Comparison of propofol/remifentanil and sevoflurane/remifentanil for maintenance of anaesthesia for elective intracranial surgery

J. R. Sneyd1*, C. J. H. Andrews2 and T. Tsubokawa2

1Peninsula Medical School, C310 Portland Square, University of Plymouth, Drake Circus, Plymouth PL4 8AA, UK. 2Department of Anaesthesia, Pain Management and Critical Care Medicine, Derriford Hospital, Plymouth PL6 8DH, UK

*Corresponding author. E-mail: robert.sneyd@pms.ac.uk

Background. Propofol and sevoflurane are suitable agents for maintenance of anaesthesia during neurosurgical procedures. We have prospectively compared these agents in combination with the short-acting opioid, remifentanil.

Methods. Fifty unpremedicated patients undergoing elective craniotomy received remifentanil 1 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) followed by an infusion commencing at 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) reducing to 0.25 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) after craniotomy. Anaesthesia was induced with propofol, and maintained with either a target-controlled infusion of propofol, minimum target 2 \( \mu \text{g} \cdot \text{ml}^{-1} \) or sevoflurane, initial concentration 2%ET. Episodes of mean arterial pressure (MAP) more than 100 mm Hg or less than 60 mm Hg for more than 1 min were defined as hypertensive or hypotensive events, respectively. A surgical assessment of operating conditions and times to spontaneous respiration, extubation, obey commands and eye opening were recorded. Drug acquisition costs were calculated.

Results. Twenty-four and twenty-six patients were assigned to propofol (Group P) and sevoflurane anaesthesia (Group S), respectively. The number of hypertensive events was comparable, whilst more hypotensive events were observed in Group S than in Group P (\( P = 0.053 \), chi-squared test). As rescue therapy, more labetolol [45 (33) vs 76 (58) mg, \( P = 0.073 \)] and ephedrine [4.80 (2.21) vs 9.78 (5.59) mg, \( P = 0.020 \)] were used in Group S. Between group differences in recovery times were small and clinically unimportant. The combined hourly acquisition costs of hypnotic, analgesic, and vasoactive drugs appeared to be lower in patients maintained with sevoflurane than with propofol.

Conclusion. Propofol/remifentanil and sevoflurane/remifentanil both provided satisfactory anaesthesia for intracranial surgery.

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random number function of Microsoft Excel Version 7.0 and concealed in individual opaque envelopes until shortly before the start of anaesthesia. We carefully considered the use of a double-blind design for this study but rejected it as placebo syringes of Intralipid with the necessary ‘tag’ to operate the target controlled infusion system are not available. The easy detection of sevoflurane by smell would also have made blinding difficult. In practice, the choice of anaesthetic agents was easily concealed from the operating surgeons and the nurses in the recovery area. The arterial pressures were recorded by direct measurement from the radial artery and stored at 1-min intervals on the Datex™ AS/3 clinical monitoring system (Datex-Ohmeda, Helsinki, Finland). Episodes of ‘hypertension’ and ‘hypotension’ were determined by inspection of the stored electronic record on the monitor. We therefore considered that an adequate degree of blinding and a satisfactory means of objectively identifying haemodynamic instability were established.

Anaesthesia
After establishment of standard monitoring and arterial and venous cannulation, all patients received a bolus of remifentanil 1 μg kg⁻¹ followed by an infusion of 0.5 μg kg⁻¹ min⁻¹ reducing to 0.25 μg kg⁻¹ min⁻¹ after craniotomy. Patients were questioned about the onset of drug effect and when they began to feel light-headed or sleepy anaesthesia was induced with propofol. In patients randomized to receive propofol anaesthesia (Group P) anaesthesia was induced with a target-controlled infusion of propofol (Grassey 3500 infusion pump, Diprifusor® software, initial plasma concentration target, 1 μg ml⁻¹), which was increased progressively until satisfactory anaesthesia was achieved. Anaesthesia was maintained by the target-controlled infusion of propofol with a minimum target concentration of 2 μg ml⁻¹.

In the patients randomized to receive sevoflurane (Group S) anaesthesia was induced with a bolus injection of propofol, 0.5 mg kg⁻¹ with supplementary doses of 10 mg every 10 s until loss of consciousness. Anaesthesia was then maintained with sevoflurane, initial end tidal concentration 2%, minimum concentration 1%. Tracheal intubation was facilitated with atracurium given as a bolus and followed by an infusion until dural closure. All patients were artificially ventilated to normocapnia using a circle breathing system and a fresh gas flow of 0.5 litre min⁻¹ oxygen and 1.0 litre min⁻¹ air during anaesthesia. At the end of surgery, residual neuromuscular blockade was then antagonized with 2.5 mg neostigmine and 0.5 mg glycopyrrolate. Remifentanil infusion was stopped after skin closure whilst sevoflurane and propofol were continued until head bandaging was completed. Mannitol 1 g kg⁻¹ was given between induction of anaesthesia and craniotomy unless clinically contraindicated. Additional mannitol was given if clinically indicated. The surgeons, blind to anesthetic technique, evaluated the state of brain as ‘tight’, ‘adequate’, or ‘soft’. The dose of mannitol was recorded.

Hypertensive episodes, defined as mean arterial pressure (MAP) more than 100 mm Hg for more than 1 min, were treated with remifentanil 1 μg kg⁻¹ and the infusion rate increased by 0.125 μg kg⁻¹ min⁻¹. If the response was present 2 min later this was repeated. If the haemodynamic response persisted for a further 2 min the propofol target concentration or sevoflurane concentration were increased. Labetalol or hydralazine was given, if clinically appropriate. Hypotensive episodes, defined as MAP less than 60 mm Hg for more than 1 min, which did not respond to a fluid bolus, were treated by reducing the propofol target or sevoflurane concentration. A vasopressor was administered if necessary. Hypertensive and hypotensive episodes were recorded.

Arterial pressure was recorded on the ward using an automated sphygmomanometer and before induction of anaesthesia and continuously thereafter using an arterial cannula.

Times to adequate respiration, extubation, eye opening and obeying commands were recorded. Analgesia in the recovery area was provided by bolus injections of morphine 2 mg, given at 5-min intervals according to standard hospital protocol. Nausea and vomiting and the time of discharge from recovery were recorded by the nursing staff.

Statistical analysis
Data were recorded on specially produced paper record forms and then transferred to a database (Microsoft Access, Version 7.0). Statistical analysis was performed using Statview (version 5.0), and Excel Version 7 running on a personal computer. The size of the study was determined by a priori power calculation using data from a previous study, which suggested that enrolment of 20 patients per group would determine a difference in time to tracheal extubation of 4 min with a power of 80% and \( P<0.05 \). The comparison of continuous variables was performed by Mann–WhitneyU-test. Categorical valuables were analysed using the chi-squared test. \( P<0.05 \) was considered statistically significant. Drug acquisition costs were calculated post-hoc.

Results
Fifty patients were recruited into the study. Twenty-four were assigned to propofol anaesthesia (Group P) and 26 to sevoflurane anaesthesia (Group S). One patient in

| Table 1 Patient characteristics. Data are presented as median and range |
|-----------------|-----------------|-----------------|-----------------|
|                  | Group P (n=24)  | Group S (n=26)  | \( P \)-value  |
| Age (yr)         | 56 (34–73)      | 58 (31–78)      | 0.491          |
| Male/Female      | 11/13           | 10/16           | 0.598          |
| Height (cm)      | 168 (155–195)   | 168 (160–182)   | 0.995          |
| Weight (kg)      | 69.5 (50–152)   | 68 (53–92)      | 0.567          |
| BMI (kg m⁻²)     | 25.3 (20.0–40.0) | 23.4 (19.9–32.7)| 0.200          |
| Hypertension (%) | 40.0            | 30.4            | 0.518          |
| Operation (tumour/aneurysm/microvascular) | 18/6/0 | 17/7/2 | 0.363 |
| Location (supratentorial/posterior fossa) | 22/2 | 21/5 | 0.267 |
Group S required overnight ventilation for surgical reasons. We included intra-operative but not recovery data from this patient. The patient characteristics of the two groups were well matched (Table 1).

Propofol infusion rate was 5.45 (SD 1.0) mg kg\(^{-1}\) h\(^{-1}\) in Group P. Group S received 1.06 (0.6) mg kg\(^{-1}\) h\(^{-1}\) of propofol for induction and an end-tidal concentration of sevoflurane of 1.13 (0.19)\%\%. Remifentanil infusion rate was similar in the two groups (Table 2). Anaesthesia time was longer in Group P, but the difference was not statistically significant. The brain condition evaluated by the surgeon and mannitol dosage was comparable in the two groups (Table 2).

Arterial pressure before, during, and after surgery was similar in the two groups (Fig. 1). Hypertensive episodes were seen in seven and eight patients in Groups P and S, respectively. These patients experienced a median of 1 (range 1–7) and 1 (range 1–4) hypertensive episodes, respectively. There was no significant difference (\(P=0.374\), chi-squared test) (Fig. 2A). To control hypertension, labetolol was given to 14 patients [mean total doses 45 (SD 33) mg] in Group P and 19 [76 (58) mg, \(P=0.073\)] in Group S. Hydralazine was given to two and five patients in Groups P and S, respectively. These agents were mainly used to control arterial pressure during emergence from anaesthesia. Hypotensive episodes were seen in 15 and 23 patients in Groups P and S, respectively. These patients experienced a median of 2 (range 1–4) and 3 (range 1–7) hypotensive episodes, respectively (Fig. 2B). There was no significant difference between groups (\(P=0.053\), chi-squared test). Ephedrine was given to 63 and 88\% of patients in Groups P and S, respectively. The total dose of ephedrine was 4.8 (2.2) mg in Group P and 9.8 (5.6) mg in Group S (\(P=0.02\)).

Time to spontaneous respiration, was significantly shorter in Group P than in Group S (\(P=0.02\)) (Table 3). Time to spontaneous respiration was 7.0 (2.0–31.0) and 10.0 (1.0–24.0) min in Groups P and S, respectively [median (range), Mann–Whitney \(U\)-test]. Time to eye-opening was 7.5 (3.0–30.0) and 12.0 (3.0–33.0) min in Groups P and S, respectively. Time to extubation was 8.5 (3.0–40.0) and 11.0 (3.0–33.0) min in Groups P and S, respectively. Time to obeying commands was 10.5 (3.0–40.0) and 13.0 (4.0–48.0) min in Groups P and S, respectively. These differences were not statistically significant (Fig. 3). We performed a regression analysis to explore the relationship between recovery time and hypotensive episodes, these were not significantly correlated (\(P=0.5280\) by Spearman Rank correlation).

### Table 2 Surgical and anaesthetic data. Data are presented as median and range.

<table>
<thead>
<tr>
<th></th>
<th>Group P (n=24)</th>
<th>Group S (n=26)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain condition</td>
<td>4/10/9</td>
<td>10/6/6</td>
<td>0.208</td>
</tr>
<tr>
<td>(soft/adequate/tight)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mannitol (g)</td>
<td>80 (0–100)</td>
<td>80 (35–100)</td>
<td>0.687</td>
</tr>
<tr>
<td>Anaesthetic time (min)</td>
<td>200 (107–310)</td>
<td>164 (90–350)</td>
<td>0.082</td>
</tr>
<tr>
<td>Remifentanil</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Average dose</td>
<td>0.33 (0.17–0.63)</td>
<td>0.32 (0.22–0.62)</td>
<td>0.727</td>
</tr>
<tr>
<td>((\mu)g kg(^{-1}) min(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose (mg)</td>
<td>4.21 (2.20–19.00)</td>
<td>3.94 (1.83–10.5)</td>
<td>0.321</td>
</tr>
</tbody>
</table>

### Fig 1
Systolic arterial pressure measured at each perioperative point for propofol (Group P) or sevoflurane (Group S). Thin lines, range; boxes, 25–75th centiles; thick horizontal lines, median values. There were no significant differences between the two groups (Mann–Whitney \(U\)-test).
The requirement for morphine, dosages of morphine, incidences of nausea and vomiting and recovery room stay of the two groups were similar.

Propofol, sevoflurane, and remifentanil are expensive agents with associated equipment costs. Although this was not a health economic study, we conducted a post-hoc calculation of drug acquisition costs (Table 4). Propofol acquisition cost was £3.83 per 20 ml ampoule for Group S and £9.58 per 50 ml syringe for Group P. Remifentanil cost £5.98 per mg. The cost of sevoflurane was calculated by the method of Rosenberg \(^{16}\) with an acquisition cost of £137.30 per 250 ml and total flow 1.5 litre min\(^{-1}\). The total hypnotic and analgesic drug acquisition costs of Group P were significantly higher than in Group S, median cost £58.63 vs £39.03. Group S required more vasoactive medications (labetolol, £2.94 per 100 mg; hydralazine, £1.62 per 20 mg; and ephedrine £1 per 30 mg). Even after allowing for this, the combined hourly costs of hypnotic, analgesic, and vasoactive medications were higher in Group P than in Group S, median values £19.31 and £15.52 h\(^{-1}\), respectively, \(P=0.016\).

**Discussion**

We found that both sevoflurane and propofol, in combination with remifentanil, are satisfactory agents for maintenance of anaesthesia in neurosurgical patients. Surgical conditions in the two groups were similar, possibly because of the frequent use of mannitol and differences in recovery times were not clinically significant.

We observed an increased number of hypotensive episodes in Group S, which also received a larger total dose of ephedrine as rescue therapy. One possible explanation is that the sevoflurane group was simply more deeply

![](Fig2.png)

Fig 2 Frequencies of (A) hypertensive and (B) hypotensive episodes with propofol (Group P) or sevoflurane (Group S). There was no significant difference between the groups for hypertension (\(P=0.374\), \(\chi^2\)-squared test) or hypotension (\(P=0.053\)).

![](Fig3.png)

Fig 3 Times to spontaneous respiration, eye-opening, extubation, and obeying commands in patients whose anaesthesia was maintained with propofol (Group P) or sevoflurane (Group S).
anaesthetized. Although doses of individual inhalation agents can readily be compared by describing them as fractions of the MAC, it is not possible to make a direct comparison with an i.v. agent. The CP50 of propofol for depression of bispectral index is 5.45 μg ml⁻¹, whereas the IP50 of sevoflurane for depression of bispectral index was 1.14%. In our study, the average target propofol concentration was 3.67 (0.46) μg ml⁻¹, and average end-tidal sevoflurane concentration was 1.13 (0.19)%.

Posterior fossa surgery poses different problems to supratentorial surgery and haemodynamic instability may be more common in these patients. We explored our data and found no excess of haemodynamic instability in the patients undergoing posterior fossa surgery who were anaesthetized with sevoflurane.

We found small and clinically unimportant differences in recovery between Group P and Group S. There are many reports to compare recovery characteristics between propofol and sevoflurane anaesthesia. These reports concluded sevoflurane anaesthesia gave faster, similar, or slower recovery than propofol anaesthesia. Yli-Hankala and colleagues reported no difference of recovery time between propofol/fentanyl/nitrogen oxide and sevoflurane/fentanyl/nitrogen oxide anaesthesia under bispectral index control. We explored our data to evaluate whether hypotensive episodes, which might be a result of a deeper anaesthesia were associated with delayed recovery and found no correlation. The experiences of the two groups of patients whilst in the recovery area were similar, perhaps because this phase is dominated by clinical and nursing factors rather than the small differences between short-acting hypnotic agents.

Many studies have reported that sevoflurane caused postoperative nausea and vomiting (PONV) more frequently than propofol anaesthesia. PONV occurs in about 30% of patients receiving sevoflurane. In the present study, PONV occurred in only 15% of patients with no difference between propofol and sevoflurane.

Although there was a small difference in drug acquisition costs between the two groups, these differences in costs are very small in relation to the total cost of a neurosurgical procedure and should be interpreted cautiously as they ignore associated costs of equipment and disposables.

We selected realistic doses of propofol and sevoflurane, which recognize the strong synergism between these agents and remifentanil. We have evaluated previously remifentanil alone and as a sequential infusion following alfentanil in neuroanaesthesia practice. Common clinical doses of remifentanil give substantial sparing of sevoflurane and propofol when these agents are used for induction and maintenance of anaesthesia. In our previous study, the propofol infusion rate (100 μg kg⁻¹ min⁻¹) was probably too high.

We have carefully evaluated sevoflurane and propofol as maintenance agents with remifentanil for elective intracranial surgery. Both agents were satisfactory.

### Acknowledgements

Abbott Laboratories Limited, the manufacturers of sevoflurane, provided the drug free for patients participating in this study. Professor Sneyd has received lecture fees and research support from Astra-Zeneca, the manufacturers of propofol, and other research support from Abbott Laboratories Limited. Financial support: supported by a grant from Abbott Laboratories Limited, the manufacturers of sevoflurane.

### References


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**Table 4** Costs of anaesthetic drugs. Data are presented as median and range. Total hypnotic and analgesic costs means the sum of propofol, sevoflurane, and remifentanil costs. Sevoflurane costs were calculated based on the background flow of 1.5 litre min⁻¹. Vasoactive drugs means the cost of labetolol, hydralazine, and ephedrine. Antibiotics and muscle relaxants are excluded from these calculations.

<table>
<thead>
<tr>
<th></th>
<th>Group P (n=24)</th>
<th>Group S (n=26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypnotic and analgesic costs (£ h⁻¹)</td>
<td>58.63 (37.10–177.08)</td>
<td>39.03 (20.87–88.54)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vasoactive drugs (£)</td>
<td>18.30 (11.42–38.22)</td>
<td>14.01 (9.04–22.16)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total hypnotic, analgesic and vasoactive drug costs (£ h⁻¹)</td>
<td>76.93 (37.10–215.30)</td>
<td>53.04 (20.87–177.08)</td>
<td>0.001</td>
</tr>
</tbody>
</table>


Olofsen E, Dahan A. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. *Anesthesiology* 1999; 90: 1345–53


