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Prospective comparison of sevoflurane and desflurane in formerly premature infants undergoing inguinal herniotomy

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Background. Formerly premature infants having inguinal herniotomy have been at a high risk of postoperative apnoea, newer less soluble anaesthetic agents may reduce this risk.

Methods. Thirty infants, under 37 weeks gestation and under 47 weeks post-conceptional age, undergoing inguinal herniotomy had an inhalational induction with sevoflurane and were randomly allocated to sevoflurane (group S) or desflurane (group D) for maintenance. All infants received i.v. atracurium 0.5 mg kg^{-1}, rectal acetaminophen 20 mg kg^{-1} and caudal bupivacaine 0.25% 1 ml kg^{-1}. Infants were monitored for apnoeas (using nasal thermistry and impedance), haemoglobin oxygen desaturations and bradycardias for 12 h before and after operation with an Alice® 4 polysomnograph. Emergence timings were recorded.

Results. There was no difference between pre- and postoperative incidence of apnoeas in either group, and no group difference between desflurane and sevoflurane in terms of pre- and postoperative ventilatory events or in the number of apnoeas in the postoperative period (nine patients in group D and five patients in group S had apnoeas). Median times to first movement, tracheal extubation, eye opening and first cry were all faster with group D (group D: 3.0, 10.0, 9.0 and 11.0 min and group S: 7.0, 15.1, 13.5 and 16.1 min, respectively). No infant had problems with airway irritation on emergence and no infant required airway intervention for apnoea.

Conclusions. Infants wake faster from general anaesthesia when maintained with desflurane as compared with sevoflurane, but no difference in postoperative respiratory events was demonstrated between the groups.

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The formerly premature infant presenting for surgery has significant risk for life-threatening apnoea and oxygen desaturation. Combined analysis[1] of the original data from eight studies concluded that the main determinants of risk of postoperative apnoea are gestational and post-conceptional age, the presence of continuing apnoeic episodes at home and anaemia (haematocrit <30%). Infants with a gestational age of 35 weeks have a risk of postoperative apnoea of more than 5%, up to a post-conceptional age of 48 weeks. Infants who are 'small for dates' have a lower incidence of apnoea compared with gestation-matched infants who have an appropriate weight.[1]

Unlike volatile anaesthesia, awake regional anaesthesia does not appear to exacerbate this background incidence of ventilatory disturbance[2 3] but spinal anaesthesia has a failure rate of 10–20% and has not been widely adopted as a technique.[4] Caudal anaesthesia, in awake infants, has been described but is technically difficult and has problems of limited duration.[5] An alternative technique is to use light general anaesthesia and a caudal epidural block with local anaesthesia. The newer inhalational agents, desflurane and sevoflurane, have enhanced recovery characteristics compared with other volatile agents, including isoflurane, which in the newborn infant is associated with emergence that is twice as long as that of desflurane.[6] Available clinical data suggest that desflurane may have more rapid recovery characteristics than sevoflurane because of its considerably lower blood : gas solubility.[7 8]

We hypothesized that the formerly premature infant recovers faster after desflurane anaesthesia and that desflurane anaesthesia is therefore associated with less disturbance of ventilatory control.

We undertook a prospective randomized controlled trial comparing sevoflurane and desflurane anaesthesia in high-risk infants to compare emergence characteristics in this population and to measure preoperative and postoperative respiratory function in order to identify postoperative ventilatory disturbance.

Methods

After local ethics committee approval and informed parental consent, we studied 30 infants presenting for elective inguinal herniotomy. All were less than 37 weeks gestation at birth and less than 47 weeks post-conceptional age at time of operation. Infants either ventilated before surgery or expected to be ventilated in the postoperative period were excluded from the study. Infants with severe neurological deficit or spina bifida, those with any contraindication to caudal anaesthesia or who had received sedative agents within 48 h of surgery were also excluded.

All infants were monitored for 12 h before operation and immediately after operation with an Alice® 4 polysomnograph (Respironics, Inc., Murrysville, PA, USA). The infants were starved as per our hospital guidelines—3 h for breast milk and 4 h for formula milk. Anaesthesia was commenced with an inhalational induction with oxygen/air and up to 8% inspired sevoflurane using an Ayres T-piece. Atracurium 0.5 mg kg^{-1} was administered once i.v. access was gained and the trachea was intubated with an appropriately sized Portex tracheal tube, ensuring a small gas leak at 20 cm H_2O. Pressure control ventilation was commenced and standard anaesthetic monitoring was applied, including pulse oximetry, ECG, non-invasive arterial pressure, oesophageal temperature and airway gas analysis. Fresh gas flows were set to ensure that no rebreathing of CO_2 occurred. Acetaminophen 20 mg kg^{-1} was administered per rectum and bupivacaine 0.25% 1 ml kg^{-1} administered to the caudal epidural space using a 23 g needle using a sterile 'no touch' technique, after negative aspiration for blood or cerebrospinal fluid.

After induction of anaesthesia, the volatile agent was immediately changed to desflurane 6.7% end-tidal (group D) or remained with sevoflurane 2.5% end-tidal (group S) as dictated by sealed envelope randomization. The volatile agent was discontinued at the time of the last skin suture. The research fellow, who was blinded to patient allocation, was admitted to the operating room once anaesthesia was discontinued and timed the undisturbed patient to the following end points: first gross movement, eye opening, establishment of regular respiration, tracheal extubation (which was decided by the anaesthetist on clinical grounds) and the time to first cry after tracheal extubation. Mechanical ventilation was continued at the end of anaesthesia, maintaining a constant minute volume, to ensure uniform volatile agent elimination. Ventilation was stopped once the infant regained vigorous spontaneous respiratory effort. Any adverse event in the recovery period such as coughing or laryngospasm was recorded. The study monitoring was reapplied as soon as was practical after tracheal extubation, and this usually occurred before leaving the operating room.

The Alice® 4 monitoring system provided continuous recording, onto a memory disc, of heart rate (ECG and pulse oximeter), ventilatory frequency and pattern (nasal thermistry, thoracic impedance from ECG channel and abdominal movement belt), haemoglobin oxygen saturation (pulse oximeter) and limb movement sensor (to aid artifact recognition). The research fellow applied the monitoring to the infant on the ward, on the evening before surgery. Pre-existing alarmed monitoring (e.g. apnoea monitor or pulse oximetry) was continued concurrently. Events such as nursing care or feeds were recorded to aid subsequent monitoring validation and artifact elimination. In accordance with departmental guidelines on the care of high-risk infants, all patients underwent at least 12 h of apnoea monitoring in the postoperative period.

The research fellow, blinded to treatment group, manually analysed the entire monitoring periods, in 30 s windows on a laptop computer using Alice® Sleep Diagnostic Software, version 1.8. The blinded manual analysis was used to exclude artifactual data and to identify significant (non-artifactual) periods of apnoea, bradycardia and decreases in measured oxygen saturation (Sp_{O_2}). These events were categorized according to predefined criteria: bradycardia (heart rate less than 100 beats min^{-1}); oxygen desaturation (an acute decrease in Sp_{O_2} from baseline >8%; or significant apnoea which includes either long apnoea (greater than 15 s) or short apnoea (10–15 s) associated with either bradycardia or oxygen desaturation. Apnoea was defined as a cessation of nasal airflow with either an absence (central apnoea) or presence (obstructive apnoea) of evidence of respiratory effort via the abdominal band or thoracic impedance monitoring. An example of a central apnoea is shown in Figure 1.

Both emergence timings and postoperative events were assumed to be non-parametric and were compared using the Mann–Whitney test, statistical significance was assumed at $P<0.05$. A group size of 30 patients was calculated on the basis of having a 95% chance of detecting a 30% difference in time to extubation between the groups (estimated mean difference 6 min, SD of 5 min, $P=0.05$, power=95%), based on a previous similar study.[7] Emergence data are expressed as median times from cessation of volatile agent.

Results

Thirty infants were recruited equally to group D and S. Both groups were comparable in age, weight and duration of surgery (Table 1). There is weak evidence supporting a faster emergence when anaesthesia is maintained with

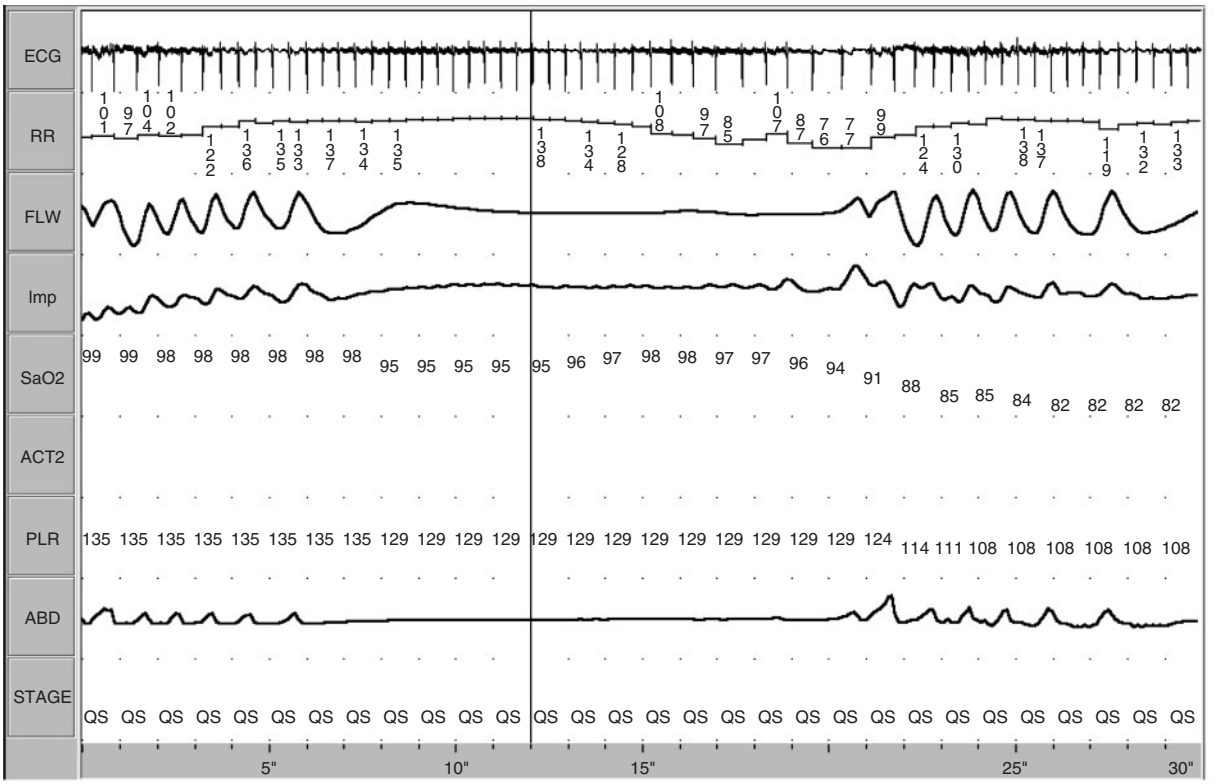

Fig 1 A 13 s central apnoea in a 30 s window. Channels shown (from top) are: ECG, R–R interval, nasal thermistry (FLW), thoracic impedance (Imp), haemoglobin saturation (Sa_{O_2}), movement sensor (ACT2), heart rate (beats min^{-1}) from Sa_{O_2}(PLR), abdominal movement sensor (ABD) and sleep stage (STAGE). Breathing ceases as demonstrated in the FLW, Imp and ABD channels, this is followed by a slowing in heart rate and a decrease in Sa_{O_2}. This event was self-limiting.

Table 1 Patient characteristics. Median (range)

	Desflurane (group D) *n* = 15	**Sevoflurane (group S) *n* = 15**
Gestational age (weeks)	29 (25–36)	31 (26–36)
Post-conceptional age (weeks)	40 (36–45)	38 (33–46)
Birth weight (g)	1300 (770–2550)	1200 (815–2750)
Operative weight (g)	2890 (1870–4840)	2480 (1400–5500)
Duration of anaesthesia (min)	52 (37–75)	51 (31–85)
Haemoglobin (g dl^{-1})	10.5 (8.6–13.0) (*n*=12)	11.4 (9.7–15.7) (*n*=11)

Table 2 Emergence times in minutes. Median (interquartile range). **P*<0.01; ***P*<0.05

	Desflurane (group D) *n*=15	**Sevoflurane (group S) *n*=15**
First movement	3.0 (1.3–6.3)	7.0 (5.7–11.1)*
Tracheal extubation	10.0 (6.3–14.4)	15.1 (11.5–17.0)
Eye opening	9.0 (8.1–13.5)	13.5 (10.5–17.5)
First cry	11.0 (7.3–14.1)	16.1 (14.5–18.5)**

desflurane. Time to first gross movement in the desflurane group occurred in under half the time of the sevoflurane group (3.0 min compared with 7.0 min, *P*=0.006) (Table 2). Time to first cry occurred 5 min faster in the desflurane group compared with those maintained on sevoflurane for their operation (11.0 min compared with 16.1 min, *P*=0.04).

There was no clear relationship between patient grouping and the frequency of postoperative apnoea, bradycardia and oxygen desaturation (Table 3). The likelihood of postoperative respiratory events, for individual patients, correlated reasonably closely with their baseline preoperative frequency. There was no statistical correlation between the anaesthetic used and the change in number of respiratory events from before to after operation. However, neither was there evidence supporting a worsening of respiratory events after operation. There was no consistent chronological relationship between the apnoea occurrences and time since anaesthesia. The events were fairly evenly distributed throughout the 12 h observation period.

There was no proportional change, with anaesthesia, in apnoea origin when all events were pooled. The apnoeic episodes were distributed as follows: preoperative apnoea—41% central, 31% mixed and 28% obstructive in origin; postoperative apnoea—38% central, 29% mixed and 33% obstructive in origin. There was no difference in the relative distribution when compared with the anaesthetic group. The median length of apnoea greater than 15 s, was 18.5 s before and 18 s after operation.

Table 3 Distribution of respiratory events in a 12 h observation window before and immediately after operation for group D (desflurane) and S (sevoflurane). Weight, current weight; GA, gestational age; PCA, post-conceptional age; SFD, small for dates; Hb, haemoglobin; desat, desaturation; brady, bradycardia

ID	Weight	GA	PCA	SFD	Hb	Desat		Brady		Apnoea	
						Pre	Post	Pre	Post	Pre	Post
Desflurane											
2	2.00	31	40	n	9.4	10	5	0	1	0	2
4	1.87	29	37	n	8.7	25	16	15	15	3	39
5	2.90	25	37	n		3	5	0	0	0	0
7	2.11	27	37	y	11.6	68	30	3	2	1	4
10	3.65	35	42	n		1	0	0	0	0	0
12	2.30	30	39	n	8.6	43	13	2	4	5	1
14	2.50	36	38	n		10	4	0	0	0	2
19	3.50	36	42	n	8.8	0	0	2	3	0	0
20	2.67	27	40	n	10	1	0	2	0	0	0
22	2.50	26	38	n	11	7	37	0	40	0	5
24	4.17	29	42	n	10	18	18	0	1	9	3
25	2.89	26	37	n	11.8	30	50	0	0	0	5
28	4.84	29	45	n	11.2	15	88	2	2	1	2
30	2.90	34	41	n	11.9	8	2	1	2	1	0
Sevoflurane											
1	2.80	28	38	n	13.6	17	33	2	5	2	1
3	4.50	34	41	n		2	7	9	0	0	0
8	4.25	36	46	n		0	0	5	0	0	0
9	2.48	36	37	n		6	0	24	0	0	0
11	2.50	32	37	n	11.2	1	6	0	0	0	1
15	4.30	28	43	n	12.4	2	5	3	2	1	0
16	1.56	31	37	y	10.2	34	91	5	13	0	2
17	4.19	34	43	n	11.4	0	1	0	0	0	0
18	5.50	36	47	n	15.7	6	8	1	5	0	0
21	1.40	29	33	y	11.9	28	56	22	5	6	12
23	2.30	27	40	n	10.5	1	3	0	0	0	0
26	2.33	26	39	n		91	26	7	3	1	1
27	1.85	27	37	n	10	11	12	2	6	0	0
29	1.72	32	35	y	12.1	12	46	0	0	0	0

Two patients were recruited but did not have postoperative study monitoring. One patient (in group D) was withdrawn from the study by the parents shortly after returning to the ward after surgery for personal reasons unrelated to the study. The other patient, who had Pierre Robin sequence, was felt to be inappropriate, before group allocation, as the severe micrognathia constituted a significant risk for ventilatory problems in the postoperative period that was unrelated to prematurity. This patient had a severe life-threatening apnoea in the neonatal unit after operation. Patient 16 had prolonged episodes of apnoea in the recovery room that required the intervention of stimulation only. No other patient had any recovery room problems, and no patient had any sign of airway irritation, such as coughing or laryngospasm. No patient required any oxygen therapy, in addition to their preoperative requirements, or active intervention with bag and mask ventilation. No infant required additional analgesia in the first 6 h after operation suggesting they all had clinically effective caudal anaesthesia.

Discussion

Maintenance of anaesthesia with desflurane resulted in faster recovery from anaesthesia as compared with sevoflurane. The time from the end of anaesthesia to the return of spontaneous movement and the time to the first cry was significantly reduced with desflurane. However, there was a considerable individual range of response times and this suggests that other factors such as individual pharmacodynamic responses to the drugs appear to be at least as important to recovery as the speed of washout of the volatile agent. Compared with isoflurane, desflurane has both a lower blood : gas coefficient and a lower oil : gas coefficient, and this physicochemical property accounts for its faster elimination. Sevoflurane has a blood : gas coefficient similar to desflurane but a higher oil : gas coefficient, closer to that of isoflurane. There is good theoretical evidence to suppose that the difference between oil gas solubilities will have a significant effect on recovery time as the duration of exposure increases i.e: a context-sensitive effect on emergence.[9] Recent paediatric clinical data comparing recovery from desflurane with isoflurane after different durations of exposure supports this view.[10]

We were unable to demonstrate differences between the two groups in terms of postoperative apnoea, or the relationship of pre- and postoperative respiratory events within the groups. This lack of change associated with surgery and anaesthesia was interesting and unexpected. Despite comprehensive monitoring, we could not show a relationship with either desflurane or sevoflurane in terms of an increase in postoperative respiratory events, as previously demonstrated.[1] While several patients had a considerable increase in apnoea rate in the postoperative period, a large proportion had a reduction in observed apnoea. Also of note, was the lack of temporal relationship between the events and the timing of the anaesthetic. The events were scattered throughout the 12 h observation period. If there was a significant link between general anaesthesia and respiratory events, it would be expected that the events would, as in previous studies, be grouped early in the postoperative period. However, this was not the case.

One potential criticism of this study is that it may be underpowered to observe a difference in respiratory events. Our sample size of 30 patients was powered to demonstrate a difference in emergence times and is comparable with previous individual studies in terms of sample size and patient characteristics. There are no previous data with which to perform a power calculation to determine the group size required to demonstrate a difference in respiratory events in the postoperative period. We have intentionally left our data in Table 3 in a format that we hope will provide pilot data for future studies. Recording these data can be difficult and prone to artifactual error, but we used well-described methods and have considerable local experience with this type of monitoring technique through the regional paediatric sleep studies unit. Larger sample sizes are difficult to achieve, even from a large institution, in that because of current health care constraints, an increasing proportion of infants requiring inguinal herniotomy are admitted on the day of surgery. This makes it difficult to obtain preoperative

monitoring. Studies that require the preoperative observation of formerly premature infants may not, in the future, be feasible in a single institution and may need to be carried out in several centres to ensure enough patient recruitment in a timely fashion.

We designed our study to reflect as closely as possible the current practice at our institution. Our use of air and oxygen removes the confounding effects of nitrous oxide on MAC of the agents. We assumed minimum alveolar concentration (MAC) values in this population of 9.0 and 3.3 for desflurane and sevoflurane respectively and maintained anaesthesia with 0.67 MAC equivalents. Some may consider our maintenance volatile levels to be higher than that required with a working neuro-axial block, an end-tidal volatile level closer to 0.5 MAC should be sufficient. However, some practitioners at our institution felt uncomfortable with this lower concentration.

Interestingly, the results from this study support the conclusions from a previous study comparing awake spinal anaesthesia with sevoflurane anaesthesia.[3] This study found little difference between the groups in terms of the ventilatory disruption with sevoflurane and suggested that while halothane has been shown to cause postoperative complications, the newer shorter acting volatile agents do not. The physiochemical difference between sevoflurane and desflurane is less than the difference in previously studied agents such as halothane and isoflurane. This would perhaps account for the lack of observed difference between the two groups but not the reduced overall effect that anaesthesia appears to have, when compared with older studies.[2]

Awake regional anaesthesia, via either the spinal or the caudal route, is associated with a lower incidence of postoperative apnoea but is technically difficult in an awake infant and has a significant failure rate and a short duration of action.[3 5] The use of clonidine to prolong the action of the local anaesthetic is associated with an increase in the incidence of apnoea.[11 12] We suggest that light general anaesthetic with sevoflurane or desflurane, controlled ventilation and a caudal block is the current 'best technique' for high-risk infants.

While desflurane has been used for gaseous induction in children, its use is limited owing to airway irritation.[13] Sevoflurane is much better tolerated for inhalational induction. Various emergence events have also been attributed to desflurane such as respiratory irritation, emergence delirium and agitation, none of our infants had such problems.[8 14 15]

Desflurane is currently more expensive than sevoflurane. Used in a semi-closed circuit on low flows the actual cost difference is low and becomes marginally less with longer anaesthetic times. However, when used with higher gas flows and open circuits, such as an Ayre's T-piece, the anaesthetist must make a pharmaco-economic decision as to the relative benefits of using a more expensive technique. It is our opinion that gaseous induction of anaesthesia with sevoflurane followed by maintenance with desflurane utilizes, to the most benefit, the properties of these newer less soluble volatile anaesthetic agents and results in the fastest recovery and may be of particular benefit in high-risk formerly premature infants.

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