not was 0.94 mg/kg (IQR: 0.72–1.04) and 1.03 mg/kg (IQR: 0.95–1.36), respectively ($P = 0.009$, Mann-Whitney U-test). In patients reporting a VAS reduction of ≥ 20 mm, 82.5% received only a single dose of ketamine. In patients who did not report a VAS reduction ≥ 20 mm, only 56.3% received a single ketamine dose. This difference was statistically significant ($P = 0.02$ Fisher's exact). The differences in percentage reporting satisfaction with analgesia and need for additional analgesia at 30 min between the two groups were statistically significant (Table 3).

For all 72 patients, change in pain severity at 30 min was described as being 'a lot better', 'a little better', 'the same', 'a little worse' and 'a lot worse' by 34.7%, 31.9%, 26.4%, 1.4% and 5.6% of patients, respectively. At 30 min, 59.7% were satisfied with treatment, 12.5% were unsure and 27.8% were not satisfied. At 30 min, 19.4% patients were given other analgesia. Table 3 compares characteristics of subjects reporting a VAS improvement in

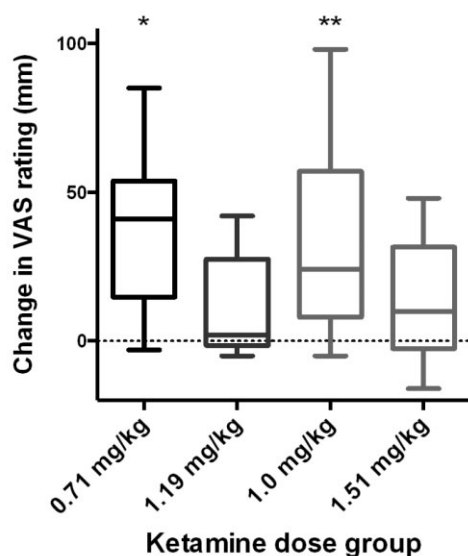


Figure 2. Box and whisker plot of change in VAS rating at 30 min from baseline for each ketamine dose group (median scores with boxes showing IQR range and whiskers showing range of scores at each time-point). * $P = 0.02$ for 0.71/mg/kg versus 1.19 mg/kg (Mann–Whitney U-test). **Not significant for 1.0 mg/kg versus 1.51 mg/kg.

pain of ≥ 20 mm with those who did not.

At 60 min, 58 patients had not been given other analgesic agents at 30 min. Fifty-two (89.7%) provided a VAS rating (median 44.5 mm, IQR: 21–68). The median reduction in VAS rating from enrolment to 60 min was 28.5 mm (IQR: 2.5–51). Fifty-five per cent had a reduction of ≥ 20 mm, of whom 82.8% had reported this level of reduction at 30 min. At 60 min, 89.7% reported on satisfaction, of whom 67.3% were satisfied, with 88.6% of these having been satisfied at 30 min. At 60 min, 39.7% patients received additional analgesia, of whom 22 (95.7%) had reported a 60 min VAS rating. Of these, 14 (63.6%) had reported a reduction in VAS rating of < 20 mm from enrolment.

Safety and adverse effects

Self-reported level of sedation was recorded from all 72 patients at 30 min and from 51 of 58 patients at 60 min. Satisfactory sedation was reported by 43.1% and 49.0% patients at 30 and 60 min, respectively. Unwanted sedation was reported by 51.4% and 41.2% at 30 and 60 min, respective-

ly. RSS scores were available for 71 of the 72 patients at 30 min, and 51 of 58 patients at 60 min. At 30 min, scores of 1, 2 or 3 were recorded for 21.1%, 71.8% and 7.0% of the patients, respectively. At 60 min, scores of 1, 2 or 3 were recorded for 13.7%, 84.3% and 2.0% of the patients, respectively.

Seventy-nine per cent of subjects (57/72) reported a total of 96 adverse effects (Table 4), the most common being dizziness (31.9%).

Discussion

In this study, ED patients with pain from a variety of causes had a median reduction in VAS of 24 mm, with an IN ketamine dose around 1 mg/kg. Clinically significant VAS reduction of ≥ 20 mm was only seen in 56% of subjects. When VAS reductions of ≥ 20 mm were reported, the median IN ketamine dose (0.94 mg/kg) was lower than the dose given to those with less pain improvement (1.03 mg/kg). The majority of subjects requiring supplementary ketamine at 15 min failed to attain clinically significant pain rating reductions by 30 min. This was regardless of the initial dose given. In general, when improvement was seen

by 30 min, it was maintained at 60 min. Delayed responses were uncommon, regardless of initial dose or receipt of supplementary doses.

Results are not consistent with those we reported in children with isolated limb injury, where IN ketamine was given in similar doses.¹⁶ In that study, a total dose of around 1.0 mg/kg resulted in a median VAS reduction of 43 mm at 30 min, with 82% reporting a reduction of ≥ 20 mm. The paediatric study included only children with limb injuries. The effect of adjunctive analgesic measures, such as limb splinting, was not assessed. Although limb injuries figured prominently in this study, ketamine was also given for other painful conditions. As a result, the response to IN ketamine might depend upon the underlying condition. Also, the lack of increasing analgesic effect at the higher ketamine dose was unexpected. Ketamine dosing volume was greater and might have resulted in incomplete absorption. Also, dysphoria might have been interpreted as lack of response in some patients.

Comparison of these results for IN ketamine with results for IN fentanyl in adults is difficult. Reports of IN fentanyl use are mainly from non-emergency settings.^{10,17} In a retrospective pre-hospital observational trial, IN fentanyl was given by paramedics to adults with acute pain.¹⁸ On a 0 to 10 scale, reported reductions in mean pain rating with IN fentanyl were from 7.6 initially to 6.0 at 5 min, and 4.4 by hospital arrival. Differences in study design make direct comparison with our study difficult. However, IN fentanyl appeared to provide better analgesia in adults in the pre-hospital setting.

Adverse effects were common but mild. Dizziness was reported frequently and is similar to our paediatric study. Adults reported excessive sedation more frequently, as well as sensations such as feeling 'spaced out', 'euphoric' or 'disconnected'. Children (or their parents) might perceive acceptable sedation differently. Children might not have the vocabulary to report more complex sensations. No hallucinatory or emergence phenomena were reported by subjects in this study.¹⁶

TABLE 2. Primary outcome measures at 30 min for the four dose groups

	Period using 0.7 mg/kg initial + 0.5 mg/kg supplementary dosing tables		Period using 1.0 mg/kg initial + 0.5 mg/kg supplementary dosing tables	
	Single dose (n = 32)	Initial + supplementary (n = 8)	Single dose (n = 27)	Initial + supplementary (n = 13)
Total dose, median (IQR) (mg/kg)	0.71 (0.68–0.75)	1.19 (1.12–1.25)	1.0 (0.95–1.03)	1.51 (1.43–1.56)
VAS reduction, median (IQR) (mm)*	41 (16.5–52.5)	2 (–1–27)	24 (8–57)	10 (0–24)
VAS reduction ≥ 20 mm, number (%) (95% CI)**	18 (75.0) (55.1–89.2)	3 (37.5) (10.6–72.2)	15 (55.6) (36.7–73.3)	4 (30.8) (10.6–58.7)

For the four dose groups: *Comparison of the reduction in VAS at 30 min were statistically significant, $P = 0.02$ (Kruskal–Wallis). **The percentage reporting a reduction of ≥ 20 mm was statistically significant, $P = 0.04$ (Fisher's exact).

TABLE 3. Comparison of variables between those who reported VAS reductions of ≥ 20 mm at 30 min, and those who did not

Variable	VAS reduction ≥ 20 mm (n = 40)	VAS reduction < 20 mm (n = 32)	P-value
Age, median (IQR) (years)	33 (25.5–51.5)	39 (27–54.5)	0.54*
Male sex, n (%) [95% CI]	26 (65.0) [49.4–78.5]	20 (62.5) [45.0–77.9]	0.83**
Initial VAS rating, median (IQR) (mm)	76.5 (62.5–82)	76 (67–86)	0.22*
Diagnostic group, n (%) [95% CI]			
Musculoskeletal	16 (40.0) [25.8–55.6]	14 (43.8) [27.5–61.1]	0.34**
Back pain	3 (7.5) [1.9–19.1]	6 (18.8) [8.0–35.0]	
Abdominal pain	9 (22.5) [11.6–37.3]	3 (9.4) [2.4–23.4]	
Wound infections	4 (10.0) [3.3–22.4]	2 (6.3) [1.1–19.2]	
Perineal abscess	3 (7.5) [1.9–19.1]	3 (9.4) [2.4–23.4]	
Renal colic	1 (2.5) [0.1–11.7]	3 (9.4) [2.4–23.4]	
Other	4 (10.0) [3.3–22.4]	1 (3.1) [0.2–14.5]	
Total dose, median (IQR) (mg/kg)	0.94 (0.72–1.04)	1.03 (0.95–1.36)	0.009*
Single dose only, n (%) [95% CI]	33 (82.5) [68.4–92.0]	18 (56.3) [38.9–72.5]	0.02**
Symptoms 'a lot' or 'a little' better, n (%) [95% CI]	39 (97.5) [88.3–99.9]	9 (28.2) [14.7–45.4]	<0.001**
Satisfied with analgesia, n (%) [95% CI]	35 (87.5) [74.5–95.3]	8 (25.0) [12.3–42.0]	<0.001**
Required other analgesia at 30 min, n (%) [95% CI]	2 (5.0) [0.8–15.6]	12 (37.5) [22.2–55.0]	0.001**

*Mann–Whitney U-test. ** χ^2 -test. CI, confidence interval; IQR, interquartile range.

This study has a number of limitations. It was observational in nature. We did not use a comparator analgesic. Improvement in pain rating could be attributed to the natural course

of the condition or placebo effect. Sample size was not sufficient to allow subgroup analyses. The study was unblinded. Pain rating reports might be influenced by attending staff.

Adult ED nursing staff might be less familiar with IN drug delivery than paediatric ED nurses. Ineffective drug delivery could have contributed to treatment failures. However, in-service

TABLE 4. Reported adverse effects

Adverse effect type	Frequency (n = 72)† (%)
Dizziness	23 (31.9)
'Spaced out', 'euphoric', 'disconnected'	17 (23.6)
Unpleasant taste	16 (22.2)
Drowsiness	14 (19.4)
Nausea	9 (12.5)
Numbness (usually face/hands/feet)	6 (8.3)
Blurred vision	4 (5.5)
Nasal congestion	3 (4.2)
Cough/throat irritation	2 (2.8)
Headache	2 (2.8)
None	15 (20.8)

†Total adverse effects exceed 72 as some people reported multiple effects.

training was undertaken for IN administration. We did not assess patients' prior chronic analgesic use. Detection bias through choice of reduction in VAS of ≥ 20 mm as equating with clinical significance is debatable. This level of change was consistently reported by subjects describing their pain as either 'a lot' or 'a little' less and they were satisfied with analgesic treatment. Such correlations support the use of this measure, which is consistent with previous observations assessing analgesic effectiveness.^{12,13}

Conclusion

IN ketamine produced clinically significant pain relief in only 56% of the study population in a dose around 1.0 mg/kg. Analgesia onset was rapid and lasted for at least 1 h. Ketamine was relatively safe, although mild AEs, such as sedation and dizziness, were common. Notably, lack of effect by 15 min suggests alternative supplementary IN or i.v. analgesic should be used.

Given the relatively low response rate, IN or i.v. opioids might be more effective first-line analgesics for adults in the emergency setting. IN ketamine might have a greater role as adjunctive analgesia in patients with poor response to large doses of opioids or in opioid-dependent patients. The place of sub-dissociative dose IN ketamine

as analgesia in the ED requires further assessment.

Competing interests

AG and DE-W are section editors for *Emergency Medicine Australasia*.

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