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Sub-dissociative dose intranasal ketamine for limb injury pain in children in the emergency department: A pilot study

Fiona Yeaman,[1] Ed Oakley,[1,2] Robert Meek[1] and Andis Graudins[1,2]
[1]Southern Health Emergency Medicine Research Group, Southern Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia, and [2]Paediatric Emergency Department, Department of Emergency Medicine, Monash Medical Centre, Southern Health, Clayton, Victoria, Australia

Abstract

Objective: The present study aims to conduct a pilot study examining the effectiveness of intranasal (IN) ketamine as an analgesic for children in the ED.

Methods: The present study used an observational study on a convenience sample of paediatric ED patients aged 3–13 years, with moderate to severe (≥6/10) pain from isolated limb injury. IN ketamine was administered at enrolment, with a supplementary dose after 15 min, if required. Primary outcome was change in median pain rating at 30 min. Secondary outcomes included change in median pain rating at 60 min, patient/parent satisfaction, need for additional analgesia and adverse events being reported.

Results: For the 28 children included in the primary analysis, median age was 9 years (interquartile range [IQR] 6–10). Twenty-three (82.1%) were male. Eighteen (64%) received only one dose of IN ketamine (mean dose 0.84 mg/kg), whereas 10 (36%) required a second dose at 15 min (mean for second dose 0.54 mg/kg). The total mean dose for all patients was 1.0 mg/kg (95% CI: 0.92–1.14). The median pain rating decreased from 74.5 mm (IQR 60–85) to 30 mm (IQR 12–51.5) at 30 min ($P < 0.001$, Mann–Whitney). For the 24 children who contributed data at 60 min, the median pain rating was 25 mm (IQR 4–44). Twenty (83%) subjects were satisfied with their analgesia. Eight (33%) were given additional opioid analgesia and the 28 reported adverse events were all transient and mild.

Conclusions: In this population, an average dose of 1.0 mg/kg IN ketamine provided adequate analgesia by 30 min for most patients.

Key words: *analgesia, intranasal administration, ketamine, paediatric, pain.*

Introduction

The provision of adequate and timely analgesia to people presenting with painful conditions to EDs is considered a core component in the provision of quality care.[1] In paediatric emergency practice, delivery of i.v. opioids for moderate to severe pain can be problematic. Intravenous access can be difficult to obtain,[2] fear of

Correspondence: Professor Andis Graudins, Southern Health Emergency Medicine Research Group, Department of Emergency Medicine, Monash Medical Centre, Clayton Road, Clayton, Vic, 3168, Australia. Email: andis.graudins@monash.edu

Fiona Yeaman, Medical Student; Ed Oakley, MBBS, FACEM, Director of Paediatric Emergency Medicine; Robert Meek, MBBS, MPH, FACEM, Director of Emergency Medicine Research, Dandenong Hospital; Andis Graudins, MBBS, PhD, FACEM, FACMT, Professor of Emergency Medicine and Toxicology Research, Southern Health and Southern Clinical School, Monash University.

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needles might compound the difficulty[3] and most topical anaesthetic agents applied prior to i.v. cannula placement take at least 30 min to be effective.[4]

For these reasons, use of the intranasal (IN) route for analgesia administration has been explored in recent years. Drug administration by this route is fast, simple and pain free.[5] Drug absorption and onset of action are rapid, aided by avoidance of first-pass metabolism.[3] IN fentanyl is now commonly administered as an analgesic for pain in children, both in the pre-hospital and ED settings.[6–8] However, there would be benefit in having other agents available for IN use. The availability of complementary analgesic agents is useful if an incomplete analgesic response results to opioids. This would include situations where fentanyl is given IN[8] or when side-effects, such as marked sedation, might result from repeat dosing of opioids for relief of severe pain.

Ketamine is an N-methyl D-aspartate receptor antagonist used as a dissociative anaesthetic and analgesic agent.[9] In sub-dissociative doses, it acts as a potent analgesic without causing dissociation or anaesthesia, and has been used intravenously in conjunction with opioids to produce an opioid dose-sparing effect in moderate to severe pain.[10]

The use of IN ketamine in analgesic doses is reported in adults,[11–15] with doses varying between 0.2 and 0.7 mg/kg.[11–15] Adverse effects reported with sub-dissociative doses of ketamine have been limited to mild sedation, dysphoria and psychomimetic effects.[10–13] Currently, there are no data available on either the effectiveness of IN ketamine as an analgesic in paediatric ED patients with moderate to severe pain or the IN dose likely to be required in this setting.

The present study was designed as a pilot to determine prospectively if IN ketamine provided effective and safe analgesia for moderate to severe pain from limb injuries in children attending the ED. The purpose was to provide some information on the potential utility of IN ketamine in this setting, and to determine an appropriate dose for use in future clinical trials to compare the analgesic effectiveness of IN ketamine with other currently used analgesic agents.

Method

Study design, setting and period

A prospective, open-label study was conducted at Monash Medical Centre, a tertiary referral hospital, where the Paediatric ED has an annual census of 25 000 patients. The study was approved by the Southern Health and Monash University ethics committees and is registered as a clinical trial with the Australian and New Zealand Clinical Trials Registry (ACTRN 12612000012875). Recruitment of a convenience sample of eligible patients took place between 1 March and 30 June 2012.

Inclusion/Exclusion criteria

Inclusion criteria was as follows: age 3–13 years; weight 10–50 kg; isolated limb injury with self-reported pain score of ≥6 (0–10 numerical rating scale) as part of the triage nurse assessment.

Exclusion criteria was: inability to self-report pain severity (any reason); known ketamine allergy; prior administration of opioid analgesia (oral or parenteral); trauma to >1 body region; known aberrant nasal anatomy or acute/chronic nasal problems likely to limit IN administration/absorption of medication.

Prior use of non-opioid analgesics did not necessitate exclusion.

Study procedure

Following parental consent, the child self-reported pain severity was recorded using the age-appropriate scale. An initial dose of IN ketamine (Ketalar® Solution for injection 100 mg/mL, Hospira Pty Ltd, Melbourne, Victoria, Australia) was then administered. After 15 min, the need for a smaller supplementary dose was assessed using pain severity rating, description of change and level of sedation. Outcome measures were then recorded 30 and 60 min after the initial ketamine dose. At the conclusion of the study period, patient/parent satisfaction was rated, occurrence of adverse events was noted and use of 'rescue' analgesics (drug/dose at the discretion of the treating ED doctor) was recorded. The initial and supplementary ketamine dose guideline is shown in Supporting Information Table S1. The initial dose of ketamine was aimed to be around 0.7 mg/kg as determined from the literature as the most effective dose in adult studies relieving postoperative dental pain.[11] It was decided empirically that patients requiring a supplementary dose would receive 0.5 mg/kg. Dosing was undertaken using a dosing table, in 5 kg weight bands. As a result, ketamine doses were rounded in the table to the nearest 5 mg for ease of dose and volume calculation, as well as to reduce risk of dosing error. Consequently, after analysis of the actual doses received by children, the initial ketamine dose approximated

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0.85 mg/kg, and the secondary dose was 0.5 mg/kg, each varying slightly depending on the exact weight of the child. Prior to administration, the ketamine was diluted with saline to a total volume of 0.5 mL and was administered as 0.25 mL per nare using a Mucosal Atomiser Device (MAD, Wolfe Tory Medical, Salt Lake City, UT, USA).

Measurement tools

Pain severity rating scales

1. Faces Pain Scale – Revised (FPS-R): for children aged 3–6 years, requires choice of one of a line of six faces described as progressing from 'no pain' at the left-hand end, to 'very much pain' at the right-hand end. The faces are allocated numerical ratings of 0, 20, 40, 60, 80 and 100 from left to right. This rating is used for severity calculations at a single time point, whereas change is recorded as positive for face selection towards the left (less pain) and negative towards the right (more pain).
2. VAS: for children aged 7 years and older, required marking of a standard 100 mm line labelled 'no pain' at the left-hand end and 'worst pain ever' at the right-hand end. The severity rating at a single time point is the measurement (mm) from the left-hand end of the line. Change in severity is recorded as positive for movement to the left (less pain) and negative towards the right (more pain).

Description of change in pain severity required a choice of pain being: 'a lot less', 'a little less', 'the same', 'a little more' or 'a lot more'.

Patient/parent satisfaction required a choice of 'satisfied', 'not satisfied' or 'no opinion'.

Sedation was graded by the attending doctor using the University of Michigan Sedation Scale (UMSS): 0, 'awake and alert'; 1, 'mild sedation'; 2, 'moderate sedation'; 3, 'deep sedation'; and 4, 'unrousable'.[16]

Outcome measures

The primary outcome measure is change in pain rating 30 min after initial administration of ketamine.

The secondary outcome measures were change in pain rating 60 min after initial administration of ketamine; percentage of patients reporting pain to have decreased by ≥20 mm (minimum clinically significant difference) and percentage of patients describing pain to be 'a little less' or 'a lot less' at 30 and 60 min; level of sedation at 15, 30 and 60 min; patient/parent satisfaction with analgesic effect; and occurrence of adverse events.

Sample size

This was a pilot study with a convenience sample of 30 patients at the proposed ketamine dose. The aim was to utilise the data from the present study to determine sample size for subsequent comparative analgesic studies assessing the efficacy of IN ketamine in children.

Data analysis

Data were stored in an Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA) and analysed using the Stata version 8.0 statistical package (Stata Corporation, College Station, TX, USA). Baseline variables of sex, age and type of injury are described as number and percentage or median with interquartile range (IQR) as appropriate. Pain severity for each time point is presented as median with IQR, as is the amount of change to each time point. Combining VAS and FPS-R measures to form one pool of data has been previously validated in paediatric pain research.[17] The number and percentage, with 95% confidence intervals (CI), of patients whose change in pain scores from baseline exceeded 20 mm are also reported, along with the number and percentage who described their pain as being reduced ('a little' or 'a lot'). Number and percentage for each level of sedation on the UMSS at each time are described, as are all other adverse events. Number and percentage reporting satisfaction with the medication and those requiring additional analgesia are also described. As this was a pilot investigation of analgesic effectiveness, formal sample size and power calculations were not relevant.

Results

Of the 30 eligible patients recruited, two (6.7%) were excluded because pain severity and change data were not collected at 30 min (Fig. 1). Of the remaining 28 patients, 23 (82.1%) were male, median age was 9 years (IQR 7–11), median weight was 31 kg (IQR 23–41), 21 (75%) had sustained a fracture and 10 (35.7%) patients used the FPS-R to rate pain. The median initial pain rating was 74.5 mm (IQR 60–85) and an initial mean dose of 0.83 mg/kg (95% CI: 0.80–0.86) of ketamine was given (Table 1).

Following the 15 min assessment, 10 (35.7%) of the patients were given a second smaller dose of ketamine (mean 0.57 mg/kg, 95% CI: 0.52–0.61). At this time, the

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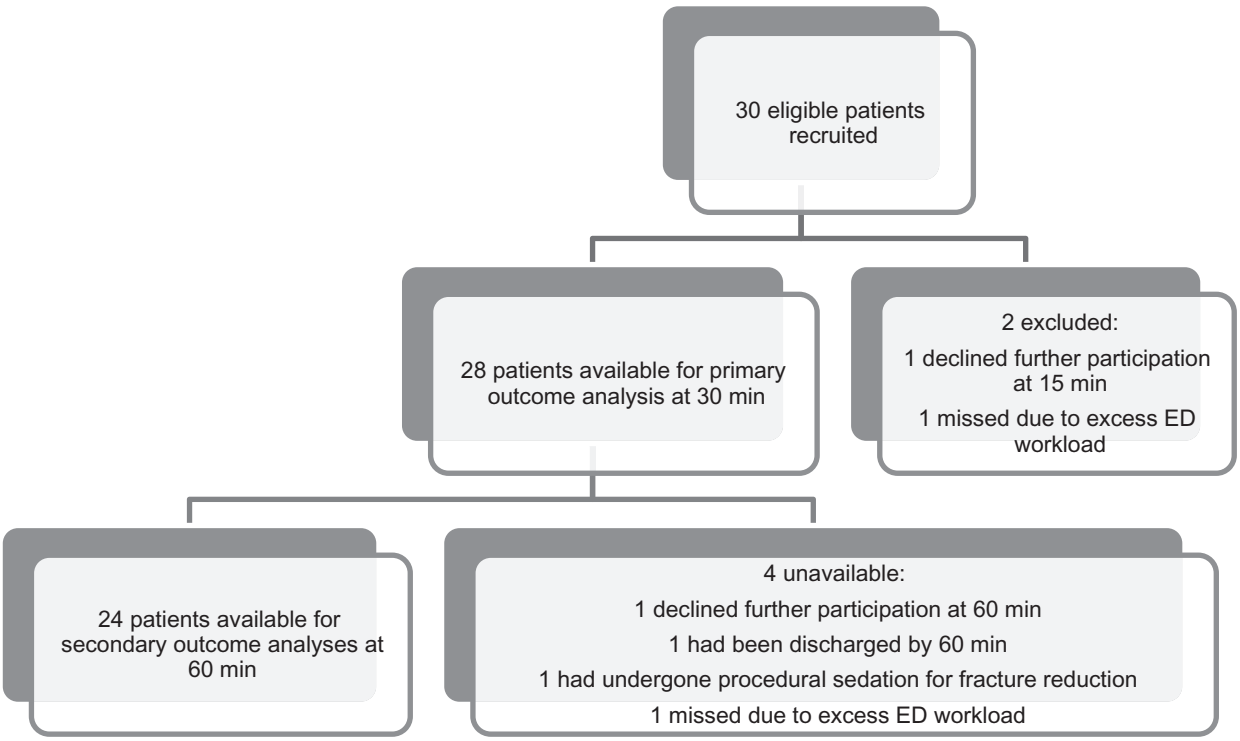

Figure 1. Patient recruitment and inclusion in the analysis.

Table 1. Baseline characteristics

Male sex, *n* (%)		23 (82.1)
Age, median (IQR) (years)		9 (7–11)
Weight, median (IQR) (kg)		31 (23–41)
Pain scale FPS-R, *n* (%)		10 (35.7)
Diagnosis (%)	Fractured radius/ulna (shaft and distal)	11 (39.3)
	Supracondylar fracture humerus	4 (14.3)
	Fractured tibia/fibula (shaft and malleoli)	3 (10.7)
	Soft tissue injury ankle	3 (10.7)
	Other, one each of: fractured finger/metatarsal/ clavicle, sprained elbow/wrist, burn thigh and foreign body foot	7 (25.0)
Initial pain rating, median (IQR) (mm)		74.5 (60–85)
Initial ketamine dose, mean (95% CI) (mg/kg)		0.84 (0.80–0.86)

IQR, interquartile range; FPS-R, Faces Pain Scale – Revised.

median pain rating for those given a second dose was 60 mm (IQR 44–80) compared with 40 mm (IQR 19–57) for those who only received a single dose (P = 0.03, Mann–Whitney). Differences in age, sex, diagnosis, initial pain rating and initial ketamine dose between those who did and did not receive an additional dose were not statistically significant (Table 2). For all 28 patients, the total mean dose of ketamine received was 1.0 mg/kg (95% CI: 0.92–1.14), which comprised a mean of 0.84 mg/kg (95% CI: 0.80–0.88) for the 18 (64.3%) single-dose patients, and 1.37 mg/kg (95% CI: 1.27–1.48) for the 10 (35.7%) dual-dose patients.

The median pain ratings at enrolment, 30 min and 60 min, were 74.5 mm (IQR 60–85), 30 mm (IQR 12–51.5) and 25 mm (IQR 4–44) (Fig. 2). The reductions from enrolment to each time point were statistically signifi-

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Table 2. Comparison of patients who did and did not require a second dose of ketamine

	Second dose given (n = 10)	Second dose not given (n = 18)	P
Age, median (IQR) (years)	9 (6–10)	10 (7–11)	0.41*
Male sex, n (%) [95% CI]	9 (90%) [59.7–99.5]	14 (77.8%) [54.7–92.5]	0.63**
Fracture, n (%) [95% CI]	9 (90%) [59.7–99.5]	12 (66.7%) [43.1–85.2]	0.36**
Initial pain score, median (IQR) (mm)	85 (60–100)	68.5 (60–80)	0.15*
Initial ketamine amount, mean (95% CI) (mg/kg)	0.81 (0.74–0.87)	0.84 (0.80–0.88)	0.36***
Pain score at 15 min, median (IQR) (mm)	60 (49–80)	40 (18–53)	0.03*

**Mann–Whitney test. **Fisher's Exact test. ***t-test, independent samples. IQR, interquartile range.*

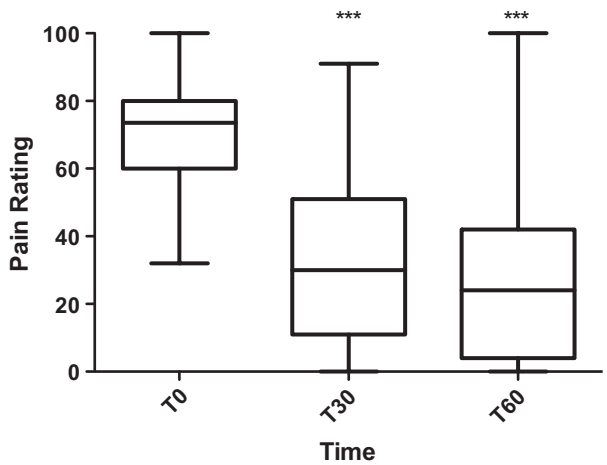

Figure 2. Box and Whisker plot of pain rating at each time point. Median values with interquartile range (box) and total range (whiskers). The fall in pain rating was significant at T30 and T60 when compared with T0 (***P < 0.001).

cant (both P < 0.001, Mann–Whitney), but the reduction from 30 to 60 min was not (P = 0.27, Mann–Whitney). From enrolment to 30 and 60 min, 23 of 28 (82.1%, 95% CI: 64.8–93.2) and 20 of 24 (83.3%, 95% CI: 64.5–94.5) patients, respectively, reported reductions in pain rating of ≥20 mm. From enrolment to 30 and 60 min, 25 of 28 (89.3%, 95% CI: 73.6–97.2) and 20 of 24 (83.3%, 95% CI: 64.5–94.5) patients, respectively, reported pain severity to be either 'a little' or 'a lot' less. Eight of 24 (33.3%) patients required opioid analgesics at 60 min.

Sedation was mild (UMSS rating of 1) in 12 of 28 (42.9%), 12 of 28 (42.9%) and 2 of 24 (8.3%) at 15, 30 and 60 min, respectively. All other participants were rated as being awake and alert (UMSS score 0). Other reported adverse events are reported in Table 3, and were mild, transient and did not require any specific treatment. Importantly, there were no episodes of dissociation or hallucination observed or reported.

Table 3. Reported adverse events following administration of intranasal ketamine to children with limb injury (n = 28)

Event	Frequency, n (%)
Dizziness	10 (35.7)
Bad taste	8 (28.6)
Dysphoria	4 (14.3)
Nausea	3 (10.7)
Sore throat	2 (7.1)
Diplopia	2 (7.1)
Amnesia	1 (3.6)
Headache	1 (3.6)
Vomiting plus abnormal jaw movements	1 (3.6)

Patient or parent satisfaction with analgesic was also collected as a part of this study. At 15, 30 and 60 min, 20 of 28 (71%), 20 of 28 (71%) and 20 of 24 (83%), respectively, were satisfied with the degree of pain relief following ketamine administration.

Discussion

This study found that for a convenience sample of children with moderate to severe pain from isolated limb injury, IN ketamine at a dose of about 1.0 mg/kg provided an adequate level of analgesia by 30 min, and that the analgesic effect was maintained to 60 min. The primary outcome measure of reduction in pain rating to 30 min of 44 mm (IQR 24–52.5) was both statistically significant and clinically meaningful, with over 80% of the patients reporting a reduction in pain score of at least 20 mm at both 30 and 60 min and stating that their pain was less. The reported minimum clinically significant difference for pain using the VAS varies in the literature,[18–20] with the 20 mm cut-off used here being reasonably conservative. Undue sedation was not an issue in this population and other adverse effects were mild and transient.

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This finding is consistent with the several small trials reporting analgesic effectiveness of sub-dissociative doses of IN ketamine in adults in the setting of postoperative dental pain, breakthrough pain in cancer patients and in incident pain for procedures such as dressing changes.[11,12,14] However, only the single case report of a child with burns receiving a single analgesic dose of 0.5 mg/kg could be located in the paediatric literature.[15] The doses used in the adult studies varied from about 0.2 to 0.7 mg/kg, with the greatest effect being at the higher end of the range. Given that ketamine pharmacokinetics are similar in children and adults,[21] we hypothesised that the effective IN ketamine dose for children was unlikely to be less than 0.7 mg/kg, but a single best dose remained unclear. We aimed for an initial dose of 0.7 mg/kg. However, utilising an incremental dosing table in 5 kg weight bands and the strategy to round up rather than round down ketamine dose to the nearest 5 mg, the initial dose of ketamine was closer to 0.85 mg/kg. The selection of 0.5 mg/kg as the supplementary dose at 15 min for children with perceived lack of analgesic effect from the initial dose was empiric. However, we theorised that given the rapid redistribution of ketamine after initial dosing and the inherent safety profile of this agent in both dissociative and subdissociative doses, this secondary dose would be safe. This meant that compared with the mean initial dose of 0.84 mg/kg, the 10 patients who received a second dose had a total mean dose of 1.37 mg/kg. Although numbers were small, there were no obvious initial differences in those whose pain had responded less well by 15 min, so whether this was really a dose-related lack of effect or just that onset of action was somewhat slower is uncertain. Importantly, even at the higher end of the dose range, we did not observe any problems with significant sedation or other adverse effects that might be seen with dissociative doses of ketamine.[9] The lack of significant adverse events with the doses of IN ketamine used in this study parallels the observations of Crellin *et al.* with IN fentanyl, where the authors noted no major adverse events, such as marked sedation, hypotension or hypoxia.[7]

For future practice, these findings suggest that our total group mean dosage of 1.0 mg/kg would be a reasonable starting point, and that this amount is likely to provide adequate analgesia for up to an hour in most children who have moderate to severe pain from limb injuries. More importantly, with regard to the planning of future studies involving IN ketamine, we would suggest 1.0 mg/kg as an appropriate initial dose. A recent small observational trial using IN fentanyl reported similar reductions in pain ratings to those of this study,[7] but properly designed clinical trials are required to compare the efficacy of different commonly used analgesics being delivered by varying routes.

This study has a number of limitations. Use of a convenience sample leaves the possibility of selection bias. We have no information on the total number of non-recruited eligible patients during the study period, and how children with pain from other causes might respond is not known. The small sample size meant that the precision of the point estimates for change in severity was relatively broad, but the fact that the lower limits still tended to exceed the desired level for clinical significance is reassuring. Although the measurement tools and their use in this type of research are well validated, it remains possible with a small sample that particular types of responses might have been systematically influenced in some way. In particular, as delivery of a second ketamine dose was at the treating doctor's discretion, it is not known what factors other than the pain ratings might have influenced this decision. Factors such as reassurance by staff, arrival of a parent and limb support in different types of splints might also have influenced pain ratings, but numbers were too small to consider adjusting for such potential confounders. Patient cooperation during ketamine delivery, along with the technique of the administrator, might also result in variations in the amount of drug received, but all nurses at the study ED have undergone standardised training in use of the MAD.

In conclusion, the present study found that in this population, a total dose of about 1.0 mg/kg of IN ketamine provided adequate analgesia by 30 min for most patients. This finding might aid current analgesic decision making in paediatric emergency practice, but more importantly gives the most accurate information to date on an appropriate dose of IN ketamine for use in clinical trials designed to compare its efficacy with that of other agents.

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Author contributions

FY – student researcher, primary data collector, data analysis, writing of manuscript. EO – data collection, writing of manuscript, student researcher secondary supervisor. RM – statistical analysis and data analysis, manuscript revision. AG – study design, ethics application and liaison with HREC, student researcher supervision, manuscript revision, data analysis.

Competing interests

AG is a Section Editor for *Emergency Medicine Australasia*.

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Supporting Information

Additional Supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Ketamine dosing schedule.

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