QUESTION 3

KETAMINE OR MIDAZOLAM: DOES IT MATTER WHICH?

SCENARIO

A 7-year-old boy presents to the emergency department having sustained a laceration to his forearm after playing pirates with his brother using kitchen knives. He has no other injuries but the laceration requires suturing. He is, unsurprisingly, not keen on the idea of stitches and is very upset and won't co-operate. Midazolam and ketamine are commonly used sedative agents; which would be preferable in this emergency room scenario?

STRUCTURED CLINICAL QUESTION

In children with simple lacerations requiring suturing [patient], is midazolam [intervention] more effective than ketamine [comparison] in achieving adequate sedation [outcome]?

SEARCH STRATEGY AND OUTCOME

Primary sources

MEDLINE was searched from 1950 to November 2008 and EMBASE from 1980 to week 51 2008 via the OVID interface. The advanced search mode was used with the terms ('midazolam' and 'ketamine') and ('suturing' or 'laceration'). Limits were: MEDLINE, 'all child 0–18 years' and EMBASE, 'child <unspecified>'.

Secondary sources

The Cochrane Library was searched using the search terms 'midazolam' and 'ketamine'.

Outcome

The search of MEDLINE revealed 15 papers, three of which were relevant. EMBASE yielded 24 articles with one additional relevant article. No other papers were identified in The Cochrane Library, but all four relevant papers were listed on the Cochrane register of trials (see table 1).

COMMENTARY

Emergency departments are often presented with children requiring minor procedures, for example, wound closure, wound exploration or incision and drainage of minor collections. These children are often scared, tired and in pain, which can make these procedures difficult. In order to facilitate treatment, a two-part approach should be taken. The first part is non-pharmacological, relevant to all aspects of paediatric services and involves provision of the following:

- Child-friendly environment
- Distraction with use of play specialists where available
- Experienced paediatric medical and nursing staff who can reassure the child and perform any interventions in a timely fashion
- Analgesia
- Consideration of Entonox; this can be particularly useful in the older child.

If these measures do not facilitate the procedure, then sedation can be considered. The aims of sedation should be to produce reliable sedation, minimal side effects and a quick onset and offset times (thus allowing procedures to be conducted in a time efficient manner). If sedation can be performed within the emergency department, it can prevent

Clinical bottom line

- Ketamine is an alternative to midazolam for the effective sedation of children requiring minor procedures and can prevent unnecessary admission and general anaesthesia.
- In children with difficult venous access, intramuscular ketamine is an option and is preferable to intranasal midazolam.
- The guidelines published by the College of Emergency Medicine provide an excellent summary of ketamine use.[1]

Table 3 Ketamine or midazolam: does it mater which?

Study	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Younge and Kendall[4]	59 Children aged 1–7 years with lacerations requiring LA injection or topical application+anxiety score >1 followed by suturing. Received either IV midazolam or IV ketamine	Randomised, double blinded trial (level 1)	Anxiety/tolerance score (4=uncontrolled crying, 1=co-operative)	Ketamine vs midazolam=2 vs 1 (medians); p=0.0029	No power calculation performed as non-continuous ordinal scale. No 95% CI given. Acknowledges larger study needed
			Sedation score (5=agitated, 1=barely rousable)	Ketamine vs midazolam=2 vs 3 (medians); p=0.039	
			Time to sedation score of <4	Ketamine vs midazolam=20 vs 43 min (medians); p=0.001	
			Time to discharge	Ketamine vs midazolam=105 vs 110 min	
McGlone *et al*[5]	87 Children aged 1–7 years with wounds needing suturing. Received either IM ketamine or IM midazolam with or without IN flumazenil	Prospective comparative study (level 2)	Restraint	Ketamine vs midazolam: three body parts held, 2 vs 6; 0 body parts held, 27 vs 2; p=0.0001	No blinding. Active selection by doctors' assessment of combative behaviours into the ketamine group, although this strengthens ketamine results. No 95% CI given
			Agitation	Ketamine vs midazolam: uncontrolled crying 2% vs 10%; co-operative 83% vs 42%; p=0.001	
			Time to discharge	Ketamine vs midazolam=102 vs 95 min	
McGlone *et al*[6]	102 Children aged 1–7 years with simple wounds needing suturing. Received either IM ketamine or IN midazolam	Prospective comparative study (level 2)	Oxygen saturation	Median SpO_2 97% in both groups	No blinding. Text unclear as to place of p values quoted. No 95% CI given
			Restraint measured by restraint score (score 3=3 body parts held, score 0=no body parts held)	Ketamine vs midazolam: score 3=3 vs 15; score 0=41 vs 7	
			Agitation measured by agitation score (score 3=agitated, score 0=quiet)	Ketamine vs midazolam: score 3 1 vs 3; score 0=34 vs 31	
			Time to discharge	Midazolam vs ketamine=75 vs 82 min	
Acworth *et al*[7]	53 Children aged 6 months to 12 years requiring minor procedures, received either IN midazolam or combination IV ketamine and midazolam	Single blinded randomised trial (level 1)	Degree of sedation on sedation score (score 5=agitated, 1=unconscious)	Mean score ketamine vs midazolam=2.5 vs 3.5; p=0.001	Well performed and written study. Two children in IN group inadequately sedated
			Time to sedation	Ketamine vs midazolam=2 vs 7.31 min (95% CI 3.2 to 7.4)	
			Time to discharge	Ketamine vs midazolam=97.9 vs 79 min; p=0.02	

IM, intramuscular; IN, intranasal; IV, intravenous; LA, local anaesthesia.

admission and the need for a general anaesthetic and its associated risks.

Midazolam is classically the sedative agent of choice with a fast recovery time and low toxicity. There are oral, intranasal and intravenous preparations, with the oral preparation generally being well tolerated. In addition to being a sedative it is also a good anxiolytic, amnesic and hypnotic, which are all useful features in this scenario. Midazolam, like all drugs, does have undesirable side-effects. The one that causes the most concern in this scenario is that it often has the opposite effect and results in hyperactivity in approximately 2% of children, thus leading to the need for general anaesthesia. Other side-effects occurring in children include vomiting in 11% and nausea in 5%. As with any sedative there is the risk of respiratory depression, which can potentially lead to the need for respiratory support; however, flumazanil is an effective antidote.

Ketamine is an alternative sedative agent that comes in the same forms as midazolam but there is also an intramuscular preparation. It produces a 'dissociative' anaesthesia and the resultant preservation of laryngeal reflexes, respiratory drive and muscle tone means that there is less risk of respiratory depression, and thus reduced need for ventilatory support. Its other main advantage is that it does not produce a paradoxical hyperactivity. In terms of disadvantages, there is a 0.3% risk of laryngospasm[1] and occurrence of emergence phenomena. The latter is experienced as hallucinations and nightmares as the ketamine wears off. Emergence phenomena are not commonly seen in the paediatric population, although incidence increases with age.[2] This, however, may be a reflection of a pre-verbal child's inability to report these phenomena and any behavioural changes being attributed to the stress of the situation. Other side-effects include emesis (again this increases with age), flushing and increased oral secretions, the latter clearly posing a possible risk to the airway.[2] A recent meta-analysis reviewed the predictors of adverse events with ketamine and these included use in children aged less than 2 years or those aged 13 or above.[3]

It should be noted that both sedatives have the potential to cause respiratory depression. It is therefore advisable that the person administering either agent should be competent in basic airway management, that is, be able to perform a jaw thrust and bag-mask ventilation to maintain oxygenation while awaiting anaesthetic support.

Age is always a prime consideration in paediatric patients. Three of the trials included children aged from 1 to 7 years, while the fourth paper included children aged 6 months to 12 years. In accordance with the Children's British National Formulary, ketamine and midazolam can both be used from the neonatal period. The papers, however, did not review the effectiveness of either medication in terms of the age of the child.

The papers summarised in table 3 suggest ketamine should be considered as the potential sedative of choice as it offers quick, reliable sedation with minimal side effects and has a rapid onset and offset time. For children with difficult venous access, intramuscular ketamine can provide an alternative to intranasal

midazolam, which despite popular belief, is unpleasant for all involved and is less effective. All four papers commented on the views of both doctors and parents, the overall opinion being that ketamine is the preferred agent. This review leads on to the question: 'Could ketamine be used for children undergoing MRI, dimercaptosuccinic acid scan, metaiodobenzylguanidine scan, lumbar puncture, etc?'

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REFERENCES

1. Clinical Effectiveness Committee, College of Emergency Medicine. Ketamine sedation of children in Emergency Departments, 2009. http://www.collemergencymed.ac.uk/CEM/Clinical%20Effectiveness%20Committee/Guidelines/Clinical%20Guidelines/default.asp (accessed September 2010).
2. **Green SM,** Kuppermann N, Rothrock SG, *et al.* Predictors of adverse events with intramuscular ketamine sedation in children. *Ann Emerg Med* 2000;**35**:35–42.
3. **Green SM,** Krauss B, Brown L, *et al.* Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8282 children. *Ann Emerg Med* 2009;**54**:169–70.
4. **Younge PA,** Kendall JM. Sedation for children requiring wound repair: a randomised controlled double blind comparison of oral midazolam and oral ketamine. *Emerg Med J* 2001;**18**:30–3.
5. **McGlone R,** Fleet T, Durham S, *et al.* A comparison of intramuscular ketamine with high dose intramuscular midazolam with and without intranasal flumazenil in children before suturing. *Emerg Med J* 2001;**18**:34–8.
6. **McGlone RG,** Ranasinghe S, Durham S. An alternative to "brutacaine": a comparison of low dose intramuscular ketamine with intranasal midazolam in children before suturing. *J Accid Emerg Med* 1998;**15**:231–6.
7. **Acworth JP,** Purdie D, Clark RC. Intravenous ketamine plus midazolam is superior to intranasal midazolam for emergency paediatric procedural sedation. *Emerg Med J* 2001;**18**:39–45.