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# Similar excitation after sevoflurane anaesthesia in young children given rectal morphine or midazolam as premedication

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**Background:** Sevoflurane is a rapid-acting volatile anaesthetic agent frequently used in paediatric anaesthesia despite transient postoperative symptoms of cerebral excitation, particularly in preschool children. This randomised and investigator-blinded study was designed to evaluate whether premedication with an opioid might reduce non-divertible postoperative excitation more than premedication with a benzodiazepine in preschool children anaesthetized with sevoflurane.

**Methods:** Ninety-two healthy two to six year-old children scheduled for nasal adenoidectomy were randomised to be given rectal atropine  $0.02 \text{ mg kg}^{-1}$  together with either morphine  $0.15 \text{ mg kg}^{-1}$  or midazolam  $0.30 \text{ mg kg}^{-1}$  approximately 30 min before induction and maintenance of sevoflurane anaesthesia. The patient groups were compared pre- and postoperatively by repeated clinical assessments of cerebral excitation according to a modified Objective Pain Discomfort Scale, OPDS.

**Results:** There were no statistically significant postoperative differences in incidence, extent or duration of excitation between children given morphine or midazolam for premedication, whereas morphine was associated with more

preoperative excitation than was midazolam. The study groups did not differ significantly with respect to age, weight, duration of surgery and anaesthesia, and time from tracheal extubation to arrival in and discharge from the postoperative ward.

**Conclusion:** In this study morphine for premedication in young children anaesthetized with sevoflurane was associated with similar postoperative and higher preoperative OPDS scores compared with midazolam. These findings indicate that substitution of morphine for midazolam is no useful way of reducing clinical excitation after sevoflurane anaesthesia.

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**Key words:** Anaesthesia; child; excitation; inhalational; midazolam; morphine; premedication; sevoflurane.

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FOR almost a decade sevoflurane has been the volatile agent of choice for maintenance of general anaesthesia in Sweden and proved most useful in modern day-care paediatric anaesthesia (1). The smooth induction and elimination characteristics (2–4) are particularly appreciated in younger patients despite frequent agitation in the early postoperative period, particularly in preschool children (5–7), recently found to be attenuated by analgesics (6).

The aim of the present study was to evaluate whether a study group of preschool children given rectal premedication with morphine (8) would have less non-divertible postoperative excitation after sevoflurane anaesthesia compared with a control group given rectal premedication with midazolam (9).

## Patients and methods

The study was approved by the Human Research Ethics Committee at the Medical Faculty of Lund University, Lund, and by the national Medical Products Agency, Uppsala, Sweden.

In an open pilot study premedication was given with morphine ( $n=10$ ) or midazolam ( $n=10$ ) in preschool children anaesthetized with sevoflurane. Excitation, observed in five children of each group, was found to be divertible in the morphine group and non-divertible in the midazolam group. Based on these findings, 78 patients would be required to confirm a 25% difference, i.e. half of that observed in the pilot study, with 80% power and 95% probability in

the incidence of non-divertible excitation between the study groups. To compensate for exclusions, missing data and withdrawals we included 92 healthy (ASA I-II) 2–6-year-old children scheduled for adenoidectomy with or without simultaneous myringotomy.

Consents were obtained from parents and older children after oral and written information about the study. Only those children whose parents had good knowledge of Swedish, and those with no verified or suspected allergic reactions to – or ongoing drug treatment possibly interacting with – the study drugs were included. Ten patients, three from the morphine group and seven from the midazolam group, were excluded. Half of them had been given drugs not allowed for inclusion, and the others were excluded because of lack of protocol data, skin rash after premedication or cancellation of surgery. The results reported are based on data obtained in the remaining 82 patients.

A patient- and investigator-blinded study design was used. Patients were randomised (in blocks of four) to two study groups given morphine ( $n = 43$ ) or midazolam ( $n = 39$ ) for premedication.

The children were not allowed to eat or drink for at least four hours. Approximately 30 min before the induction of anaesthesia they were given atropine  $0.02 \text{ mg kg}^{-1}$  together with either morphine  $0.15 \text{ mg kg}^{-1}$  or midazolam  $0.30 \text{ mg kg}^{-1}$  for premedication.

The extent of excitation was assessed repeatedly according to predetermined criteria on 11 consecutive occasions – immediately before induction, after extubation, at arrival in the recovery room and 10, 20, 30, 45, 60, 75, 90 and 120 min later – using a clinical modification of an established Objective Pain Discomfort Scale (OPDS) scoring system (10), where one variable based on blood pressure levels was omitted (Table 1). Maximal excitation score at each assessment

was eight points. Per protocol the study groups were to be compared statistically with respect to their modified OPDS scores immediately before induction of anaesthesia and after tracheal extubation, and also with respect to their maximal postoperative OPDS scores.

Anaesthesia was induced by inhalation of 8% sevoflurane in oxygen. A peripheral venous Teflon cannula was inserted and 0.5 L of a buffered 2.5% glucose solution (Rehydrex<sup>®</sup>, Pfizer, USA) was infused slowly intravenously (iv). Fentanyl  $2 \mu\text{g} \cdot \text{kg}^{-1}$  iv was administered, and endotracheal intubation was carried out under deep sevoflurane anaesthesia following recentration of eye axes. No muscle relaxant was used. Approximately  $30 \text{ mg kg}^{-1}$  of paracetamol was given by the rectal route soon after intubation.

Anaesthesia was maintained at an expiratory sevoflurane concentration of approximately 2.5% in 50% of oxygen in nitrogen at a fresh gas flow of approximately  $21 \text{ min}^{-1}$  in a rebreathing circuit system fitted with a soda lime absorber.

Heart rate, non-invasive arterial blood pressure and percutaneous saturation of oxygen ( $\text{SpO}_2$ ) were all monitored together with end-tidal concentrations of carbon dioxide ( $\text{EtCO}_2$ ) and sevoflurane. The  $\text{EtCO}_2$  was maintained between 4.2 and 4.8 kPa by controlled ventilation. At the end of surgery, the sevoflurane and the nitrogen were discontinued, and the fresh gas flow of oxygen was increased to  $61 \text{ min}^{-1}$ .

The endotracheal tube was removed once there was no sign of bleeding and the patient was considered to breathe adequately after having regained cough and gag reflexes.

Considerable secretions, stridor, laryngospasm, bronchospasm, reduction of  $\text{SpO}_2$  or administration of adrenaline, theophylline or glucocorticosteroids together with controlled or assisted ventilation in the early postoperative period were recorded as airway problems.

Table 1

Tool used to assess clinical excitation in pre-school children given morphine or midazolam for premedication before and after sevoflurane anaesthesia in the present study, slightly modified by exclusion of the blood pressure variable from the ten-point Objective Pain Discomfort Scale (OPDS) originally introduced by Walker *et al.* (10). Maximal OPDS score at each assessment was eight points.

Assessed variable	Scoring (OPDS units)		
	0	1	2
Crying	None	Crying consolable	Crying Non-consolable
Movement	None Asleep or calm	Mild Restless	Moderate or severe Thrashing
Agitation	None Asleep or calm	Mild Divertible	Moderate or severe Non-divertible
Pain	None Asleep or states no pain	Mild Unable to localize pain	Moderate or severe Able to localize pain verbally or by pointing

One of the parents was allowed to stay with the child from arrival in the recovery room. Four anaesthesia nurses blinded to the premedication were responsible for the postoperative assessments of excitation.

Morphine in doses of  $0.05 \text{ mg kg}^{-1}$  iv was allowed for postoperative rescue analgesia based on an individual clinical assessment of each child in the recovery room.

Patients showing stable vital signs with no excessive bleeding, pain or nausea, were allowed to return home as soon as they were able to drink without problems and to walk with minimal or no assistance.

### Statistics

Modified OPDS scores are reported as median, with 25th and 75th percentiles in parenthesis, and range. Other results are reported as mean  $\pm$  1 standard deviation.

Differences between the study groups were analysed with the Mann-Whitney *U*-test regarding OPDS scores and otherwise with unpaired student's *t*-test. Fractions were compared with the Fisher exact test.

A *p*-level of 0.05 or less was considered to indicate statistical significance.

## Results

### Demographics

The study groups were comparable with respect to gender, age and weight. Demographic data are given in Table 2.

### Time variables

There were no statistically significant differences between the study groups in duration of the perioperative procedures (Table 2). The patients in the study groups had been fasted for similar periods

of time,  $12.0 \pm 3.4 \text{ h}$  in the morphine group and  $11.0 \pm 5.4 \text{ h}$  in the midazolam group.

### Excitation

An OPDS score of 1.0 or more at least once during the study period was found in 71 of 82 children. Children given morphine for premedication had significantly higher OPDS scores immediately before the induction of anaesthesia ( $P = 0.047$ ) compared with those given midazolam, but the study groups were similar with respect to postoperative scores immediately after tracheal extubation ( $P = 0.809$ ) and with respect to maximal postoperative scores ( $P = 0.621$ ) with no significant differences between boys and girls. In both study groups the OPDS scores were 0 in at least half of the patients 10 min after arrival in the recovery unit, and in at least 75% of the patients after 30 min (Table 3).

### Pain

Soon after arrival in the postoperative unit morphine was given for postoperative rescue analgesia in seven morphine patients (16%; relative dose  $0.074 \text{ mg kg}^{-1}$ ) and in 11 midazolam patients (28%;  $0.056 \text{ mg kg}^{-1}$ ) with no significant difference in incidence between the study groups ( $P = 0.28$ ). The modified OPDS scores immediately before the first injection of morphine were 5 (2; 6) 2-8 in the morphine group and 4 (2; 6) 2-8 in the midazolam group. More than half of the 18 patients given rescue analgesia had their first postoperative injection of morphine within 10 min. Seven of these injections, five in the morphine patients and two in the midazolam patients, were administered at arrival in the recovery unit. Although time to the first injection of morphine did not differ significantly ( $P = 0.09$ ) between patients given morphine,  $12 \pm 15 \text{ min}$ , or midazolam,  $22 \pm 15 \text{ min}$ , there was a tendency towards earlier postoperative administration of morphine in children given morphine for premedication.

Table 2

Demographic and time data (mean  $\pm$  1 standard deviation) used for pre-, per- and postoperative procedures in pre-school children given morphine or midazolam for premedication before and after sevoflurane anaesthesia.

	Morphine group (n = 43)	Midazolam group (n = 39)
Number (%) of girls	15 (35)	15 (38)
Age (years)	$3.8 \pm 1.2$	$3.8 \pm 1.2$
Weight (kg)	$17 \pm 4$	$16 \pm 3$
Time from induction of anaesthesia to tracheal extubation (min)	$41 \pm 13$	$44 \pm 16$
Time from start of surgery to end of surgery (min)	$14 \pm 10$	$15 \pm 12$
Time from end of surgery to tracheal extubation (min)	$14 \pm 6$	$14 \pm 6$
Time from tracheal extubation to ability to drink water (h)	$2.1 \pm 0.8$	$1.8 \pm 0.8$
Time from premedication to discharge home (h)	$4.5 \pm 1.0$	$4.4 \pm 1.0$

Table 3

Modified objective pain discomfort scale (OPDS) scores (median, 25<sup>th</sup> and 75<sup>th</sup> percentiles, range) in pre-school children given morphine or midazolam for premedication before and after sevoflurane anaesthesia. The maximal modified OPDS score at each assessment was eight points. *P*-values indicate statistical differences between the study groups.

	Scoring (OPDS units) Morphine group (n = 43)	Midazolam group (n = 39)	<i>P</i> -value between study groups
Immediately before induction of anaesthesia	0 (0; 2) 0-6	0 (0; 0) 0-6	0.809
Immediately after tracheal extubation	3 (0; 5) 0-8	2 (0; 5) 0-8	0.809
At arrival in the recovery unit	2 (0; 5) 0-8	1 (0; 5) 0-8	
10 min after arrival in the recovery unit	0 (0; 2) 0-7	0 (0; 3) 0-8	
20 min after arrival in the recovery unit	0 (0; 1) 0-7	0 (0; 2) 0-8	
30 min after arrival in the recovery unit	0 (0; 0) 0-4	0 (0; 0) 0-6	
45 min after arrival in the recovery unit	0 (0; 0) 0-1	0 (0; 0) 0-5	
60 min after arrival in the recovery unit	0 (0; 0) 0-6	0 (0; 0) 0-3	
75 min after arrival in the recovery unit	0 (0; 0) 0-1	0 (0; 0) 0-0	
90 min after arrival in the recovery unit	0 (0; 0) 0-0	0 (0; 0) 0-1	
120 min after arrival in the recovery unit	3 (0; 5) 0-2	2 (0; 5) 0-0	
Maximal postoperative value	3 (0; 6) 0-8	3 (1; 5) 0-8	0.621

### *Nausea and vomiting*

Although an almost twice as high incidence of postoperative nausea and vomiting (PONV) was found in children given morphine for premedication compared with those given midazolam, 17 of 43 vs. eight of 39 patients, this difference did not reach statistical significance ( $P = 0.16$ ).

### *Airway problems*

Eleven study patients (13%), eight in the morphine group and three in the midazolam group, had perioperative airway problems with no difference between the groups.

### *Other characteristics*

Each child was accompanied by at least one parent immediately before and after the period of anaesthesia.

## Discussion

Psychomotor excitation after sevoflurane anaesthesia in children, proposed to be associated with postoperative anxiety, remaining drug effects or pain (1, 2, 6, 10), represents a considerable clinical problem (6, 11), particularly in preschool children (5, 12), after rapid emergence procedures (13) and in noisy postoperative environments (5, 6, 14).

The residual effects of any cerebral depressant drug used for premedication could theoretically be expected to counteract sevoflurane-induced symptoms of excitation in the postoperative period, at

least by delaying and prolonging the emergence period (5, 10, 11). We found no significant differences in these aspects between preoperative morphine and midazolam, and to our knowledge there is no previous clinical comparison of postoperative excitation after sevoflurane anaesthesia in children given midazolam or morphine for premedication.

For the studied doses, the hypothesis that premedication with morphine in preschool children would result in less excitation after sevoflurane anaesthesia than premedication with midazolam was rejected. Previously, preoperative oral midazolam has been reported to have little or no influence on the postoperative incidence or extent of excitation in young children anaesthetized with sevoflurane (15, 16). In the present study, midazolam was associated with significantly less excitation than morphine immediately before the exposure to sevoflurane. Although no placebo group was included, some depression on preoperative agitation by midazolam is probable considering that oral midazolam has been reported to reduce preoperative agitation (15). Even better clinical sedation has been reported with rectal midazolam (9), particularly in gelatinous formulations (8), as used here. The rectal dose of midazolam proposed for premedication in children is 0.25–0.35 mg kg<sup>-1</sup> bodyweight (17). Approximately three times higher relative doses of morphine than of midazolam have been reported to be required for comparable clinical sedation in adults (18), whereas no similar information is available in children. In the present study, morphine and midazolam were compared at a relative dose ratio of 1:2. This low dose of

morphine had been found to reduce the incidence and extent of postoperative excitation in the initial pilot study. Opioids have been shown to reduce postoperative excitation, and endonasal administration of  $2.0 \mu\text{g kg}^{-1}$  of fentanyl to be associated with less postoperative agitation than half of this dose in children anaesthetized with sevoflurane for myringotomy (19, 20).

Rectal morphine should be administered approximately 30 min and rectal midazolam 15–20 min in advance to attain an optimal effect before the induction of anaesthesia. The average time from administration of the study drug to induction of anaesthesia in the present study corresponds better with pharmacokinetic properties of morphine than of midazolam. Nevertheless, rectal morphine was found to be associated with significantly more preoperative agitation than was rectal midazolam in this study.

Postoperative excitation after sevoflurane anaesthesia has been suggested both to be (1, 2, 6, 10) and not to be (3, 5) associated with postoperative pain. Accordingly, adequate pain relief has been found to reduce (2, 10) or have no effect on (11) agitation early after sevoflurane anaesthesia. Agitation has been reported in preschool children anaesthetized with sevoflurane despite adequate regional anaesthesia (5) or analgesia (11) after surgery, and even following truly painless procedures (3).

The earlier, though non-significant, postoperative i.v. administration of morphine in the group given morphine for premedication – although this group would be expected to have better pain relief than the midazolam group in the early postoperative period – indicates, as previously suggested (3, 5, 11), that factors other than pain play an important role in the development of postoperative excitation in young children after sevoflurane anaesthesia.

The lack of differences in postoperative use of rescue analgesic between the study groups does not seem to have resulted from different individual assessments of agitation, since similar OPDS scores were recorded immediately before the first injections of morphine in the two groups.

Different methods have been used to assess agitation in previous studies. Some authors (1, 14, 21) have used a modification of the OPDS score (10) similar to that used here, but including more variables. The non-invasive blood pressure component of the original scoring system (10) was not included in this study for two reasons. First, blood pressure measurements are not part of our clinical routine after short anaesthetic procedures in children. Second, pre- and postoperative repeated inflations of the cuff were

considered to interfere with clinical assessments of excitation.

The difference in incidence of PONV between the study groups was not statistically significant despite an almost twice as high incidence in the morphine group. In this respect the statistical power of the study may have been insufficient, but the study was primarily designed to detect clinically important differences in excitation between the study drugs.

In conclusion, premedication with morphine instead of midazolam in the studied doses was associated with higher preoperative OPDS scores and with no difference in postoperative OPDS scores. These findings indicate that substitution of morphine for midazolam is no useful method of reducing clinical excitation after sevoflurane anaesthesia in preschool children.

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