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# Is atropine needed with ketamine sedation? A prospective, randomised, double blind study

**P Heinz, G C Geelhoed, C Wee, E M Pascoe**

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See end of article for authors' affiliations

Correspondence to: Dr P Heinz, Department of Paediatrics, Box 181, Addenbrooke's Hospital, Cambridge University Hospital Foundation Trust, Hills Road, Cambridge CB2 2QQ, UK; Peter.Heinz@addenbrookes.nhs.uk

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**Objective:** To compare atropine with placebo as an adjunct to ketamine sedation in children undergoing minor painful procedures. Outcome measures included hypersalivation, side effect profile, parental/patient satisfaction, and procedural success rate.

**Methods:** Children aged between 1 and 16 years of age requiring ketamine procedural sedation in a tertiary emergency department were randomised to receive 0.01 mg/kg of atropine or placebo. All received 4 mg/kg of intramuscular ketamine. Tolerance and sedation scores were recorded throughout the procedure. Side effects were recorded from the start of sedation until discharge. Parental and patient satisfaction scores were obtained at discharge and three to five days after the procedure, with the opportunity to report side effects encountered at home.

**Results:** A total of 83 patients aged 13 months to 14.5 years (median age 3.4 years) were enrolled over a 16 month period. Hypersalivation occurred in 11.4% of patients given atropine compared with 30.8% given placebo (odds ratio (OR) 0.29, 95% confidence interval (CI) 0.09 to 0.91). A transient rash was observed in 22.7% of the atropine group compared with 5.1% of the placebo group (OR 5.44, 95% CI 1.11 to 26.6). Vomiting during recovery occurred in 9.1% of atropine patients compared with 25.6% of placebo patients (OR 0.29, 95% CI 0.09 to 1.02). There was a trend towards better tolerance in the placebo group. No patient experienced serious side effects.

**Conclusion:** Ketamine sedation was successful and well tolerated in all cases. The use of atropine as an adjunct for intramuscular ketamine sedation in children significantly reduces hypersalivation and may lower the incidence of post-procedural vomiting. Atropine is associated with a higher incidence of a transient rash. No serious adverse events were noted.

Children undergoing short, painful procedures should not be denied effective, safe sedation and analgesia. Ketamine seems an obvious choice in the setting of an emergency department: its onset of action is rapid and it provides adequate levels of anxiolysis, amnesia, and analgesia without compromising spontaneous respiration and protective airway reflexes. Ketamine is used commonly in emergency departments in Australasia, North America, and the UK, and its excellent safety record in the hands of non-anaesthetists is well documented.[1–5] For practical reasons the intramuscular route seems preferable as it avoids having to gain intravenous access in a potentially uncooperative and frightened child. Establishing intravenous access does not lead to a perceivable increase in patient safety, given that the sedation should take place in an environment where relevant expertise is in immediate attendance anyway. Rapid intravenous injection has also been associated with respiratory depression.[6]

Side effects of ketamine include nausea, vomiting, transient rash, and unpleasant emergence phenomena although the latter seem to be less of a problem in children. In addition, ketamine leads to increased production of salivary and tracheobronchial secretions. The most feared complication of intramuscular ketamine sedation necessitating advanced airway management is laryngospasm. Laryngospasm is commoner in the presence of increased secretions and with direct instrumentation including suction.[7 8]

Antisialagogues therefore have been recommended as a routine adjunct, a view particularly favoured by anaesthetists.[9] Atropine with its antimuscarinic effects is most commonly used, glycopyrrolate being an alternative drug.[10] The routine coadministration of antisialagogues has been challenged recently.[11] There are several reasons why combining ketamine and atropine could be problematic: from a pharmacokinetic point of view, the onset of effect on salivation is delayed, peaking at 100 minutes after intramuscular injection, a long time after the problems related to hypersalivation would have occurred.[12] Due to its prolonged action its side effects may also occur during the recovery phase. Reports from the early days of ketamine anaesthesia seem to suggest that atropine may increase the incidence of emergence phenomena.[13] There is a considerable overlap in the side effect profile between the two agents including tachycardia, transient rashes, nausea, and vomiting. Finally, administration of two rather than one drug increases the risk for drug errors. Currently the coadministration of an antisialagogue is seen as best practice despite doubts about its effectiveness and the lack of robust research.[2 14 15]

In the present study, we compared the incidence of hypersalivation, related side effects, and parent/patient satisfaction when using either atropine or placebo as an adjunct to intramuscular ketamine sedation in the emergency department.

## METHODS

We undertook a randomised, double blind, placebo controlled trial in the emergency departments of a tertiary paediatric hospital and an urban general district hospital. The relevant human research ethics committees approved the study.

Children requiring ketamine sedation for short painful procedures were recruited into the study after obtaining written consent and were assigned the next available trial number. Patients were excluded from the trial if they required immediate intravenous access. According to the departmental ketamine sedation protocols, patients had to be

**Box 1: Sedation score**

1—Asleep but does not respond to minor motor stimulation
2—Drowsy, but responds to minor motor stimulation
3—Calm, sitting/lying comfortably with eyes open
4—Awake but not clinging to parent/carer, may whimper
5—Agitated, crying or clinging to parent/carer

**Box 2: Tolerance score**

1—Cooperative
2—Some movement or crying, intermittent restraint required
3—Crying with thrashing movements, continuous personal restraint required
4—Unable to complete procedure without additional sedation

fasted for more than three hours. Sedation and procedure were performed in a dedicated room equipped with oxygen, suction, and resuscitation equipment for advanced airway management. A senior doctor was responsible exclusively for the sedation, tolerance and sedation scoring, and the documentation of side effects on a proforma (stridor/laryngeal spasm, apnoea, failed procedure, muscle rigidity, random movements, rash, vomiting, and emergence phenomena). A nurse monitored and documented vital signs (heart rate, respiratory rate, oxygen saturations, blood pressure) and interventions (suction, restraint). The actual procedure was performed by another doctor. Hypersalivation was defined as any increase in oral secretions from the onset of sedation, noted by the observing doctor and nurse. Parents were encouraged to be present during the procedure.

All sedation given on the day of procedure including oral opioid analgesia was recorded on the structured data collection form. Ketamine (Ketalar, Pfizer, Australia; 100 mg/ml) was given at a dose of 4 mg/kg bodyweight intramuscularly with the option of a single top-up dose of 2 mg/kg 5–10 minutes later if deemed necessary by the doctor responsible for the sedation. Ketamine and either atropine or placebo were coadministered in the same syringe. The adjunct was taken from a vial with the patient's trial number, previously prepared by pharmacy. The pharmacy also provided the randomisation by a simple randomisation list. The code was not disclosed until the termination of the study. Each vial contained either atropine, 1.2 mg in 3 ml or an equivalent amount of normal saline. The dose of atropine was 0.01 mg/kg with a minimum total dose of 0.1 mg and a maximum total dose of 0.5 mg. No other medications were added. Observations were recorded prior to injection, two minutes thereafter, and then every five minutes during the procedure. At the same time intervals until the end of the procedure, levels of sedation and tolerance were recorded using previously validated analogue scales (boxes 1 and 2).[15 16]

When recovering, patients were transferred to a short observation ward and monitored every 10 minutes until the time they fulfilled discharge criteria. At this point a patient/parent satisfaction score was obtained. A five point Likert scale was used, the five ratings being: excellent, good, satisfactory, poor, and extremely poor. Between three and five days after discharge the parents/patients were contacted by telephone and asked to score their satisfaction again. They were also asked about sleep and behavioural problems and any other complaints perceived to be related to the sedation.

### Sample size

The incidence of hypersalivation with intramuscular ketamine without any adjuncts in children is unknown but is reported to be as high as 26% when ketamine is given orally and 86% when given intravenously.[17 18] We anticipated that the incidence of hypersalivation under intramuscular ketamine sedation with a placebo adjunct would be within the above range and with atropine as an adjunct it would be about 2%.[1] To detect a difference in incidence of 24% at the 5% significance level with 90% power would require approximately 42 patients per treatment group. A simple randomisation schedule was prepared by the Princess Margaret Hospital Pharmacy Department to allocate patients to the two treatment groups.

### Statistical analysis

Categorical data are presented as frequencies and percentages and odds ratios with 95% confidence limits. Continuous data and numerical ratings were not normally distributed and are presented as medians with 25th and 75th percentiles. $\chi^2$ tests for independence were used to compare the treatment groups on binary outcomes (hypersalivation and other adverse events). Previous sedation, top-up medication, and patient age were determined a priori to be potential confounding variables for binary outcomes and, where indicated, logistic regression was used to control for confounding. Mann–Whitney U tests were used to compare the treatment groups on sedation, tolerance, and satisfaction ratings. Analyses were performed on SPSS version 11.5 (SPSS Inc.). A 5% significance level (two tailed) was used for all tests.

## RESULTS

We enrolled 83 patients (ages ranging from 13 months to 14.5 years) in the study: 44 (53%) were randomised to the atropine group and 39 (47%) to the placebo group. The treatment groups were similar in terms of medical procedures. A total of 55 (30 atropine, 25 placebo) patients (66.3%) underwent laceration repair and wound debridement, 14 (7, 7) (16.9%) had fracture and joint reductions, 11 (6, 5) (13.2%) had a foreign body removed, and 3 (1, 2) (3.6%) had incision and drainage of an abscess. Every procedure was successfully completed.

Patients' baseline demographic characteristics are shown in table 1. Characteristics were similar in the atropine and placebo groups with the exception of top-up medication: four of five patients who required top-up medication received atropine.

Hypersalivation and other binary (present/absent) adverse events recorded during the study procedure are listed in table 2. Hypersalivation was observed in 17 patients (20.5%). Of these, only eight required suction (four per treatment group). Patients who received atropine were significantly less likely to hypersalivate than those who received placebo ($p = 0.03$). The odds ratio of 0.29 (95% CI 0.09 to 0.91)

**Table 1** Baseline demographic characteristics

| Characteristic | Atropine | Placebo |
|---|---|---|
| Age (years) | 3.3 (2.3–4.5) | 3.8 (2.2–5.1) |
| Sex (male)* | 28 (63.6) | 29 (74.4) |
| Weight (kg) | 15.7 (13.6–18.3) | 14.9 (13.2–20.2) |
| Procedure time (min) | 10.5 (6.0–16.8) | 10.0 (6.0–15.0) |
| Ketamine (mg) | 62.0 (54.0–73.5) | 60.0 (53.0–80.0) |
| Total dose (ml) | 0.39 (0.34–0.45) | 0.38 (0.33–0.50) |
| Top-up* | 4 (9.1) | 1 (2.6) |
| Previous sedation†* | 5 (11.4) | 6 (15.8) |

Data are median (25th–75th percentile) unless otherwise stated: *data are number (%).
†Opioid analgesia or nitrous oxide.

**Table 2** Adverse events. Data are n (%)

| Event | Atropine n = 44 | Placebo n = 39 | Odds ratio* | 95% CI |
|---|---|---|---|---|
| Hypersalivation | 5 (11.4) | 12 (30.8) | 0.29 | 0.09 to 0.91 |
| Rash | 10 (22.7) | 2 (5.1) | 5.44 | 1.11 to 26.6 |
| Vomiting | 4 (9.1) | 10 (25.6) | 0.29 | 0.09 to 1.02 |
| Stridor/laryngospasm | 4 (9.1) | 6 (15.4) | 0.55 | 0.14 to 2.11 |
| Muscle rigidity | 6 (13.6) | 8 (20.5) | 0.61 | 0.19 to 1.95 |
| Random movements | 9 (20.5) | 9 (23.1) | 0.86 | 0.30 to 2.44 |
| Intervention | 12 (27.3) | 8 (20.5) | 1.45 | 0.52 to 4.04 |

*Odds ratio, odds for atropine relative to placebo.

represents a greater than threefold reduction in hypersalivation under atropine compared with placebo. The odds ratio was largely unaffected by adjustment for age (OR 0.27; 95% CI 0.08 to 0.87; p = 0.03), previous sedation (OR 0.30; 95% CI 0.09 to 0.95; p = 0.04), and top-up medication (OR 0.31; 95% CI 0.10 to 0.99; p = 0.05). None of the adjustment variables were significant predictors of hypersalivation in their own right (all p>0.22).

A transient rash was observed in 12 patients (14.5%) and was significantly more common in the atropine group (p = 0.02). The odds ratio of 5.44 (95% CI 1.11 to 26.6) indicates a greater than fivefold increase in rash under atropine compared with placebo. In contrast, vomiting occurred in 14 patients (16.9%) but it was less common in the atropine group (p = 0.05). The odds ratio of 0.29 (95% CI 0.09 to 1.02) suggests atropine may contribute to a threefold reduction in vomiting when compared with placebo. When adjusted for patient age, there was a small reduction in the odds ratio for treatment group (OR 0.24; 95% CI 0.06 to 1.03; p = 0.06). The odds ratio for age was 1.41 (95% CI 1.15 to 1.74; p = 0.001), indicating on average a 41% increase in the odds of vomiting with each one year increase in age. When patients were arbitrarily categorised at five years of age, of those under five years (n = 63), only 9.5% vomited, but in the age group five years and older (n = 20) 25% vomited.

There were no reliable differences between the treatment groups on the remaining adverse events. Four atropine and six placebo patients experienced stridor/laryngospasm (p = 0.38). Stridor/laryngospasm was mild in the vast majority of cases and resolved spontaneously with the exception of two patients where airway opening manoeuvres were applied (both were given atropine). Emergence, defined as unpleasant dreams and inconsolable crying in small children but not hallucinations if the child was not distressed by them, occurred in only one patient: a 13 month old girl in the placebo group exhibited short lived inconsolable crying during recovery after laceration repair.

**Table 3** Sedation and tolerance scores. Data are number (%)

| | Atropine | Placebo |
|---|---|---|
| Sedation category (score)* | | |
| Asleep (1) | 26 (59.1) | 30 (76.9) |
| Drowsy (2) | 12 (27.3) | 5 (12.8) |
| Calm (3) | 3 (6.8) | 2 (5.1) |
| Awake (4) | 1 (2.3) | 1 (2.6) |
| Agitated (5) | 2 (4.5) | 1 (2.6) |
| Tolerance category (score)* | | |
| Cooperative (1) | 30 (68.2) | 34 (87.2) |
| Some movement or crying (2) | 13 (29.5) | 3 (7.7) |
| Crying with thrashing movements (3) | 1 (2.3) | 1 (2.6) |
| Unable to complete procedure (4) | 0 (0.0) | 1 (2.6) |

*Full category labels are given in box 1 for sedation and in box 2 for tolerance.

**Table 4** Satisfaction ratings

| | On discharge | | 3–5 days after discharge | |
|---|---|---|---|---|
| Rating | Atropine n = 43 | Placebo n = 39 | Atropine n = 41 | Placebo n = 36 |
| Excellent | 32 (74.4) | 28 (71.8) | 32 (78) | 27 (75) |
| Good | 8 (18.6) | 8 (20.5) | 7 (17.1) | 8 (22.2) |
| Satisfactory | 1 (2.3) | 2 (5.1) | 1 (2.4) | 1 (2.8) |
| Poor | 2 (4.7) | 0 | 1 (2.4) | 0 |
| Extremely poor | 0 | 1 (2.6) | 0 | 0 |

Vital signs were similar for the treatment groups. There was one instance of a drop in oxygen saturations below 96%: a three year old boy desaturated to 87% for less than two minutes when undergoing wound exploration of a limb and removal of a foreign body. He required suction for excessive hypersalivation and supplemental oxygen. The procedure was completed successfully and no further adverse events occurred. The patient was ready for discharge one and a half hours later. He had received atropine.

Results for sedation and tolerance are shown in table 3. For both rating scales, the worst rating during the observation period was used as the patient's score. Although relatively more placebo than atropine patients were in the most favourable category for both scales, these differences were not statistically significant by conventional standards (sedation p = 0.11 and tolerance p = 0.06).

Table 4 shows the results for parent/patient satisfaction ratings at discharge and three to five days following discharge. The ratings are overwhelmingly favourable for both treatment groups with no evidence of a difference between them at discharge (p = 0.78) or at follow up (p = 0.81). Of those who provided both ratings, 92% (71/77) gave identical ratings. For the remaining six patients, four follow up scores were one category below the initial rating and two were one category above.

On follow up parents were also asked about sleep and behavioural problems and any other complaints perceived to be related to the sedation. No sleep problems or nightmares were reported. Four parents perceived their children (aged between two and four years) to be unusually ''grumpy'' and ''moody'' the day after the sedation, two parents felt their children (aged two and three years) were ''hyperactive''. Six patients were lost to follow up.

## DISCUSSION

Atropine administered intramuscularly in the same syringe with ketamine significantly reduces hypersalivation, with its onset of action occurring earlier than previously thought. It is important though to point out that atropine is not effective in all instances: even when given atropine, 11.4% of patients in the present study experienced hypersalivation, the same proportion observed elsewhere, with patients receiving a lower ketamine dose of 2–2.5 mg/kg.[3]

The incidence of stridor/laryngospasm (12% overall) is in contrast to much lower figures found by Green *et al* examining larger, pooled data.[1] It is plausible that some occurrences documented on the observation sheets were due to airway malalignment rather than laryngospasm, given the easily manageable nature of these incidents. This highlights two issues: first, even experienced emergency clinicians may find the clinical differentiation difficult, and second, patient airway monitoring and management requires the full attention of a dedicated senior clinician not involved with the procedure. Serious adverse events associated with ketamine sedation are extremely rare and any effect of atropine on the reduction of those would require trials

enrolling large numbers of patients, although one would expect a benefit by reducing risk factors for laryngospasm, namely increased secretions and the need for suction.

A transient rash is a known side effect of both ketamine and atropine and therefore it is not surprising to see that the incidence of rashes was higher when atropine was added (22.7% *v* 5.1% with placebo). Rashes were transient and mild in every instance and did not require any intervention.

The onset of vomiting occurred well into the recovery period when the children were responsive again. No patient had to be readmitted because of vomiting; no child started vomiting after discharge. Given that nausea and vomiting are side effects of both agents we would have expected a higher incidence of vomiting in the atropine group. The incidence of vomiting, however, was much higher in the placebo group (25.6%) compared with the atropine group (9.1%). Age is a significant independent predictor for vomiting: Green *et al* found the incidence of vomiting to be 3.5% in those aged under five years and 12.1% in those aged five years or older.[19] In our cohort 9.5% of the under five year olds and 25% of children five years and older vomited. Of the eight children who vomited and were five years and older, six were randomised to the placebo group. Overall, 16.9% of children vomited which is a higher percentage than that reported by Green *et al* but similar to the findings of other trials from the UK using intramuscular ketamine and atropine.[3 4] Although showing an interesting trend, the difference between the groups was not statistically significant.

Sedation and tolerance scores were similar with a trend towards the more favourable categories in the placebo group without being statistically significant due to the small sample size. Overall, for both groups the majority of ratings were in the top two categories, suggesting that ketamine sedation was very well tolerated and effective in most if not all cases and with or without atropine. Patient/parent satisfaction with the sedation was very high in both treatment groups and this was no different for the patients who vomited. It can be assumed that, even if there were atropine related side effects lasting into the recovery period and beyond, they did not alter the perception of the sedation experience judged by the satisfaction ratings.

Emergence phenomena in children are rarely distressing and seem to be less common with intramuscular ketamine.[5] We were only looking for obviously unpleasant experiences. Given the young age of the only patient who was distressed during the recovery period one may argue that this was merely a case of recovery agitation but this distinction is somewhat artificial and difficult to make in young children.

To our knowledge, this is the first randomised controlled study of atropine with placebo as an adjunct to ketamine sedation. The common practice of combining the two agents so far has been based on experts' advice rather than clinical evidence. One potential drawback of this study is that hypersalivation was recorded on clinical findings rather than quantitative measurements and therefore the true incidence of hypersalivation may yet still be higher. Clinically, however, this would not make any difference. The main limitation of any randomised controlled trial is the insufficient power to detect rare but serious, adverse outcomes and further studies and pooling of data are required to establish the true safety profile.

## CONCLUSION

Atropine as an adjunct to intramuscular ketamine sedation in children significantly reduces hypersalivation. Using atropine as an adjunct may also reduce the risk of vomiting in the recovery period, although further studies are needed to confirm this finding. We recommend the routine use of atropine as an adjunct for intramuscular ketamine sedation of children in the emergency department.


### Authors' affiliations

**P Heinz,** Department of Paediatrics, Addenbrooke's Hospital, Cambridge University Hospital Foundation Trust, Cambridge, UK
**G C Geelhoed, E M Pascoe,** Emergency Department, Princess Margaret Hospital for Children, Subiaco, WA, Australia
**C Wee,** Emergency Department, Joondalup Health Campus, Joondalup, WA, Australia


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