The Lancaster experience of 2.0 to 2.5mg/kg intramuscular Ketamine for Paediatric Sedation: 501 cases and analysis

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Abstract

OBJECTIVES

To report our experience of using Ketamine 2.0 or 2.5mg/kg IM for minor painful procedures in children in a medium sized district general hospital accident and emergency department. To demonstrate the safety and acceptability of ketamine and determine if the incidence of adverse effects is related to dose or other variables.

METHODS

Retrospective review of prospective data on all cases of ketamine sedation, including follow-up information. Odds Ratios using Statsdirect software, multiple logistic regression statistical analysis using SPSS.

RESULTS

From August 1996 to April 2002 we had compiled a database of 501 children who had received 2.0mg/kg (310 cases) or 2.5 mg/kg (191 cases) ketamine IM for sedation. 26 received a second dose. There were 7 instances of oxygen desaturation below 93% on air including one of laryngospasm, 3 of which fell below 90%. All clinically relevant falls in oxygen saturation occurred in children given more than 2mg/kg. No cardiovascular complications occurred. In total, 8 cases received suctioning of the mouth or oropharynx; 5 of these were to facilitate mouth or lip wound repairs. Significant restraint was required during local anaesthesia in 2%, and during suturing in 2%. Vomiting occurred in 17%, all during recovery or after discharge, with one patient requiring admission. Muscle hypertonicity or clonus was observed in 6.8%. Disturbed sleep or nightmares occurred in 2%. The median time to discharge was 85 minutes. 97% of parents' experiences were "the same as" or "better than" expected. No children suffered any lasting or troublesome complications.

2.0mg/kg may produce a lower incidence of airway complications (difference of 3.4%, with a 95% confidence interval of 1.6%, 6.8%).

CONCLUSIONS

IM Ketamine sedation is a safe and acceptable technique when used within a defined protocol by trained and experienced staff, with appropriate monitoring and equipment available. Low dose ketamine (2mg/kg) warrants further study in view of lower airway complications and quicker discharge time than previously reported.

(KEY WORDS: ketamine; paediatric; sedation; emergency department)

INTRODUCTION and BACKGROUND

Ketamine is a unique drug giving complete anaesthesia and analgesia with preservation of vital brainstem functions. This “dissociative” state has been described as “a functional and neuro-physiological dissociation between the neocortical and limbic systems” [1] Ketamine dissociation results in a clinical state of lack of response to pain or other noxious stimuli, with preservation of respiratory and cardiovascular functions despite profound amnesia and analgesia. 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. Functional residual capacity and tidal volume are preserved, with bronchial smooth muscle relaxation and maintenance of airway patency and respiration. [1-3]

There is a wealth of evidence documenting the suitability and safety of ketamine in the hands of non-anaesthetists in various settings: remote locations in third-world countries, [4,5] “office” or outpatient surgeries and dental practices, [6-10] battlefields, [11] and diagnostic imaging.[12] Ketamine has been used by emergency physicians in the United States, Australia, and the UK for paediatric sedation with an excellent safety record, side-effect profile, and staff and parent satisfaction.[2,13-22] Midazolam, still commonly used in the UK for paediatric sedation, has been shown to offer less suitable conditions, with child restraint being required, and staff and parent dissatisfaction. [15-18] Ketamine sedation/analgesia as used by emergency physicians may be considered as the technique of choice in the emergency department for short procedures when analgesia and distraction techniques have failed.[2,15,16,18,19,21,23-28]

Our department – Lancaster Royal Infirmary, Lancaster, UK with an annual new patient attendance of 37,000 - began using intramuscular (IM) Ketamine as part of a defined protocol in a randomised comparison with intranasal Midazolam.[15] The same protocol for ketamine administration continued during a second study comparing it with high dose intramuscular Midazolam;[16] both studies received the approval of the Local Research Ethics Committee, and patients gave written informed consent. The protocol was devised after literature searches, and personal communications with leading authors in the field of ketamine sedation. After completion of these studies, ketamine became the sole agent used in our department for paediatric sedation.

OBJECTIVES

To report our experience of paediatric sedation using lower-dose intramuscular ketamine including adverse events, and to determine if adverse events were related to any patient factors, or the dose given. A review of the literature concerning ketamine sedation in children follows.

PROTOCOL

Children with injuries requiring wound toilet and suturing, minor surgery such as nail bed repair, and removal of foreign bodies, were sedated after failure of analgesia and distraction techniques. During the two initial study periods, patients were enrolled into one of the two study arms (ketamine or midazolam) and those who received ketamine are included in this study. Once these studies had been completed only IM ketamine was used for sedation. Children with wounds requiring formal surgical exploration and those with significant head injuries (knocked unconscious, vomiting, mentally obtunded) or other injuries requiring admission were excluded; a three-hour

fast prior to sedation was enforced. Those children presenting late at night were sometimes deferred until after 0900 hours the next day to comply with department senior staffing levels. A written parental advice sheet [(appendix)] was given and explained. If a delay in commencing the procedure was anticipated topical local anaesthetic cream was applied to the child's thigh. The sedation and procedure was performed in a dedicated theatre within the A&E department with oxygen, suction, and full paediatric resuscitation equipment available; a trained nurse and senior doctor with advanced airway and paediatric resuscitation skills (Consultant, Staff Grade, or Specialist Registrar) were present to perform and supervise the sedation and perform the procedure. Written informed consent was gained after explanation of the procedure verbally and supplemented by the written information sheet. Parents were encouraged to stay throughout. Monitoring consisted of oxygen saturation probe, and observation of the child. Supplemental oxygen was not routinely given. Ketamine (Ketalar, Parke-Davis; 100mg/ml) was mixed with atropine 0.01mg/kg in the same 1 or 2mL syringe; during the initial trials ketamine was universally used in a dose of 2.5mg/kg, thereafter 2.0mg/kg was used by some - this choice of dose was operator-dependent using their favoured dose and not randomised. A chart kept available in the theatre aided safe calculations of doses and drug volumes. The injection was given into the lateral thigh using a 25-gauge needle, with the child on the parent's knee or lying on the trolley. Local anaesthesia of the wound with lignocaine by local infiltration or nerve blockade where appropriate was performed once dissociation had occurred. If required, further ketamine IM doses of 1mg/kg were given. After completion of the procedure, the child was observed and monitored in the theatre room for thirty minutes after injection time, and then moved to the dedicated children's' examination cubicle. Parents were encouraged to keep the child still and

undisturbed, and background noise and light kept to a minimum. Once they were able to respond fully and weight-bear unaided, they were discharged. The written information sheet included discharge advice regarding child care post sedation, and a vomit bowl was supplied. Parents were also given verbal and written advice regarding wound care. Reattendance was not arranged unless required for the purposes of wound monitoring.

DATA COLLECTION

The following details were collected prospectively on a standardised proforma by the nurse caring for the child: Patient and wound details; behaviour prior to procedure, during local anaesthesia, during suturing; occurrence of vomiting, dysphoria, muscular hypertonicity, clonus, lacrimation, salivation, rash; timing of completion of procedure, time to discharge; child behaviour during recovery. The degree of restraint of the child required was recorded as “number of limbs” with the head counted as a “fifth limb.” “Restraint” of a limb or head was recorded if any physical alteration of body posture was used.

Follow-up was by written questionnaire given to parents at discharge with an addressed, pre-paid envelope. This was supported by telephone enquiry within 72 hours, and the following were recorded: occurrence, frequency, and timing of vomiting; occurrence of nightmares; time needed for child supervision after discharge, length of time the child’s walking remained unsteady; child recollection of suturing; parental satisfaction with their experience in A&E.

STATISTICAL METHODS

To investigate the association of dose levels with the complications being studied - airway complications (defined as oxygen saturation below 93), the need for restraint during anaesthesia or suturing, salivation, dysphoria, and vomiting - exact Fisher Odds Ratios were calculated prior to adjustment. Multiple logistic regression was used to yield Odds Ratios both with and without adjustment for the main confounding factors (age, weight, size of wound, site of wound). Cross-tabulation was used in the case of oxygen saturation below 93% against dose category, as the figures were very low. The Statsdirect and SPSS packages were used for the analysis.

RESULTS

504 cases of ketamine sedation were identified from the proformae. These were checked against the log in the theatre room for discrepancies and none were found giving a consecutive series. 2 cases involved intravenous administration, and were excluded from this analysis; these were both head injured children for wound toilet and suturing who had returned to A&E from a ward after a period of observation with cannulae already sited. A child with cyanotic congenital heart disease with a normal oxygen saturation of 84% on air, who received ketamine for wound closure, was also excluded; this child's oxygen saturation dropped to 78% despite supplemental oxygen, though the child recovered normally without incident. None of these three excluded cases suffered any long-term sequelae.

Of the remaining 501 cases an initial dose of 2.0mg/kg (n = 310) or 2.5mg/kg (n = 191) IM Ketamine was given, with one case receiving 3mg/kg – a protocol violation. 26 received a second dose of 1mg/kg IM (16 of these initially received 2mg/kg). Two cases received second doses of 2mg/kg – again, protocol violations. The mean age of

the children was 3.6 years (median 3, mode 2, range 0-12). Injuries were located on the limb in 144, face 313, head 36, and trunk in 8. Excluding wounds, 4 were abscesses, 8 were nail or fingertip injuries, and 5 were foreign bodies for removal. One case involved toilet and lavage of an eye contaminated with “Superglue.” Mean number of sutures required was 5.4 (median 5, mode 4), and the procedure was completed in a mean time from injection of 18 minutes (median 15, mode 15). Restraint of arms, legs, and head was required in only 2% of cases for local anaesthesia and suturing. None of these children remembered the events. Overall, adult reaction during the procedure was recorded as “upset” or “felt faint” in 19%. During sedation, there were 8 instances of oxygen desaturation below 93% **(Table 1).** These all occurred in children given more than 2.0mg/kg. One case of laryngospasm occurred in a 2 year old having a lip wound sutured. There was a brief dip in SpO_2 to 90%, returning to 100% with oxygen supplementation and airway repositioning. No secretions in the oro- or hypopharynx were noted and suctioning was not performed. The other episodes of desaturation were attributed to hypoventilation alone; no interventions were made and all recovered quickly. Two children were reported to cough during sedation; their lowest oxygen saturations were 94% and 96% respectively. One child breath held (during recovery whilst micturating) but did not desaturate below 98%. There were no episodes of apnoea and no episodes of vomiting during the procedure.

A transient rash, consisting of facial and/or truncal flushing or blotchy erythema, was observed in 56 cases (11%). Hypersalivation occurred in 59 (12%), despite the administration of atropine 0.01mg/kg in all cases. Muscle hypertonus or clonus was observed in 34 cases (6.8%).

During recovery the main problem was vomiting, which occurred in 52 cases (10%), 8 of who had received a second dose of ketamine. The behaviour of the children during recovery was uneventful in 406 cases (81%), mild agitation in 74 (15%), moderate agitation in 16 (3%) and pronounced agitation in 4(0.8%). Median time to discharge was 85 minutes (mean 89, mode 90, range 40-185).

Follow-up was completed in 469 cases, the rest not responding with the prepaid questionnaire and not contactable either through lack of a telephone in the household, or moving out of the area (Lancaster and surrounds attract holidaymakers and tourists). Parents reported the following adverse events after discharge: vomiting 53 cases (11%); unsteady gait 62% (no falls or other accidents occurred, and most children went to bed on arrival home due to the late hour). Nightmares or disturbed sleep were reported in 2%, none of which persisted longer than the first night. The overall incidence of vomiting, either in the department or at home, was 17%; this incidence fell to 15% if children given a second dose are excluded. One child was admitted for observation due to vomiting - the only child requiring admission in our study. He was discharged well the next day. 4 children said they remembered the suturing, but were cooperative during the suturing, with no form of restraint required. 380 (81%) of parents described their experience in A&E as “better than expected”, 74 (16%) as “the same as expected”, and 15 (3%) as “worse than expected” – only 4 of these related their dissatisfaction to the sedation, commenting respectively “not expecting sedation, but otherwise happy,” “upset because monitor kept alarming” (the nurse reported difficulties obtaining a satisfactory pressure wave), “vacant expression of child was concerning,” and “disturbed by child’s eyes being open.” The other 11 complaints were due to waiting times and attempts at wound treatment in an uncooperative child before sedation was offered.

ASSOCIATION OF ADVERSE EVENTS WITH CONFOUNDING VARIABLES

As the number of people receiving a total dose over 2.5 mg/kg of ketamine was only 5% of the sample, the dose was categorised into 2 mg/kg and 2.5 mg/kg or over, for the purpose of analysis. As a measure of airway complications, oxygen saturation below 93% was used, as the number of people who would have fitted the US reporting of 90% [14,19] were too low for any useful analysis. Again, the number of people with all 5 body appendages restrained were too few to be useful, and it was decided by the clinicians that the restraint of 3 or more limbs would be a useful restraint variable. The variables examined were dose given, age, weight, size and site of wound. The complications examined were airway problems including desaturation, vomiting, emergence dysphoria, salivation, and restraint.

The unadjusted Odds Ratios and those resulting from logistic regression are shown in **Table 2**. For airway complications, owing to the small numbers, a confidence interval for the difference in proportions was calculated instead; the difference in proportions is 3.4%, with a 95% confidence interval of (1.6%, 6.8%). Thus there is evidence that a lower dose of ketamine is associated with a lower rate of airway obstruction. When other factors are adjusted for in logistic regression, the small figures create a large standard error for the estimated Odds Ratio; this also happens for dysphoria.

Table 2 also shows that a lower dose of ketamine is associated with a lower rate of salivation, and the pattern persists when confounding factors are adjusted for. An association of a lower dose of ketamine with a lower rate of dysphoria emerges after confounding factors are adjusted for.

There is no evidence of any association of a lower dose of ketamine with restraint required during either suturing or LA, or with vomiting.

COMMENTS

It is possible that some instances of ketamine sedation were not recorded, though this is unlikely, as administration required the use of the observation form included in the proforma. In addition, all instances of ketamine sedation were recorded in a separate log in the theatre room. There were missing data on several proformae, and it is possible that some instances of harmful, or potentially harmful, side-effects went unrecorded. However this is unlikely as the lowest oxygen saturation obtained was recorded in every case save one, and follow-up was completed in the majority of cases (94%). Accuracy of data recording may vary between the nurses particularly when recording subjective data such as agitation, child behaviour, and restraint. The requirement for any restraint of the child during local anaesthesia, or during suturing, may seem to show our technique was ineffective. Previous randomised trials have shown ketamine to be superior to Midazolam with less distress shown by the children and less restraint required. [15-18] It is felt by the authors that "restraint" was over-reported by our nursing staff, who admitted that any limb or head repositioning or support was documented as restraint. Random, uncoordinated movements often occur during ketamine dissociation and can interfere with wound treatment. True restraint (immobilisation of all limbs and head) was documented in 12 cases (2%) during local anaesthesia, and 9 (1.8%) during suturing. The lower dose used may in some instances mean children are not always fully dissociated, but our data collection did not specifically report this. We found our median discharge time to be 85 minutes, somewhat lower than the reported US time of 110 minutes, which may be relevant to a busy emergency department.

The wide confidence intervals quoted mean any lower rates of complications for the various variables should be interpreted with caution. The study was not powered to detect any significant differences in adverse events between the confounding variables, as the primary objective was to report our experience using intramuscular ketamine.

During the initial studies strict adherence to protocol ensured 2.5mg/kg was universally adopted; after recruitment had ceased, selection of the dose occurred by personal choice of operators. Both doses are 50% lower than those cited in other reports on paediatric sedation with ketamine. Follow-up data collection by telephone risks biased answers, but is difficult to perform any other form of follow-up in the A&E setting.

DISCUSSION

This report is the largest case series published on ketamine sedation of children in the UK. Controversy still surrounds the issue of ketamine sedation in the UK, where the technique is still little used. The experience in the USA and Australia is somewhat greater, where doses of 4-5mg/kg IM are commonly used, but many departments still use other drugs when sedation is indicated. Green recommended in his review of 1999[29] that 4mg/kg is the minimum intramuscular dose required to achieve consistent dissociation. The painful stimulus of local anaesthesia is less than that of, say, fracture reduction (a common indication for ketamine sedation in the US)[2,14,19,20,22,31] and so a lower dose can be justified, particularly as the primary aim of sedation in our study was to facilitate local anaesthesia in an otherwise uncooperative child. Dissociation may not be consistently occurring at this lower dose level but conditions were adequate for the procedure, with overall staff and parent satisfaction; a quicker

discharge time may also be beneficial. Our lower incidence of airway complications in children given 2.0mg/kg deserves further investigation. However, Green et al.[29] calculated 7,216 subjects would be required to detect a 50% relative difference in airway complications from a 1.4% baseline incidence in the context of a randomised controlled trial.

Table 3 summarises the eight largest observational studies reporting experience with ketamine for paediatric sedation in emergency departments. Of note are the variations in doses, and the variations in incidences of vomiting. However data collection was often incomplete, with some studies reporting no follow-up, so the true incidence of vomiting after discharge may be higher in these reports. The use of ketamine as a sedative/analgesic for children in the emergency department has been published extensively, particularly by Steven Green in California, USA. His largest case series[19] documented 1022 cases given a median IM dose of 4mg/kg. The safety profile was good, though 9 cases desaturated below 90% including 4 cases of laryngospasm and 7 of partial airway obstruction; these were quickly recognised and treated effectively. There are few published randomised trials comparing ketamine with other sedative agents; those that have been published (including two from our institution comparing ketamine with midazolam) [14-17] show ketamine to be superior in terms of operating conditions, physician and parent satisfaction, and recovery profile. Departments in the UK have since successfully introduced a protocol for ketamine sedation, with Holloway et al publishing 100 cases in 2000.[13]

Our overall incidence of vomiting (15%) may appear unacceptably high for a technique designed to alleviate suffering in children. This incidence is somewhat higher than that reported by Green et al,[19] but his case series did not report on adverse events after discharge. Holloway [13] reported an incidence of 19%, with follow-up

being completed up to 14 months after discharge. The alternatives to sedation are no sedation (physical restraint) or general anaesthesia. The incidence of post-operative nausea and vomiting (PONV) in day-case surgical paediatric patients varies from 6 – 60%, depending on the surgical procedure and the anaesthetic technique used; incidences of PONV are reported to be higher in emergency procedures and those where the patient may be anxious or distressed, and where the patient is mobilised early after the procedure.[34] Motion sickness (in the car going home), and concurrent head injury may be confounding factors contributing the reported incidence of vomiting after discharge in our study. The overall parent satisfaction of 97% for ketamine sedation of their children shows the side-effects appear acceptable to them, at least.

Emergence phenomena and hallucinations or dreaming have been described as a major problem with ketamine sedation. The published series on ketamine sedation in children do not appear to support this conclusion. The incidence of troublesome emergence reaction rises over the age of 10,[29] and may be due to the brain maturation around the time of puberty.[1-3] Some authors have recommended co-administration of Midazolam in an effort to reduce hallucinations and emergence reactions, but two randomised trials[35,36] have shown this to be ineffective, with oxygen desaturation occurring more frequently in the midazolam treated group.[35] Green and Johnson conclude *"it is highly unlikely that ketamine causes permanent changes in personality or intellectual function."* [2]

An anti-sialogogue is often used to help reduce the incidence of hypersalivation seen with ketamine and many authors recommend this. We found an incidence of hypersalivation of 12% despite all patients receiving atropine; the trend towards a lower incidence of salivation in the lower dose group (2 mg/kg) warrants further

comment, particularly as many authors suggest excess secretions and suctioning may precipitate laryngospasm. The incidence of hypersalivation reported by Green et al.[19] was only 1.7% despite co-administration of atropine with a larger dose of ketamine, though this data was collected retrospectively by review of medical records. 14 children in this study did not receive atropine and hypersalivation was observed in none of these cases. It has been suggested that the side-effects of ketamine particularly airway complications, agitation, and vomiting are not dose-related if dissociation has occurred.[29]

We report a quicker median time to discharge compared to that reported by Green et al. [19] though both the ranges are wide. The times quoted by both are times from injection of ketamine to actual departure from the emergency department. Green's original study [32] and that of Dachs and Innes [22] recorded time to "ready for discharge," a better measure of sedation recovery time as it would exclude department management issues such as completion of paperwork and organisation of transport. The comparisons of subjective events such as hypersalivation, agitation, and dysphoria are difficult without rigid standardised definitions and complete prospective data.

Intramuscular administration does have drawbacks not least the pain of an injection. We used topical anaesthetic cream ("Ametop") to help alleviate this where possible. Haematoma formation and inadvertent intravascular or intraneural injection are reported, but were not observed in our study. We postulate that some instances of sedation failure requiring second doses may be due to accidental injection into fat or other tissue planes where absorption of the drug may be slower. Generally, IM injection was tolerated well. Intravenous administration would obviously require

cannulation of an uncooperative child, a procedure possibly more stressful and painful than an IM injection.

It appears the practice in many institutions in the USA is to use ketamine in doses up to or over 5mg/kg IM to facilitate fracture reduction and other surgical procedures such as abscess incision; these procedures are not commonly performed in UK departments largely through staffing and service provisions, and these patients are usually referred to specialist teams for treatment in an operating theatre under general anaesthesia.

The Scottish Intercollegiate Guidelines Network published the most recent UK guideline on paediatric sedation in February 2002. [37] This advised ketamine *"a general anaesthetic agent"* should be *"only used by those who are formally trained in paediatric or neonatal anaesthesia or intensive care and who have adequate ongoing experience"* The section recommending Accident and Emergency practice stated, *"Although ketamine can be given orally, intravenously or intramuscularly in so-called sub-anaesthetic doses there is a high incidence of adverse effects (vomiting, ataxia, delirium."* The data available contradict this statement.

It is apparent that ketamine sedation has become a technique familiar to many emergency physicians, and few anaesthetists.[38] These large case series and the reviews published show that this technique can be used safely within defined protocols by trained and experienced staff.[2,13,14,19,22-28,31-33]

Classification of ketamine as a general anaesthetic implies that partial or complete loss of airway reflexes is inevitable – this is clearly not the case. Ketamine dissociation does not demonstrate the classical planes of anaesthesia described by Guedel; yet the term "conscious sedation" is also not relevant as there is no verbal or other purposeful response. [26] Definitions of ketamine dissociation may appear

semantic; adverse events clearly can and do occur. Our case series is not unique in reporting potentially life-threatening complications,[39] and it must be emphasised that the procedure is only safe if the monitoring, environment, staffing and training are all capable of identifying and treating the rare adverse events quickly and effectively.

CONCLUSIONS

IM Ketamine sedation in the Accident and Emergency department is a safe and acceptable technique when used within a defined protocol by trained and experienced staff, with appropriate monitoring and equipment available. Low-dose (2-2.5mg/kg) is sufficient for treatment of most conditions likely to be undertaken in UK Emergency Departments. There appears to be little difference in clinical effect between these two doses, though 2.0mg/kg may offer a lower incidence of airway problems and salivation. A quicker discharge time may be a supplementary benefit.

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TABLE 1. Airway complications

	Age/injury	Dose mg/kg	Complication	Interventions	Outcome
1	2/lip	2.5	Laryngospasm (with skeletal muscle hypertonicity) SpO2 fell to 90%	Oxygen and change in airway position	Resolved quickly
2	6/facial wound	2.0+1.0	SpO2 fell to 84%*	Oxygen given	Resolved quickly
3	1/head wound	2.5	SpO2 fell to 92%	none	Resolved quickly
4	5/facial wound	2.5	SpO2 fell to 92%	none	Resolved quickly
5	6/lip wound	2.5	SpO2 fell to 92%	suctioning	Resolved quickly
6	4/facial wound	2.5	SpO2 fell to 84%	none	Resolved quickly
7	1/facial wound	2.5	SpO2 fell to 89%	none	Resolved quickly

*SpO2 fell after second dose

Table 2. Association of complications with confounding factors.

Outcome complication	Low Dose 2.0 mg/kg fraction (%)	High Dose 2.5+mg/kg fraction(%)	O.R. (not adj)	Conf. Interval (Exact Fisher)	O.R. (adj.)	Conf. Interval
Oxy sat <93	0/294(0.0)	7/207(3.4)	See text		0.0	(0, infinity)
Restraint (sut)	28/289(9.7)*	30/207(14.5)	0.63	(0.35, 1.34)	0.65	(0.36, 1.18)
Restraint (LA)	12/294(4.8)	19/207(9.2)	0.42	(0.18, 0.94)	0.38	(0.17, 0.86)
Salivation	23/294(7.8)	37/207(17.9)	0.39	(0.21, 0.70)	0.41	(0.22, 0.75)
Dysphoria	2/293**(0.7)	9/207(4.3)	0.15	(0.016, 0.74)	0.0	(0, infinity)
Vomiting	47/289*(16.3)	38/207(18.4)	0.86	(0.53, 1.43)	0.79	(0.48, 1.31)

* 5 missing **1 missing

One other association that may be of interest is that vomiting is associated with ages 3 to 7, and the Odds Ratio persists even when other confounders are adjusted for. The adjusted Odds ratio is 3.18, the C.I. being (1.79, 5.66)

	Numbers of cases	Dose	Airway Problems	Emergence dysphoria/agitation	Vomiting	Data collection	Time to discharge (range)	Follow-up	Parent satisfaction
Green et al.(1990)[32]	108	4mg/kg IM	1 emesis-induced laryngospasm (no sequelae)	1	7(6.5%)	Complete prospective	Median 87 ins (30-175)	77 (71.3%)	94.8%
Dachs and Innes(1997)[22]	30	1 – 2mg/kg IV	nil	4 “mild”	2(6.7%)	Complete prospective	Median 25 mins.(range not given)	29 (96.6%)	100%
Green et al.(1998)[19]	1022	4mg/kg IM	4 laryngospasm, oxygen and ventilatory assistance given. No sequelae. 7 airway malalignment, 2 apnoea, 1 resp. depression	Mild in 76, moderate/severe in 7. 2 given midazolam	6.7%	Complete but only 431(42%) were prospective	Median 110 (86-130) minutes	Nil	Not reported
Green et al.(1998)[31]	156	0.5-3mg/kg IV	Transient apnea 1, resp. depression 1	Nil (2 – mild agitation)	6	Complete	Median 103 mins(76-146)	Nil	
Holloway et al.(2000)[13]	100	3.65-8.91mg/kg IM	Nil	6 “agitation”	14(14%)	Complete prospective	Not reported	61	99%
McCarty et al.(2000)[14]	114	2mg/kg IV or 4mg/kg IM	SpO_2 <90% in 2 - oxygen given	1 – given midazolam	8(7%)	Complete	Not reported	100%	99%
Ng and Ang(2002)[33]	500	3-4mg/kg IM or 1-2mg/kg IV	Reporting incomplete. 1 patient with Myoclonus admitted for observation	Not reported	Not reported	Incomplete	All < 3 hours	None	Not reported
McGlone et al.(2002)	501	2-2.5mg/kg IM	1 laryngospasm (oxygen given), SpO_2 < 93% in 7, < 93% in 3	2%	52(10%) in dept. 53(11%) at home. 17% overall	Complete	Median 85 mins (40-185)	469 (94%)	97%