Comparative Study between Isoflurane, Sevoflurane and Desflurane in Neurosurgical Paediatric Patients Undergoing Craniotomy for Supratentorial Tumour Resection

AYMAN A. GHONEIM, M.D.; MAGDA S. AZER, M.D. and HOSSAM Z. GHOBRIAL, M.D.
The Department of Anesthesia & Pain Management, National Cancer Institute, Cairo University

Abstract

Background: The aim of this prospective, comparative and randomized study was to compare the inhalational anaesthetics isoflurane, sevoflurane and desflurane in pediatric patients undergoing craniotomy for excision of supratentorial tumours. We assessed early postoperative recovery outcome, intra-operative haemodynamics and degree of brain swelling, as well as postoperative vomiting and shivering.

Methods: Sixty patients scheduled for supratentorial brain tumour excision were randomly allocated into one of three groups (20 patients each); isoflurane, sevoflurane, and desflurane group. After IV induction of anaesthesia, maintenance was achieved using the inhalational anaesthetic according to its group. Emergence and tracheal extubation times and the interval time needed to reach Aldrete score $^9$ were the primary endpoints. The secondary endpoints included intraoperative degree of brain swelling, intraoperative HR and MAP as well as postoperative vomiting and shivering.

Results: The mean emergence time, extubation time and the interval required to reach Aldrete score $^9$ were significantly shorter in desflurane and sevoflurane groups than isoflurane group. No statistically significant changes in the three groups regarding intraoperative brain swelling, haemodynamics, and postoperative shivering or vomiting.

Conclusion: Desflurane and sevoflurane can be used safely in maintenance of anesthesia in neurosurgical paediatric patients. Emergence times are shorter with desflurane or sevoflurane than with isoflurane. They have similar intraoperative and postoperative incidence of adverse effects compared with those who received isoflurane. Thus, desflurane can be considered to be a suitable alternative to isoflurane for paediatric neurosurgical anaesthesia.

Key Words: Neurosurgical – Anaesthesia – Desflurane – Sevoflurane – Isoflurane – Paediatric neuroanaesthesia.

Introduction

INHALED volatile anaesthetics remain the most widely accepted drugs for maintenance of general anaesthesia in neurosurgical operations due to their ease of administration, the availability of end-tidal agent monitoring, and predictable intra-operative and recovery characteristics. Isoflurane was formerly considered to be an appropriate anaesthetic for intracranial surgeries due to its vigorous suppression of cerebral metabolism [1], and it is still considered the most common anaesthetic used in Egypt due to its minimal effects on cerebral blood flow and intracranial pressure (ICP) in hypocapnic patients [2] as well as the lowered cost compared with the other inhalational anaesthetics.

A new dimension had been added to recovery from anaesthetics especially after the introduction of less soluble inhalational anaesthetics, sevoflurane and desflurane. Sevoflurane is a fluorinated ether inhalational agent with low blood/gas partition coefficient (0.6). Its insolubility provides rapid onset and offset thus facilitating early postoperative evaluation of the patients especially in the neurosurgical cases [3]. However it appears that with prolonged administration, recovery times may be delayed and this benefit would be lost. The effects of sevoflurane on cerebral hemodynamics are similar to isoflurane [3]. Several studies in humans revealed less cerebral vasodilatation with sevoflurane than with isoflurane. However, the probable toxicity from sevoflurane resulting from the relatively high rate of its metabolism as well as its reaction with carbon dioxide ($\text{CO}_2$) absorbents has been a source of considerable concern.

Desflurane is a volatile anaesthetic known to have early recovery from anaesthesia due to its low blood solubility and low blood-gas (0.42) and tissue-blood partition coefficients resulting in a more rapid wash in and wash out in comparison to the other known volatile anaesthetics. This rapid
recovery constitutes one of the important goals of neuroanaesthesia for early neurological evaluation of the patient after neurosurgery [4] and hence to hasten the diagnosis and treatment of a life threatening complication [5]. However, there was much debate on its use in neurosurgery because it possesses a vasodilator effect on cerebral blood vessels [6,7]. More studies had demonstrated the safety of desflurane anaesthesia when used in normocapnic patients undergoing excision of supratentorial brain tumours [8,9] and found that there was no variation in intracranial pressure (ICP) in normocapnic patients undergoing removal of supratentorial tumours using the desflurane as inhalational anaesthetic. To our knowledge, there is no prospective works have studied the effect of desflurane in paediatric patients undergoing cranietomy for tumour resection.

This prospective, comparative and randomized study was designed to compare the main three inhalational anaesthetics isoflurane, sevoflurane and desflurane in paediatric patients undergoing cranietomy for excision of supratentorial tumours. Early postoperative recovery outcome variables (including emergence time, extubation time and the time required to reach Aldrete score 9) were assessed as a primary outcome variables. Secondary variables included intra-operative haemodynamics and degree of brain swelling, as well as postoperative vomiting and shivering.

**Patients and Methods**

Following Institutional Review Board approval and written informed consent, 60 paediatric patients were randomly enrolled in this study in the Children Cancer Hospital- Egypt. The selected patients were ASA physical status I-II, aged 7-18 years, Glasgow Coma Scale ≥15, and undergoing scheduled, elective cranietomy for supratentorial tumour excision. The criteria of exclusion were known allergies to any used anaesthetic drug, Glasgow Coma Scale < 15, if they were haemodynamically or neurologically unstable and/or refusal to sign the consent. Additionally, patients who had been exposed to general anaesthesia in the preceding 7 days before study were excluded.

Using a computer-generated randomization list, the patients were randomly allocated into one of three groups (20 patients each): Isoflurane Group, Sevoflurane Group and Desflurane Group in which anaesthesia was maintained using Isoflurane, sevoflurane or desflurane, respectively. After sedation with midazolam (0.1 mg/kg IV) in the preoperative holding area, patients were transferred to the operating theatre. Pre oxygenation with 100% oxygen for 3 minutes was applied to all patients during which non-invasive monitoring (Non invasive blood pressure, ECG, and pulse oximetry (SpO₂) were applied. Anaesthesia was induced intravenously with thiopental (6mg/kg), fentanyl (2ug/kg), and atracurium (0.5mg/kg) to facilitate endotracheal intubation. Then, all patients were mechanically ventilated using fresh gas flow (FGF) at 2L/min with a mixture of air-oxygen (50% oxygen+ 50% air) in addition to the anaesthetic gas according to the study group using the anaesthesia work station (Zeus®, Dräger, Luebeck, Germany). Tidal volume was set at 8mL/kg and with respiratory frequency adjusted according to patient’s age in order to maintain an end-tidal CO₂ (Et CO₂) between 30-35 mmHg. Et CO₂, inspired & expired tidal volumes, airway pressure and oxygen-agent concentrations were continuously monitored.

Arterial catheter was inserted into the radial artery and connected to a transducer (Hemomed, Siemens, Germany) to monitor the invasive blood pressure throughout the anaesthesia. Muscle relaxation was monitored throughout the anaesthesia by peripheral nerve stimulator applied to the adductor pollicis using train-of- four mode.

A local anaesthetic of 1% lidocaine with epinephrine 1:200,000 was infiltrated at the sites of fixation of Mayfield head holder into the patient’s head and on the scalp over the surgical field.

Maintenance of anaesthesia was obtained using intravenous infusion of fentanyl at rate of 0.5ug/kg/h, atracurium at rate of 0.5mg/kg/hour and administration of the inhalational anaesthesia (either isoflurane, sevoflurane or desflurane, according to the study group) which was started at 1 MAC and then subsequently adjusted to maintain mean arterial blood pressure (MAP) and heart rate (HR) within a range of 20% of pre-anaesthesia level. Persistent relative hypertension or tachycardia episodes lasting more than 1min (defined as MAP or HR rises more than 20% of baseline value) not responding to the maximal allowed anaesthetic concentration were treated with labetalol 25mg intravenous bolus.

Episodes of hypotension (MAP <20% of the baseline value) not responding to intra-operative fluid replacement could be managed with vasopressor (ephephrine 5mg IV). Bradycardia (HR <20% of baseline value) and lasting more than 1 min were treated with atropine sulphate 0.02mg/kg IV. These episodes of haemodynamic changes were recorded and notified to the neurosurgeon.
Arterial blood samples for gas analysis were collected every hour during the anaesthesia as well as postoperatively for the first two hours to monitor oxygen and carbon dioxide tensions as well as blood sodium and potassium levels.

Intraoperative normothermia was actively maintained with a forced air warming system (Bair Hugger) and continuous monitoring of body temperature using axillary temperature probe.

At dural opening, the attending neurosurgeon who was blinded to the study group assessed the degree of brain swelling which was evaluated and scored as: 1 = No swelling; 2 = Moderate brain swelling; and 3 = Pronounced brain swelling [10].

During securing the bone flap, the atracurium and fentanyl infusion were stopped. At the end of surgery after skin closure and detachment of Mayfield head holder from the patient, the inhalational anaesthetics were discontinued. The residual muscle relaxation was antagonized with neostigmine 0.04 mg/kg IV and atropine 0.02 mg/kg IV. Patients were extubated when respiratory function was adequate (as indicated by adequate respiratory rate according to the age; tidal volume >4 ml/kg; SpO2 continued maintained above 95% on FiO2 <60%), haemodynamics were stable and upper airway reflexes were fully recovered. Patients then were transferred into the Post Anaesthesia Care Unit (PACU) where they received paracetamol (Perfalgan) 10 mg/kg IV and supplemental oxygen at a flow rate of 6-8 L/min (fraction of inspired oxygen 40%) was administered throughout the period of observation.

The primary endpoint of this study was the post-anaesthesia recovery which was assessed by measuring the Emergence time which was defined as the time elapsing from end of anaesthesia until the patients were able to open their eyes (spontaneously or on verbal prompting); Tracheal extubation time that was defined as the time elapsing from discontinuation of inhalational anaesthesia to extubation after adequate spontaneous ventilation (tidal volume 4 ml/kg) was established; and lastly the interval time required to reach an Aldrete score ≥ 9. The Aldrete Score is a score (ranged 0-10) used by doctors and nurses in the operating theatres and PACU to evaluate the post anaesthetic recovery status of the patients and their abilities to be discharged [11] (Table 1).

The secondary endpoints included intraoperative degree of brain swelling, intraoperative HR and MAP as well as postoperative vomiting and shivering.

Table (1): Aldrete score.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I- Activity</td>
<td>• Voluntary movement of all limbs to command</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>• Voluntary movement of 2 extremities to command</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>• Unable to move</td>
<td>0</td>
</tr>
<tr>
<td>II- Respiration</td>
<td>• Breaths deeply and cough freely</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>• Dyspnea, hypoventilation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>• Apneic</td>
<td>0</td>
</tr>
<tr>
<td>III- Circulation</td>
<td>• BP ±20 mm Hg of pre-anaesthesia level</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>• BP &gt;20-50 mm Hg of pre-anaesthesia level</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>• BP &gt;50 mm Hg of pre-anaesthesia level</td>
<td>0</td>
</tr>
<tr>
<td>IV- Consciousness</td>
<td>• Fully awake</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>• Arousable on calling</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>• Unresponsive</td>
<td>0</td>
</tr>
<tr>
<td>V- Color</td>
<td>• Pink</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>• Pale, blotchy</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>• Cyanotic</td>
<td>0</td>
</tr>
</tbody>
</table>

Statistical analysis:

Data were analyzed using the Statistical Package for Social Sciences for windows (SPSS 13.0.1; SPSS Inc; Chicago, Ill, USA).

A group size of 20 patients was chosen according to a power analysis in which a need of 20 patients was calculated for the assumed probabilities of $\alpha < 0.05$ and $\beta < 0.10$. Quantitative variables were expressed as means (SD) or median (range) according to normality of distribution. Categorical variables were expressed as number (%).

One way ANOVA was used to compare continuous variables between groups. Categorical variables were compared using the chi-square test or Fisher’s exact test as appropriate. $p < 0.05$ was considered to indicate statistical significance.

Results

This prospective, comparative, randomized clinical study was conducted in Children’s Cancer Hospital of Egypt (CCHE) between December 2012 and May 2013. Data were normally distributed. Baseline demographic data including age, sex, weight, surgery and anaesthesia times were similar in both groups (Table 2).

The mean emergence time, extubation time and the interval required to reach Aldrete score ≥ 9 were significantly shorter in desflurane and sevoflurane.
groups than those in the isoflurane group, however, there was no significant difference between sevoflurane and desflurane groups (Fig. 1).

The neurosurgeon who was blinded to the group of study reported moderate brain swelling (grade 2) in 2 patients (10%) in the isoflurane group, 3 (15%) in Sevoflurane group and 3 (15%) in the desflurane group \( (p=0.86) \). These cases responded to further dose of 0.5g/kg mannitol and 0.1mg/kg furosemide and the surgical field had been explored well. There was no brain swelling in the rest of patients in any group.

Bradycardia was documented in 2 patients (10%) in Sevoflurane Group meanwhile no bradycardia was detected in the other groups \( (p=0.22) \); tachycardia was present in 2 patients (10%) in isoflurane group versus 3 patients (15%) in Desflurane group \( (p=0.13) \) (Fig. 2).

The three groups showed significant decrease in MAP after induction of anaesthesia than the pre induction level and this decrease maintained throughout the study and returned non-significant at the end of anaesthesia. However, no statistically significant differences between groups had been detected (Fig. 3).

Three patients (15%) in Isoflurane group, two (10%) in Sevoflurane group and one (5%) in Desflurane group developed postoperative vomiting on recovery that required rescue medication ondansetron 0.1 mg/kg \( (p=0.57) \).

Postoperative shivering was recorded in 3 patients (15%) in the isoflurane group, 4 patients (20%) in the sevoflurane group and in 2 patients (10%) in desflurane group \( (p=0.68) \) and relieved by nalbuphine 0.1 mg/kg I.V. No neurological complications had been observed in either group.

Table (2): Patients’ characteristics and demographic data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Isoflurane group</th>
<th>Sevoflurane group</th>
<th>Desflurane group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>10.2±2.4</td>
<td>9.9±2.43</td>
<td>10.72±2.43</td>
</tr>
<tr>
<td>Male/female (ratio)</td>
<td>9/11</td>
<td>11/9</td>
<td>8/12</td>
</tr>
<tr>
<td>Weight (in Kg)</td>
<td>31.84±7.49</td>
<td>33.12±6.84</td>
<td>30.1±9.84</td>
</tr>
<tr>
<td>Surgery time (in min)</td>
<td>178.6±10.08</td>
<td>169±15.15</td>
<td>173±11.15</td>
</tr>
<tr>
<td>Anesthesia time (in min)</td>
<td>227.6±9.73</td>
<td>208.8±17.3</td>
<td>216.8±14.44</td>
</tr>
</tbody>
</table>

Data are represented as Mean±SD (except male/female represented as ratio).

Discussion

The most distinctive finding in this prospective, randomized study is the faster recovery in patients receiving desflurane or sevoflurane anaesthesia than in those receiving isoflurane. The times to emergence, extubation as well as the interval required to reach an Aldrete score to 9 were all about
more than 50% faster in the desflurane group than in the isoflurane group with no statistically significant differences between desflurane and sevoflurane. Such a difference in minutes might not be of crucial importance in the general population of surgical patients, but in neurosurgical patients it might help in early assessment and detection of a new neurological deficit that necessitate an early intervention to prevent a future permanent disability and hence to improve in outcome of the surgery.

The inhalational anaesthetic desflurane has low blood-gas and tissue-blood partition coefficients leading to a more rapid wash in and wash-out when compared with other volatile anaesthetics [12,13]. According to these pharmacokinetic properties of desflurane, recovery times were assumed to be faster, and our results approved this hypothesis. Emergence from desflurane anaesthesia was faster than that from sevoflurane, but this was statistically non significant. However, it was faster in emergence than that of isoflurane. Kaye et al., [8] reported that neurosurgical patients when anaesthetized with desflurane for craniotomy for supratentorial tumours opened their eyes and obeyed commands 50% faster than those who received isoflurane. Although, this study was conducted on adult patients but it was near to our results which was on paediatric patients. Wolf and co-workers [14] studied 20 infants undergoing general anaesthesia for pyloromyotomy with either desflurane or isoflurane and reached to similar results; they observed that approximately twice the speed of recovery was elicited with desflurane anaesthesia when compared with isoflurane. Similar results have been mentioned in a randomized study [15] on 45 elderly patients underwent major orthopaedic surgery and received desflurane, isoflurane or propofol to maintain anaesthesia and the results showed that the immediate recovery times were significantly shorter with desflurane than with isoflurane or propofol.

Beaussier and coworkers in 1998 found that after prolonged anaesthesia up to three hours, desflurane allowed the patients to recover in half the time taken by isoflurane [16]. Thus, in all studies the more rapid desflurane wash-out and slower elimination rate of isoflurane from the brain tissue was accompanied by a clinically measurable accelerated speed of recovery.

Gupta and co-workers, in a systematic review, reported statistically significant differences between sevoflurane and isoflurane regarding the “time to opening eyes,” and “time to obeying commands”. The weighted mean difference in recovery between anaesthetics was small and in favour of sevoflurane. They also found that drowsiness was significantly more frequent with isoflurane than sevoflurane in the postoperative period [17].

White and co-workers compared desflurane versus sevoflurane for maintenance of outpatient anaesthesia and their results revealed that the time to eye opening, following commands, and orientation were significantly shorter in the desflurane 18. However, the mean anaesthesia time was 39 ± 14 and 45 ± 23min in sevoflurane and desflurane groups respectively which is relatively shorter than that found in our study.

This rapid emergence may provide an additional benefit in reducing the patient morbidity by lessening the likelihood of complications associated with somnolence like hypoxemia and intermittent airway obstruction [19].

Our study showed that there was no significant difference in brain swelling after dural opening. Two patients from the isoflurane group, three from the sevoflurane and another three from desflurane group (p=0.38) showed moderate brain swelling of grade 2 that was improved after additional dose of mannitol 0.5g/kg and furosemide 0.1mg/kg. Turner et al., [20] found in his study that there is a low association between the degree of brain swelling and lumbar cerebrospinal fluid pressure so long the intracranial pressure maintained within the normal range for pressure values. So we did not measure ICP or cerebrospinal fluid pressure during the study but instead, we relied on clinical evaluation by a blinded neurosurgeon to assess the influence of the three anesthetics on brain relaxation during surgical operation in the usual clinical scenario.

In our study the HR and MAP did not differ significantly between both groups throughout the study and we could not notice any significant difference between both groups regarding hemodynamic instability and this comes in agreement with previously published studies [21].

No remarkable tachycardia or hypertension could be detected during the administration of the inhalational anaesthetics in the current study. These findings are most likely related to the relative stability of the end-tidal anesthetic concentration throughout the surgery and the concomitant continuous infusion of both fentanyl [22] and muscle relaxant throughout the anesthesia.

In the present study, we made induction of anesthesia with intravenous drugs in all groups due to the associated high incidence of airway-
related complications in form of coughing, laryngospasm and desaturation (SpO₂ <90%) with the induction of anesthesia with desflurane or isoflurane in paediatric patients [23]. Secondly, we believe that the use of the same method of induction in all patients should have removed any bias.

As cost is a constraint upon every aspect of health care tool, the added costs associated with the use of desflurane will determine the fate of desflurane. Furthermore, because desflurane is only one fifth as potent as isoflurane [28], a large liquid volume must be vaporized to produce an equal level of anaesthesia. However, this increased cost of desflurane anesthesia can be minimized to some extent through the use of low flows or even closed circuit techniques. Currently, it is difficult to assess the impact of costs described above versus the potential benefits. So it is recommended to assess the cost weighted against the rapid recovery and short duration of stay in the recovery room against the increased costs associated with the use of desflurane.

In summary, desflurane and sevoflurane can be used safely in maintenance of anesthesia in paediatric cases undergoing craniotomies for brain tumor resection within the normal range of ICP. Furthermore, emergence times are shorter with desflurane or sevoflurane than with isoflurane. They have similar intraoperative and postoperative incidence of adverse effects compared with those who received isoflurane. Thus, desflurane can be considered to be a suitable alternative to isoflurane for paediatric neurosurgical anaesthesia.

References


