

## CLINICAL TOPIC REVIEW

# Ketamine for paediatric sedation/analgesia in the emergency department

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This review investigates the use of ketamine for paediatric sedation and analgesia in the emergency department

The injured child presents a challenge to emergency department (ED) practitioners. The pain and distress can be upsetting for staff as well as parents. The child's distress can be compounded by the fear of a painful procedure to follow, previous conditioning from unexpected "jabs" when receiving immunisations, or previous visits to an ED.<sup>1</sup>

As doctors we strive to relieve pain and suffering, and swear to do no harm. Forced restraint, still performed in some departments in the country (personal communications), is no longer acceptable and may compound the hospital—and needle—phobia throughout life.<sup>1–3</sup> Distraction techniques, play therapy, and adequate analgesia may be sufficient to produce a cooperative, relaxed child.<sup>4–5</sup> When this fails the alternatives to enable a pain free treatment of the injury are general anaesthesia or sedation.<sup>6</sup>

To compare these two approaches we must consider several factors; firstly, the ideal requirements of the agent to be used: rapid onset, adequate depth of sedation and anxiolysis, maintenance of spontaneous respiration, lack of response to the painful stimulus, rapid recovery, and minimal side effects.<sup>6–7</sup> Secondly, the staffing, equipment, and facilities required. Thirdly, the preference of the parent, who acts as the child's advocate; lastly, the procedure proposed.

The phencyclidine derivative ketamine has been described as the ideal agent for paediatric sedation in EDs,<sup>8–18</sup> with departments in the UK,<sup>19–21</sup> USA,<sup>22–23</sup> Australia<sup>24–25</sup> Europe, Japan, Mexico, the Middle East (Green SM unpublished data), and Singapore<sup>26</sup> using the technique regularly. The American College of Emergency Physicians<sup>27</sup> and the Australasian College of Emergency Medicine<sup>28</sup> both have formal guidelines for emergency physicians specifically for ketamine sedation, although the latest national guideline on paediatric sedation in the United Kingdom recommends "...the general anaesthetic agents [...ketamine...]...are only used by those formally trained in paediatric or neonatal anaesthesia or intensive care..."<sup>29</sup>

Ketamine is a unique drug giving complete anaesthesia and analgesia with preservation of vital brain stem functions. This "dissociative" state has been described as "a functional and neuro-physiological dissociation between the neocortical and limbic systems."<sup>30</sup> Ketamine dissociation results in a clinical state of lack of response to

pain or other noxious stimuli, with relative preservation of respiratory and cardiovascular functions despite profound amnesia and analgesia,<sup>10–30–32</sup> described as "cataleptic."<sup>10</sup> This trance-like state of sensory isolation provides a unique combination of amnesia, sedation, and analgesia.<sup>7–10–30–31</sup> The eyes often remain open, though nystagmus is commonly seen. Heart rate and blood pressure remain stable, and are often stimulated, possibly through sympathomimetic actions.<sup>30–31–33</sup> Functional residual capacity and tidal volume are preserved, with bronchial smooth muscle relaxation<sup>34–37</sup> and maintenance of airway patency and respiration.<sup>10–30–31–38</sup>

However, despite the enthusiasm of many authors and practitioners, ketamine may not be the ideal agent. Emergence reactions, sub-anaesthetic conditions, and airway problems do occur,<sup>10–16–39–41</sup> and it is generally recommended that only physicians skilled in airway management and resuscitation are involved in the care of sedated children.

Is ketamine sedation the answer for the unconsolable injured child requiring a painful procedure in the emergency department? Such a child could require exploration of a wound, a strange adult with instruments invading the child's personal space, and attention to functional and cosmetic outcome. Assuming distraction therapy has failed, a three part question can be formulated thus:

"In [children with injuries requiring a painful procedure] is [ketamine sedation/analgesia] a [safe and acceptable technique in the A&E department]?"

## LITERATURE SEARCH

Databases: Medline 1966 to present and Embase 1980 to present via the Ovid interface.

To specify trials involving the randomised comparison of ketamine with other sedative agents the following strategy was used:

"ketamine.mp. AND (children or child\$ or paediatric or paediatric\$ or pediatric or pediatric\$).mp." AND (maximally sensitive randomised control trial filter).<sup>43</sup>

A further search for additional papers was performed with the following strategy: (ketamine or ketamin\$).mp. AND (children or child\$ or paediatric or paediatric\$ or pediatric or pediatric\$).mp. AND (emergency or emergenc\$ or accident or accident\$ or (accident and emergency)).mp.

No limits were applied. The results were assessed for relevant articles by searching the abstracts. The references of review articles were also searched for any additional papers of

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relevance, and the following journals were hand searched for recent articles not yet included in the Medline or Embase databases that may be relevant: *Annals of Emergency Medicine*, *Academic Emergency Medicine*, *Emergency Medicine Journal*, *Emergency Medicine*, *American Journal of Emergency Medicine*, *Pediatric Emergency Care*.

Other sources include data from Lancaster Royal Infirmary and communications with authors in the field of ketamine sedation in children in A&E (Ray McGlone, Lancaster, UK, and Steven Green, California).

## RESULTS

### Randomised trials comparing ketamine with other agents

When comparing agents used for sedation the primary outcome measures must be the characteristics of our mythical "ideal agent."<sup>6,7</sup>

Only three trials were identified that directly compared ketamine alone with another sedative agent. Others used combinations of sedatives, were studying ketamine in the context of general anaesthesia for surgery in an operating environment, or studying the pharmacology of ketamine. Others studied ketamine for critical care procedures. One study was placebo controlled. Table 1 summarises these three trials. The trial published by Acworth *et al*<sup>44</sup> is included to highlight UK experience and the attempts at blinding the investigators made. The trial was confounded as ketamine was given with midazolam.

It is difficult to perform a truly blinded comparison of sedative agents.

Acworth *et al*<sup>44</sup> blinded the observers by bringing them into the sedation room to score the sedation level after drug administration and placing dummy intravenous cannulas on the patients. They also attempted to perform a quality control on their blinding by asking the observers to guess which sedation agent had been given; observers were right in 55%. However, these observers may introduce bias as the ketamine dissociated state can be recognised from other sedation levels.<sup>10,17</sup> A study blinding the data analysis from the clinicians has yet to be reported, and so additional bias remains in the published work. Varying sedation scoring systems, and definitions of "agitation" and "satisfaction" complicate the analysis. The conclusion is that ketamine appears to provide better conditions of sedation, though a somewhat different level of sedation than other agents. Definitions of sedation levels will be dealt with later in this review.

Attempts to compare side effects of sedative agents would require statistical powering. Green *et al*<sup>45</sup> calculated that 7216 subjects would be required for a study to detect a 50% relative difference in airway complications from a baseline incidence of 1.4%. Differences in defining and reporting adverse events may also invalidate reporting of such incidents. Without large, prospective, multicentre, randomised trials we have to rely on large case studies; the evidence from these studies may make a future randomised comparison unethical.<sup>45,46</sup>

### Safety and side effect profile: observational studies and reviews

Green and Johnson published a comprehensive review of ketamine sedation in 1990,<sup>10</sup> alongside a case series of 108 episodes of paediatric sedation in an ED.<sup>38</sup> The authors pooled data from published reports including their own data on the use of ketamine sedation in the intubated patient, and demonstrated an excellent safety profile in a wide range of procedures and settings, including burns ward dressing changes, cardiac catheterisation, dentistry or oral surgery, and minor surgery. Altogether 11 589 cases (97 case series) of

**Table 1** Randomised trials comparing ketamine with other sedatives

Reference	Randomisation	Number of patients	Treatment arms	Outcomes	Results	Comments
McGlone <i>et al</i> <sup>19</sup>	No (alternated treatment arms)	102	IN midazolam 0.5 mg/kg, IM ketamine 2.5 mg/kg	Behaviour, restraint, parent satisfaction	Less restraint with ketamine, parent preference for ketamine	No blinding, no randomisation, assessment of sedation by operator
Young and Kendall <sup>43</sup>	Not clear	59	Oral ketamine 10 mg/kg, oral midazolam 0.7 mg/kg	Tolerance, time to sedation, parental acceptance, adverse events	Lower sedation score with ketamine and better tolerance	Different local anaesthesia, not powered, 7blinded, low numbers, tolerance scale not validated
McGlone <i>et al</i> <sup>20</sup>	No (alternated treatment arms)	87	IM midazolam 0.4 mg/kg +/- flumazenil, IM ketamine 2.5 mg/kg	Behaviour, restraint, parent satisfaction	Less agitation and better parent satisfaction with ketamine, less restraint needed with ketamine	Initially combative children selected for ketamine, no blinding
Acworth* <i>et al</i> <sup>44</sup>	Computer, sealed envelopes	53	IN midazolam 0.4 mg/kg, IV ketamine 1 mg/kg plus IV midazolam 0.1 mg/kg	Physiology, sedation score, parent assessment of sedation	Better sedation with ketamine but "deeper," better parent and doctor satisfaction	Good blinding. 7bias

\*See text.

paediatric sedation using ketamine are discussed and this is by far the most comprehensive review of the topic.

The authors quoted incidences of adverse events as follows (with referenced comments).

**Apnoea: “exceptionally rare”**

Spontaneous respiration is maintained with ketamine dissociation, although the review<sup>10</sup> quoted incidences of transient apnoea after rapid intravenous administration or exceptionally high doses.

Apnoea has since been reported after intramuscular administration.<sup>16 41</sup>

Ketamine has been used successfully for many years as the sole agent to facilitate surgical and other procedures in remote third world locations without skilled anaesthetists present or supplemental oxygen,<sup>47-49</sup> in battlefield and prehospital trauma victims,<sup>50-53</sup> and in the ED during resuscitation of trauma victims for analgesia during manipulation and splinting of fractures (unpublished data). Green *et al*<sup>54</sup> have reported the maintenance of spontaneous respiration in children receiving 5 (n = 3), 10 (n = 5), or 100 (n = 1) times the intended doses of ketamine. Two cases required brief periods of assisted ventilation, and two maintained spontaneous breathing but were intubated prophylactically to protect the airway. None of the recent case series have reported any episodes of apnoea requiring intervention other than supplemental oxygen or brief manual ventilation assistance (table 2).

**Laryngospasm: very rare – intubation required in two cases (0.017%)**

The reported incidence in paediatric general anaesthesia is 0.87%, with children less than 10 years old more susceptible (1.74%) (Olssen and Hallen, 1984. Cited by Green *et al*<sup>10</sup> as reference 158). Although Green *et al*<sup>10</sup> highlight the safe use of ketamine sedation for dental surgery and tonsillectomy, they have subsequently reported an increased incidence (9.5%, all occurring during oesophagogastrosocopy) in procedures entailing stimulation of the oropharynx or hypopharynx.<sup>55</sup> All of these episodes were transient with minimal clinical impact.

It is accepted that instrumentation of the hypopharynx including suctioning may precipitate an episode of laryngospasm. To help prevent the salivation associated with ketamine most authors recommend concurrent administration of an antisialagogue. Salivation may still occur if atropine is given (59 of 501 cases, 12%).<sup>40</sup> Green *et al* reported an incidence of hypersalivation of 1.7%.<sup>16</sup> A randomised controlled trial may answer the question of whether antisialagogues prevent the salivation associated with ketamine.

**Emergence phenomena: 0%–10% – less common with IM administration. Rarely upsetting for children under 10 years old**

Emergence reactions (sensory misinterpretation—“trips”, vivid hallucinations, “floating feelings”, bizarre behaviour) were all reported. These are manifestations of ketamine’s unique effect of sensory isolation, recovering via sensory misinterpretation.<sup>30 31</sup> It is felt that children find this effect less disturbing than adults because of their different perception of the world and their environment. The incidence of emergence reactions is said to increase with age, but can be reduced by positive psychology (“think of a nice dream”), and avoiding ketamine in patients prone to vivid dreaming or psychosis.<sup>10</sup> Some authors advocate adjunctive midazolam to prevent emergence phenomena, but two randomised trials<sup>56 57</sup> and a topic review<sup>58</sup> have shown this to be ineffective, with oxygen desaturation occurring more frequently in the midazolam treated group.<sup>56</sup> Green and

**Table 2** Case series reporting incidence of side effects

	Number of cases	Dose	Airway problems	Emergence dysphoria	Vomiting	Data collection	Follow up	Parent dissatisfaction
Green <i>et al</i> (1990) <sup>38</sup>	108	4 mg/kg IM	1 emesis induced laryngospasm (no sequelae)	1	7 (6.5%)	Complete prospective	77 (71.3%)	5.2%
Dachs and Innes (1997) <sup>12</sup>	30	1–2 mg/kg IV	nil	4 “mild”	2 (6.7%)	Complete prospective	29 (96.6%)	0
Green <i>et al</i> (1998) <sup>16</sup>	1022	4 mg/kg IM	4 laryngospasm, oxygen and ventilatory assistance given. No sequelae. 7 airway malalignment, 2 apnoea, 1 respiratory depression	Mild in 76, moderate/severe in 7. 2 given midazolam	6.7%	Complete but only 431 (42%) were prospective	Nil	
Green <i>et al</i> (1998) <sup>61</sup>	156	0.5–3 mg/kg IV	1 respiratory depression	Nil (2 – mild agitation)	6	Complete	Nil	
Peña and Krauss (1999) <sup>62</sup>	180 IM 40 IV	3.3 mg/kg+/-0.8(IM) 1.31 mg/kg+/-0.45(IV)	Transient apnoea 1, respiratory depression 1	Nil	1	Complete prospective	Nil	
Holloway <i>et al</i> (2000) <sup>21</sup>	100	3.65–8.91 mg/kg IM	Laryngospasm 1, SpO <sub>2</sub> < 90% 2	6 “agitation”	14 (14%)	Complete prospective	61	1%
McCarty <i>et al</i> (2000) <sup>15</sup>	114	2 mg/kg IV or 4 mg/kg IM	SpO <sub>2</sub> < 90% in 2 – oxygen given	1 – given midazolam	8 (7%)	Complete	100%	1%
Ng and Ang (2002) <sup>26</sup>	500	3–4 mg/kg IM or 1–2 mg/kg IV	Reporting incomplete. 1 patient with Myoclonus admitted for observation			Incomplete	None	
McGlone <i>et al</i> (2004) <sup>40</sup>	501	2–2.5 mg/kg IM	1 laryngospasm (oxygen given), SpO <sub>2</sub> < 93% in 3	2%	53 (10.5%)	Complete	469 (96.3%)	3%

Johnson conclude “it is highly unlikely that ketamine causes permanent changes in personality or intellectual function.”<sup>10</sup>

In a series of 501 cases at Lancaster<sup>40</sup> using a lower (often subdissociative) dose of 2.0 to 2.5 mg/kg we found an incidence of emergence “euphoria” of 2%. None of these children had any recollection of the sedation, or feelings of anxiety or distress afterward, and parents reported a 98% level of satisfaction.

#### Vomiting: 8.5% from the pooled data (0%–43%), all but two cases during recovery

Postoperative vomiting from general anaesthesia in children is quoted as ranging from 0% to 70%.<sup>59</sup> Vomiting after discharge from hospital may be influenced by early mobilisation or motion sickness during the car ride home.<sup>40</sup> Despite variations in fasting recommendations including instances of sedation in unfasted patients, there were no episodes of aspiration reported. Green and Krauss have since argued that fasting recommendations for ED sedation may be unnecessary in view of the lack of evidence of pulmonary aspiration risk, particularly if ketamine is used.<sup>60</sup>

#### Other reactions: nystagmus, ataxia, myoclonus, random limb movements, opisthotonus. Transient facial rash or flushing

Rarely clinically important and resolve with recovery. Ataxia may persist for up to four hours. It is recommended that children recovering from ketamine sedation be kept still, lying down, and quiet, until nystagmus and uncoordination have resolved.<sup>10 16</sup>

Since this review was published, Green *et al* attempted to determine predictors of adverse events during intramuscular ketamine sedation,<sup>45</sup> again using their data from 1022 cases.<sup>16</sup> Multiple logistic regression analyses were used to determine the association of five variables (age, sex, ASA risk, ketamine dose, number of doses) with vomiting and recovery agitation. No variable was found to be associated with airway complications. Emesis was modestly associated with age over 5, with a difference in incidence of 8.6% (95% CI 4.9% to 12.1%). Age under 5 was associated with an increased incidence of recovery agitation (22.5% compared with 12.1% in the over 5 year age group); the reduction in incidence of vomiting in the children over 5 was –10.4% (95% CI –3% to –17.7%). The incidence of recovery agitation was 17.9% in ASA class 1 children and 33.3% in ASA class 2 or more, a difference of –15.4% (95% CI 0%–30.7%).

Further observational studies and reviews have appeared since Green’s large review<sup>10</sup> of ketamine sedation in children. These add smaller numbers to the data, but with the important emphasis on ED practice of ketamine sedation.<sup>8 12 14–16 21 24 26 40 60–67</sup>

Table 2 shows the reported incidence of side effects of ketamine from these eight observational studies reporting on the use of ketamine as a sedative/analgesic in the un-intubated patient in an emergency department setting. One of these was retrospective and incomplete in the reporting of side effects,<sup>26</sup> although the authors did report 18 patients admitted because of “failure of the procedure” (not failure of sedation), and one admission for observation (myoclonic jerks were observed in the context of a minor head injury). The rest, though prospective, varied in their data collection. The most common side effects were emesis, emergence dysphoria, and airway problems. None of the airway problems encountered resulted in patient harm, and all were effectively dealt with. No patient required intubation. Parent dissatisfaction, where reported, ranged from 1% to 5.2%. In our recent series from Lancaster<sup>40</sup> 15 parents (3%) expressed dissatisfaction: only four rated their dissatisfaction to sedation related issues. In Green’s series,<sup>38</sup> of the four

dissatisfied parents only one had a complaint related to the sedation procedure.

#### Doses of ketamine used

In Green’s original review of 11 589 administrations<sup>10</sup> dose ranges from 0.5 to 16 mg/kg IM and 1 to 5 mg/kg IV were reported. Modern ED practitioners tend to use 2 to 5 mg/kg IM or 0.5 to 2 mg/kg IV.<sup>12 15 16 20 21 26 40</sup>

In a further review, Green *et al* tried to determine the optimum dose of ketamine for paediatric sedation.<sup>66</sup> Analysis of the previously reported database of 1022 cases<sup>16</sup> was performed to compare adequacy of sedation, time to discharge, and adverse events with the dose of ketamine administered. These data had been collected prospectively in 42% of cases, the rest by retrospective review of the case notes. Cases were divided up by dose increments of 0.5 mg/kg. No clinical or statistical difference in time to discharge, adverse events, emesis, recovery agitation, time to discharge, and adequacy of sedation was found in any dose groups, though there was a non-significant trend towards improved sedation adequacy with increasing dose. The authors concede a randomised double blind comparison of two doses would be an ideal test of their findings, but calculated that they would require 1942 subjects to detect a 3% absolute improvement in sedation adequacy. They concluded that 4–5 mg/kg IM produced adequate sedation in 93%–100% of children.

Our Lancaster study reports the lowest dose used in EDs.<sup>40</sup> A dose of 2.0 to 2.5 mg/kg IM was given to 501 patients for minor wound repairs. Data collection was complete, and the measure of sedation adequacy used was “degree of restraint” required. Although full dissociation probably did not occur in a proportion of patients (discussion among the authors), “significant” restraint (defined as restraint of arms, legs, and head) was required in less than 2% of cases; it was felt that the term “restraint” was also poorly defined and the nursing staff completing the forms admitted that “repositioning” or “gentle guiding” of limbs was coded under the “restraint” heading.

The studies from the United States using doses of 4–5 mg/kg IM, show a tendency to perform more painful procedures in the ED such as fracture manipulations.<sup>10 15 16 38 62 64 67</sup> McGlone’s papers<sup>19 20 40</sup> demonstrate the use of ketamine 2.0–2.5 mg/kg IM for minor procedures such as simple wound toilet and suture with local anaesthetic. It appears that the incidences of side effects may not be dose related, though McGlone *et al*<sup>40</sup> did show a tendency to less incidence of airway complications with 2 mg/kg—the confidence intervals were wide, and the study was not randomised or blinded. It is doubtful if a randomised, controlled, blinded trial comparing doses will be ever be conducted in light of published data and ethical considerations.

#### Definitions of sedation and what does “ketamine sedation” mean?

It is generally accepted that the term “conscious sedation” refers to a state of drug induced central nervous system depression, where the verbal contact is maintained with the patient, and airway and other reflexes are preserved.<sup>27 28 68 69</sup> Sedation to a deeper level implies loss of verbal contact and response to gentle stimulation. This state of “deep sedation” risks the loss of protective reflexes, airway control, aspiration, and hypoxia. “Deep sedation” carries a requirement for a level of care consistent with general anaesthesia.<sup>6 27–29 66 68 69</sup> The drugs used should have a wide margin of safety so that loss of consciousness is unlikely.<sup>6 25–29 68 69</sup>

As described above, the state of ketamine dissociation does not follow this continuum of gradually increasing depth of sedation and concurrent cardiorespiratory depression, towards a state of general anaesthesia. Any sedative drug

used in large enough quantities, or with a susceptible patient, will produce a state of general anaesthesia.<sup>65-68,69</sup> (Midazolam, commonly used for sedation, was originally marketed and introduced as a general anaesthetic induction agent). Is the state of dissociation seen with ketamine actually general anaesthesia if no verbal, motor, or cardiovascular response to painful stimuli is observed?

It is commonly accepted that general anaesthesia, by definition, results in partial or total lack of airway reflexes, resulting in an inability to independently maintain an airway. From this topic review it seems ketamine dissociation occurs with maintenance of respiration and a patent airway in most situations probably because its primary site of action is the cerebral cortex and limbic systems and not the brain stem.<sup>30-31</sup>

There is no gradual slide from sedation to general anaesthesia with ketamine.<sup>17</sup> No dose-response continuum is observed and patients are either dissociated or they are not, with no progressive "depth" of dissociation.<sup>9,17</sup> EEG analysis of ketamine dissociated subjects fails to show the classic depression of the bispectral index seen in general anaesthesia.<sup>17,70</sup>

Ketamine cannot therefore be classified by current guidelines on sedation. Green proposed a separate sedation category to describe the dissociative state demonstrated by ketamine.<sup>66</sup> He later defined "dissociative sedation" thus:

"A trance-like cataleptic state characterised by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability."<sup>17</sup>

## CONCLUSIONS—WITH REFERENCE TO THE THREE PART QUESTION

In children with injuries requiring a painful procedure ketamine dissociative sedation is a safe and acceptable technique in the emergency department.

Ketamine "dissociative sedation" is different from conscious sedation, deep sedation, and general anaesthesia. The rare instances of serious side effects necessitate the availability of experienced staff skilled in advanced airway maintenance, with adequate monitoring and resuscitation equipment. To provide a ketamine sedation service, EDs must be able to comply with the above; it may be that staffing levels, service commitments, and workload mean that children who could otherwise be managed in the emergency department and discharged home will have to be referred to another unit, or to an in-hospital team for general anaesthesia. This may mean an inter-hospital transfer if no paediatric anaesthetist is on site.<sup>71</sup> Paediatric or general anaesthetists should not be required to assist emergency physicians sedating children with ketamine.<sup>72</sup>

As more EDs in the UK introduce a ketamine sedation protocol, our specialty must ensure, above all, the safety of our patients.<sup>9-65</sup> Full and comprehensive prospective national audit is proposed and it is hoped that all departments around the country using ketamine for paediatric sedation will participate (personal communication).

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