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Propofol and halothane *versus* sevoflurane in paediatric day-case surgery: induction and recovery characteristics†

J. K. Moore[1]*, E. W. Moore[1], R. A. Elliott[2], A. S. St Leger[3], K. Payne[2] and J. Kerr[4]

[1]Wirral Hospital Trust, Cheshire CH49 5PE, UK. [2]School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester M13 9PL, UK. [3]University of Manchester Biostatistics Group, School of Epidemiology and Health Sciences, Manchester M13 9PT, UK. [4]Yeovil District Hospital, Higher Kingston, Yeovil, Somerset BA21 4AT, UK

**Corresponding author*

Background. The aim of this study was to compare the induction and recovery characteristics associated with propofol induction and halothane maintenance with sevoflurane anaesthesia in paediatric day surgery.

Methods. In total, 322 children were assigned randomly to i.v. propofol induction and halothane/nitrous oxide maintenance or sevoflurane/nitrous oxide alone. The patients' age, sex, and type of surgery were recorded, as were the times required for anaesthetic induction, maintenance, recovery and time to discharge home. Postoperative nausea and vomiting, and the incidence of adverse events during induction and recovery were also noted.

Results. No significant differences were detected in age, sex, type of surgery performed or intraoperative opioid administration. Excitatory movement was more common during induction with sevoflurane. The mean time required for induction with propofol was 3.1 min compared with 5 min in the sevoflurane group ($P<0.001$). The recovery time was shorter in the sevoflurane group compared with propofol/halothane (23.2 *vs* 26.4 min, $P<0.002$). The incidence of delirium in recovery was greater in the sevoflurane group ($P<0.001$). There was no difference between groups in the time spent on the postoperative ward before discharge home. On the postoperative ward the incidence of both nausea and vomiting was significantly higher in the sevoflurane group ($P=0.034$). Five children were admitted to hospital overnight, none for anaesthetic reasons.

Conclusions. The increased incidence of adverse events during induction, postoperative nausea and vomiting and postoperative delirium in the sevoflurane group suggests that sevoflurane is not ideal as a sole agent for paediatric day case anaesthesia.

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Patient preferences and economic pressures are driving an increase in day-case elective surgery. In the UK, The Royal College of Surgeons and the National Health Service Executive suggest that >50% of all elective work should be managed as day surgery.[1] From an economic perspective, the comparative costs of surgical care in the day case setting are lower than in an inpatient setting.[2] From the patient's perspective, the benefit of day surgery is the avoidance of an overnight hospital admission with minimal lifestyle disruption. These advantages may be particularly important in the paediatric population and the number of paediatric day-case surgical procedures is increasing.[3 4]

For day surgery to be an acceptable option, care during and after surgery must be of the highest quality and postoperative morbidity, such as pain, or postoperative nausea and vomiting (PONV), must be minimized.[5 6] For

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Table 1 Time measures employed with their definitions

Time	Definition
Induction	Time from commencing induction to patient entering theatre
Maintenance	Time from entering theatre to time when maintenance agents discontinued
Recovery	Time from maintenance agent discontinuation to leaving the anaesthetic recovery room to return to the postoperative ward
Discharge	Time from return to the postoperative ward to discharge home

this reason, the choice of anaesthetic agent and technique has been seen as critical.[7 8]

Halothane has long been the mainstay of paediatric anaesthesia.[9] However, this role has recently been challenged, and substitution with sevoflurane or propofol suggested.[10] Sevoflurane has many features of an ideal inhalational agent; its low blood-gas solubility and non-pungent smell suggest a smooth, uncomplicated and rapid induction of, and emergence from, anaesthesia.[11] These properties may make sevoflurane especially suitable for day surgery in children. In paediatric day surgery, propofol is associated with rapid emergence and has been associated with less PONV than sevoflurane.[12]

The aim of this large study was to compare the induction and recovery characteristics associated with propofol induction and halothane maintenance anaesthesia with sevoflurane induction and sevoflurane maintenance in a paediatric day surgery population.

Methods

The study formed part of the Cost Effectiveness Study in Anaesthesia (CESA), the overall aim of which was to provide robust evidence to health care professionals and policy makers about the relative costs, patient benefits, clinical outcomes, and acceptability of alternative anaesthetic agents and related techniques. This paper describes the paediatric clinical outcomes. Full details of the methods used may be found in the Health Technology Assessment report,[9] which also describes the economic data from this trial.

CESA had full ethical approval, and all children were recruited with the informed consent of their parents or guardians. The study population consisted of children aged 3–12 yr undergoing day-case general or ENT surgery in our hospital between October 1999 and January 2001.

The study was powered to detect a reduction in PONV from 20 to 10%, with 80% power using a two-tailed significance test at the 5% level of significance. This required 440 patients (220 in each treatment arm).

To be enrolled in the study, the child needed to be assessed as fit for day-case anaesthesia using the hospital's routine day-case protocol. Factors that precluded day-case anaesthesia were a history of allergic or other serious adverse experience with anaesthesia; severe cardiovascular, respiratory, metabolic and central nervous system disease or anticipated airway management problems. Children were also excluded from the study if the anaesthetic regimen was expected to include succinylcholine.

Three hundred and twenty-two children were studied. They were assigned randomly to one of two study groups: Group P/H, i.v. propofol (with lidocaine) induction and halothane/nitrous oxide maintenance; and Group S, sevoflurane/nitrous oxide induction and maintenance. A computer-generated random number sequence was used to determine allocation to study groups.

On admission to the ward, each child had topical local anaesthetic cream applied to both hands. Sedative premedication was not given. Parents were encouraged to be present during induction of anaesthesia. All children underwent routine monitoring, which consisted of electrocardiogram, automatic blood pressure and finger or ear pulse oximetery recording. Gaseous monitoring consisted of inspired and expired oxygen, carbon dioxide and volatile agent concentrations.

Because of the obvious differences in the induction techniques, it was not possible to blind the anaesthetists to the treatment allocation. The data analysts were masked to treatment allocation until after the analysis of trial results.

The doses of anaesthetic induction and maintenance drugs were at the discretion of the individual anaesthetist, within the constraints of the agent randomization. The fresh gas flow was fixed at 70–100 ml kg^{-1} min^{-1} via a Mapleson A circuit or a Mapleson F circuit for smaller children. All children received between 50 and 70% nitrous oxide with oxygen during maintenance of anaesthesia. Airway maintenance was at the discretion of the individual anaesthetist, as was the use of non-depolarizing neuromuscular blocking agents. After induction, each child received either a 12.5 mg or 25 mg diclofenac suppository dependent on weight. Those children deemed unable to receive diclofenac were given an acetaminophen suppository. The procedure permitted the administration of intraoperative opioid analgesia with alfentanil or fentanyl, and the use of local anaesthetic infiltration or regional blocks. Patients given intraoperative morphine were excluded from the study. Prophylactic antiemetic drugs were not permitted.

All data were collected prospectively by trained research staff, who had been recruited specifically for the study. The patients' age, sex, and type of surgery were recorded, as were the times required for anaesthetic induction, maintenance, recovery and time to discharge (Table 1). The children were able to leave the anaesthetic recovery room when they were awake, protecting their airway and obeying commands. Return to the community was allowed when the children were ambulatory, taking fluids and were not bleeding or reporting excessive pain.

The primary outcome measure was PONV, which was recorded in both the recovery room and on the postoperative ward. PONV was scored using a four-point scale, 0= absence, 1=nausea only, 2=one emetic episode, and 3=mul-

Table 2 Number of parents/guardians declining to take part in the trial with their reasons

Reason for refusal	*n*
Do not want volatile induction	59
No reason/'don't like the idea'	19
No time	12
I want anaesthetist to choose anaesthetic	7
Do not want i.v. induction	6
Been in study before	5
Legal reasons	4
Concurrent disease	3
Want same anaesthetic as previously	3
Total	**118**

Table 3 Patients withdrawn from trial after randomization, with reasons

Reason for withdrawal	*n*
Protocol violation	15
Operation cancelled	5
Withdrawal of consent	5
Total	**25**

tiple emetic episodes. The incidences of adverse events during induction were noted (pain on injection, excitatory movement, laryngospasm, breath-holding, and coughing). After surgery, the recovery room nurse was asked to judge the patient's mental state by assigning one of three phrases to best describe mental state in recovery: 'alert and awake', 'drowsy', or 'agitated and distressed'. The number of children admitted for overnight stay was recorded.

As part of the economic evaluation, the patients' parents were interviewed by telephone around seven days after surgery. During the interview, they were also asked about their future preferences for anaesthetic induction technique, should their child again require anaesthesia.

The results were analysed using SAS™ 6.12 and SPSS™ 10. Categorical data were analysed using χ^2-tests; Fisher's exact test was used when expected frequencies were less than five. Anaesthetic time data were analysed using unpaired Student's *t*-test. PONV data were analysed using the Mann–Whitney *U*-test and logistic regression analysis.

Results

The primary outcome measure was PONV. Outcomes are reported here in logical order of the anaesthetic process.

Consent was sought from the parents or guardians of 465 children. The number of parents who declined to take part in the trial, together with the reasons they offered, is given in Table 2. Half (*n*=59) of those who did not want to take part in the trial were not willing to expose their child to the chance of undergoing a volatile induction, only 5% (6) were unwilling to accept the chance of an i.v. induction for their child.

Table 4 Patient's age, sex, and surgery type with randomization group (χ^2-test)

	Group P/H	Group S	*P*-value
n	159	163	
Age in years, mean (range)	7.2 (3.0–13.0)	7.1 (2.9–12.9)	n.s.
Female ENT	45	42	n.s.
Male ENT	70	65	n.s.
Female general surgery	7	6	n.s.
Male general surgery	37	50	n.s.
Intraoperative opioids	34	24	n.s.

Three hundred and forty-seven children were randomized to take part in the trial. Twenty-five patients (7%) were withdrawn from the trial after randomization but before anaesthesia commencing—the reasons for withdrawal are given in Table 3. The most common reason for withdrawal at this stage was protocol violation (60%). Most protocol violations reflected the failure to secure i.v. access in a patient randomized to receive an i.v. induction. Occasionally the specific vaporizer was not available, or drugs outside the study procedure were administered. Table 4 shows that there were no marked differences in patient characteristics and the need for intraoperative opioids between the patients completing the trial in the two randomization groups.

The mean time required for induction in the propofol group was 3.1 min compared with 5 min in the children who received sevoflurane ($P<0.001$). Maintenance time was similar in both groups ($P=0.45$). The sevoflurane group had a longer total anaesthesia time ($P<0.01$). Despite this, the recovery time was shorter in the sevoflurane group compared with the propofol/halothane group (23.2 *vs* 26.4 min, $P<0.002$). There was no difference between groups in the time spent on the postoperative ward before discharge home (Table 5).

Table 6 gives the incidence of adverse events during induction. Twenty-two children reported pain during injection of propofol. Three times as many children displayed excitatory movements during induction with sevoflurane (*n*=30) as did with propofol followed by halothane (*n*=10; $P<0.002$). There were no significant differences in the incidence of laryngospasm, breath-holding, or coughing between groups. There may be a trend towards more laryngospasm in the sevoflurane group ($P=0.12$), although the study was not powered to detect this outcome.

The assessment of the patient's mental state in the recovery area showed a significant difference between groups in the number of children described as 'agitated and distressed' or 'drowsy' (Table 7). Although in each group almost two-thirds of the children were judged to be alert and awake in recovery, there were more children described as agitated and distressed in the sevoflurane group ($P<0.001$) and more children described as drowsy in the propofol/halothane group ($P<0.001$).

Table 5 Induction time, maintenance time, total anaesthesia time, time in recovery, and time from recovery to ready for home discharge, in minutes, by randomization group. Values are mean (SD). (Student's *t*-test)

	Group P/H	Group S	*P*-value
Induction time	3.1 (1.9)	5.0 (2.3)	<0.001
Maintenance time	9.5 (7.1)	10.1 (6.7)	0.45
Total anaesthesia time	12.6 (7.8)	15.1 (7.7)	<0.01
Recovery time	26.4 (8.9)	23.2 (8.8)	0.002
Time to discharge	136.9 (127.2)	136.6 (96.4)	0.976

Table 6 Induction adverse events by randomization group

	Group P/H	Group S	*P*-value
Pain on injection	22	0	<0.001†
Excitatory movement	10	30	0.002†
Laryngospasm	0	4	0.123‡
Breath-holding	0	2	0.499‡
Cough	11	9	0.545†

†χ^2-test, ‡Fisher's exact test.

Table 7 Recovery mental state by randomization group. (χ^2-test)

	Group P/H	Group S	*P*-value
Alert and awake	98	101	0.802
Drowsy	45	20	<0.001
Agitated and distressed	15	42	<0.001

Table 8 Nausea and vomiting in recovery and on the postoperative ward by randomization group. (Mann–Whitney *U*-test)

	Group P/H	Group S	*P*-value
Recovery			
None	156	154	0.095
Nausea	2	3	
One emetic episode	1	6	
Multiple emetic episodes	0	0	
Postoperative ward			
None	149	145	0.034
Nausea	4	11	
One emetic episode	2	6	
Multiple emetic episodes	1	2	

The PONV scores in the anaesthetic recovery room and on the postoperative ward are given in Table 8. In recovery, more emetic episodes were recorded in the sevoflurane group, although this difference did not reach statistical significance. On the postoperative ward, the incidence of both nausea and vomiting was significantly higher in the sevoflurane group (P=0.034). Table 9 gives the results of a logistic regression analysis of PONV on the postoperative ward for age, sex and surgical speciality and shows that these factors are not associated with the incidence of PONV.

Five children were admitted to hospital overnight during this study; three in the propofol/halothane group and two in the sevoflurane group. The reasons for admission included more extensive surgery and postoperative bleeding, and no patients were admitted because of PONV.

Table 10 describes parental preferences for future anaesthetic induction. Two hundred and sixty (81%) of the parents were contacted by telephone around the seventh day after surgery. Two-thirds (66%) of parents whose children had received i.v. induction would prefer their child to receive i.v. induction in the future, rather than inhalational induction. Of parents whose children had received inhalational induction, 80% would prefer their children to receive a further inhalational induction, rather than i.v. induction.

Discussion

The CESA project was designed in 1997, and the anaesthetic regimens were selected on the basis of a survey of the clinical practice of paediatric anaesthetists undertaken in January 1999, when 24% were using halothane to maintain anaesthesia. When this survey was repeated on a national basis in October 2000, there was evidence of a rapid change in paediatric clinical practice, with only 0.5% of anaesthetists using halothane to maintain anaesthesia and a declining number using isoflurane. Twenty-three per cent of anaesthetists were using sevoflurane for induction, with 32% using it for maintenance.[9] Given that cost restraints are now a reality in medicine, there must be real practical benefits for a new, more expensive drug to supplant an established one; it is not sufficient for it merely to have theoretical advantages. In a cost-conscious culture, therapies that provide value for money without compromising care must be chosen.[13 14]

This large randomized controlled trial assesses the clinical outcomes of two general anaesthetic techniques for paediatric day case surgery. The primary outcome measure was PONV and the study was powered to detect a reduction in PONV from 20 to 10%. Time and funding constraints meant that the sample size target was not met. In addition, in both anaesthesia groups the PONV rates observed in this study were markedly lower than we had expected from our survey of the literature.[8] Nevertheless, there was a clear and statistically significant difference between the PONV rates for the anaesthetic regimens. Similarly, clear differences were evident when secondary outcome measures were analysed.

In order to produce a study potentially inclusive of all of the children passing through our unit it was necessary to conduct the study in a pragmatic manner. For example anaesthetists were not told how much of each anaesthetic agent to use, only which agent. However, other elements were closely controlled. All patients were preoxygenated, all anaesthetists regularly anaesthetized for paediatric day-case surgery, and only study personnel or permanent members of staff (consultant or associate specialist) gave the anaesthetics. We believe that the low figure for unexpected admission (1.2%) provides evidence of high quality appropriate care and good patient selection.

Table 9 Logistic regression for any nausea or vomiting on the postoperative ward, by randomization group, sex, surgical speciality and age

	P-value
Randomization group	0.034
Sex	0.110
Surgical speciality	0.139
Age	0.498

Table 10 Parental preference for future anaesthetic induction by randomization group. (χ^2-test)

	Group P/H		Group S	*P*-value
Lost to follow up		62		
I.V.	88		25	<0.001
Volatile	44		102	
No preference	1		0	

This study compared both quantitative and qualitative measures of induction. Propofol provided a more rapid induction than sevoflurane. We chose in this trial to measure anaesthetic times by measuring the points at which key movements of the patient occurred (e.g. leaving the anaesthetic room or entering the recovery room). In the context of an economic evaluation, this gives a robust and reproducible measurement, which has practical significance. Recognizing that the time from commencing an anaesthetic drug to loss of consciousness is only part of the time spent preparing the patient to enter theatre, we measured induction by recording the time from the start of induction until the child entered the operating theatre.

There were more adverse events during the volatile induction with sevoflurane, and this was most significant for excitatory movement. This difference is probably attributable to the prolonged time spent in the excitation phase of induction with sevoflurane, compared with the very short excitation phase of induction with an i.v. technique.[15] Twenty-two children described pain on i.v. induction with propofol despite the use of lidocaine. This was the only negative aspect of propofol induction, which was characterized as smoother and more rapid than sevoflurane.

Although there was no significant difference in anaesthetic maintenance time between groups, the longer time for induction in the sevoflurane group (1.9 min; Table 5) was sufficient to make the total anaesthesia time in the sevoflurane group statistically greater. Despite this longer total anaesthesia time, these patients were able to leave the postoperative recovery room to return to the ward more quickly than those patients in the propofol/halothane group. The difference of approximately 3 min between the groups (Table 5) represents ~10% of the recovery time. Several other smaller studies have also shown a reduction in early recovery times when sevoflurane was compared with halothane.[16 17] However, this reduction in early recovery time is unlikely to be clinically significant. To offer an economic advantage a day-case unit would have to translate this slightly shorter recovery time into an increase in patient throughput, or a reduction in staffing levels.[8 18] Like other investigators, we were unable to demonstrate any difference in times to home discharge between groups.

The quality of recovery is arguably more important than the speed of recovery.[19] The most frequently reported disadvantage of a sevoflurane and nitrous oxide anaesthetic is the experience of emergence delirium in the early recovery period.[15 20] In our study, the incidence of recovery room distress was higher in the patients who received sevoflurane. Reasons offered for this difference include inadequate analgesia or an intrinsic central nervous system effect of sevoflurane. Distress in children emerging from anaesthesia may relate to many factors, including distress at induction, residual effects of anaesthesia, confusion, pain, parental separation, hunger or thirst.[15] Postoperative agitation has been reduced with the use of improved analgesic regimens in some studies.[20] In our study, there were no differences in the analgesia provided to the two randomization groups; postoperative delirium appears to be a function of the use of sevoflurane.

Postoperative vomiting is the commonest anaesthesia-related complication limiting hospital discharge,[21] and may result in unanticipated overnight admission.[19] Persistent nausea and vomiting may result in dehydration, electrolyte imbalance and delayed discharge, particularly after day-case surgery.[7] Several factors influence the incidence of nausea and vomiting in paediatric patients undergoing surgery: the site and nature of the surgery, the use of opioid analgesia, pain, antiemetic administration, ambulation, mandatory oral intake regimens, patient age, and anaesthetic agent have all been implicated.[12 21 22] The role of anti-emetic prophylaxis is open to debate and avoidance of prophylactic anti-emetic agents has been advised for both economic and safety reasons.[23] A recent review of PONV trials in paediatric day surgery found no routine anti-emetic administration,[8] whilst a national survey of paediatric day-case anaesthetists found that 24% of practitioners administered these routinely.[9] In this trial, prophylaxis was not given, in line with unit practice. The very low incidence of PONV seen does not suggest that prophylactic anti-emetics should have been used with these patients.

In our study, the incidence of PONV was higher in the sevoflurane treatment group than in the propofol/halothane group, measured both in the recovery room and on the postoperative ward, although this difference was only significant on the postoperative ward (Table 8). Logistic regression analysis of PONV on the postoperative ward against sex, surgical speciality and age appears to confirm the link between randomization group and PONV (Table 9). The absence of a significant difference in PONV in recovery is probably a consequence of the final size of the study group, the overall low rate of PONV and the short amount of time the children spent in the recovery room.

Previous work in this field has compared volatile induction and maintenance with sevoflurane with volatile induction and maintenance with halothane. In these studies sevoflurane has been associated with less nausea and vomiting than halothane.[16 24] Studies in children that have compared propofol alone with sevoflurane alone, or halothane alone, have found lower rates of PONV in the propofol groups.[7 12 25 26] Propofol appears not only to be associated with a low PONV rate, but also to reduce the rate of PONV found with halothane.

The trial enables us to comment both directly and indirectly on parental views about i.v. or inhalational anaesthetic induction. The majority of parents were comfortable with the induction method used and wanted their child to have the same technique in the future. However, the proportion of parents expressing a preference for a repeated inhalational induction was significantly greater than that for an i.v. induction ($P<0.001$). This may seem surprising considering the increased PONV and emergence delirium in the sevoflurane group. However there are several potential confounding factors. Parents were asked specifically about their perception of the induction and were not given any information on the study outcomes. They would therefore be unlikely to be influenced by the increased risk of PONV, or have associated its occurrence with the induction method, had their child suffered from it. In addition, parents would not have witnessed the delirium in recovery, or associated it with mode of induction. Most importantly there may be a group bias in that parents with a strong objection to inhalational anaesthesia had already been removed from the trial by their refusal to take part.

In summary, the sevoflurane/sevoflurane regimen was associated with statistically higher rates of PONV than propofol/halothane, a higher incidence of adverse events during induction and agitation and distress in recovery. A reduction in time required in the postoperative recovery room in the sevoflurane group did not translate into a shorter hospital stay.

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