Clinical comparison of ‘single agent’ anaesthesia with sevoflurane versus target controlled infusion of propofol

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The introduction of total intravenous anaesthesia (TIVA) and the use of volatile induction/maintenance anaesthesia (VIMA) has led to the discovery of ‘single agent’ anaesthesia, eliminating the transition phase from induction to maintenance. We compared quality, patient acceptability and cost of TIVA using target control infusion (TCI) with propofol and VIMA with sevoflurane. Forty patients undergoing spinal surgery of 1–3 h were assigned to one of two groups. Group I received propofol–air–oxygen for induction followed by propofol–air–oxygen for maintenance. Group II received 8% sevoflurane–oxygen for induction and sevoflurane–oxygen–nitrous oxide for maintenance. Propofol had a significantly faster mean (SD) induction time (67 (20) s) than sevoflurane (97 (38) s) but was associated with double the incidence of involuntary movements. Although not significant, twice the number of interventions by the anaesthetist were required to maintain an adequate level of anaesthesia in the sevoflurane group. Emergence times, characteristics, postoperative nausea, vomiting and pain were unaffected by the anaesthetic technique. However, a more predictable emergence time was found following sevoflurane. Cardiovascular stability was good and comparable in both groups. The majority of patients found either technique acceptable and would choose the same anaesthetic again. Induction and maintenance was substantially cheaper with sevoflurane (£28.06) compared with propofol (£41.43).

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Intravenous (i.v.) agents are used commonly for induction of anaesthesia followed by inhalational agents for maintenance. A problem with this technique is the transition phase from induction to maintenance. The rapid redistribution of the i.v. agent could lead to lightening of the anaesthetic before an adequate depth is attained with the inhalational agent. This has promoted the rediscovery of ‘single agent’ anaesthesia, which avoids problems associated with a transition phase.1

Propofol is a short acting general anaesthetic agent used widely for total i.v. anaesthesia (TIVA) because of its favourable induction properties and rapid clearance. Its antiemetic properties are well acknowledged, but it is associated with pain on injection and cardiovascular and respiratory depression.2

The introduction of the target control infusion (TCI) system has enabled relatively accurate dosing by continuous infusion, based on the pharmacokinetic profile of propofol in an average patient.3 This convenient system makes TIVA with propofol an attractive option with the benefit of minimal pollution to the operating room environment.

Sevoflurane, a relatively new short acting inhalational agent has a blood:gas partition coefficient of 0.69 permitting greater control and ability to change anaesthetic depth. It is also non-irritant and pleasant smelling making it much more acceptable for induction of anaesthesia compared with other inhalational agents such as isoflurane, desflurane and enfurane.4 The availability of this non-pungent and rapid acting anaesthetic makes it an attractive option for volatile induction/maintenance anaesthesia (VIMA).

There have been several studies comparing propofol with sevoflurane for induction, maintenance, and recovery. However, TIVA (i.e. no nitrous oxide) using TCI with propofol vs VIMA with sevoflurane has not yet been compared, especially in the clinical setting of major surgery in conjunction with opioids such as morphine.

The aim of this study was to compare ‘single agent’ anaesthesia with sevoflurane with target controlled infusion of propofol. The primary objectives were to evaluate the speed of induction and recovery, and the haemodynamic differences between the two techniques.
Patients and methods

The approval of the hospital’s Research Ethics Committee was obtained. In order to detect a difference in the mean change in heart rate (HR) of 5 beats min\(^{-1}\) between the groups (\(\alpha=0.05, \beta=0.2\)), 15 patients were required in each group. After written informed consent, a total of 40 patients (ASA I–II) of both sexes, age range 25–80 yr, were enrolled onto the study. All patients were scheduled to undergo elective spinal surgery of 1–3-h duration. Patients with a history of cardiovascular, respiratory, hepatic, renal or neurological disease and those who were pregnant or had received a general anaesthetic within the previous 2 weeks, were excluded from the study.

Patients were assigned randomly to one of two groups (numbers out of an envelope). Group I (n=20) received propofol for induction followed by propofol–air–oxygen for maintenance. Group II (n=20) received sevoflurane–nitrous oxide–oxygen for both induction and maintenance of anaesthesia. All anaesthetics were administered by consultants. Preoperative medication of temazepam 10 mg was administered on the ward, at the discretion of the anaesthetist, before induction of anaesthesia. A large vein on the patient’s forearm was cannulated.

In the anaesthetic room, all patients received an initial loading dose of up to 10 mg morphine i.v. and 100% oxygen via a face mask for 2–3 min prior to induction. Thereafter alfentanil at a maximum of 4 mg h\(^{-1}\) as an i.v. bolus to supplement anaesthesia was administered intraoperatively.

Sevoflurane was administered with a Blease vaporizer (Blease Medical Equipment Ltd, Chesham, UK), and propofol with a Graseby 3500 infusion pump (Sims Graseby Ltd, Watford, UK). In Group I, the patient’s age and weight was entered into the TCI unit enabling so target propofol concentrations to be set and the infusion started. Target induction concentrations were 4–6 \(\mu\)g ml\(^{-1}\) and anaesthesia was maintained with propofol (4–8 \(\mu\)g ml\(^{-1}\), along with air and oxygen. Group II patients were induced using a face mask with sevoflurane in a circle system starting at 8% with an initial fresh gas flow of 6 litre min\(^{-1}\) decreasing to a total gas flow of 3 litre min\(^{-1}\) during maintenance (67% nitrous oxide in oxygen) with up to 3.5% sevoflurane. After paralysis with a bolus of atracurium 0.4–0.6 mg kg\(^{-1}\) i.v., and tracheal intubation, the lungs were ventilated to normocapnia throughout the procedure. The end-tidal sevoflurane concentration and the propofol maintenance target infusion were adjusted as necessary to maintain an adequate depth of anaesthesia as judged by clinical signs and haemodynamic responses to surgical stimuli. Once this was achieved, delivery of either anaesthetic was kept constant. Residual neuromuscular block was pharmacologically antagonized at the end of surgery with neostigmine 2.5 mg and glycopyrrolate 0.5 mg when necessary. A local infiltration of 0.5% bupivacaine with adrenaline was applied to the incision site at the start of the procedure.

At the end of surgery, sevoflurane and nitrous oxide, or propofol were discontinued abruptly and the lungs were ventilated with 100% oxygen at a flow rate of at least 6 litre min\(^{-1}\). After discontinuation of the anaesthetic, patients were asked repeatedly in a normal tone of voice to open their eyes until an appropriate response was obtained. The trachea was extubated when a regular spontaneous breathing pattern had been re-established and when patients were able to open their eyes on command.

In the anaesthetic room, ECG, pulse oximetry and non-invasive blood pressure monitoring were applied to all patients. Mean arterial pressure (MAP) and HR were recorded 2–3 min prior to induction of anaesthesia (baseline), and then again at predetermined times; pre- and post-intubation, pre- and post-incision, pre-extubation and after admission to recovery room. In addition, highest and lowest MAP and HR, the administration of any vasoactive drugs and intraoperative anaesthetic interventions were noted for each group. Time intervals were recorded including induction (start of anaesthetic to loss of eye lash reflex), intubation (start of anaesthetic to intubation), spontaneous eye opening (end of anaesthetic to eye opening), extubation (end of anaesthetic to extubation), and orientation (end of anaesthetic to until the patient stated his or her name, birth date and ward number). All adverse effects associated with induction such as involuntary movements, coughing, breath holding, restlessness, laryngospasm and pain on injection were noted.

On admission to the recovery room, patients were evaluated for orientation, assessed for nausea and vomiting on a scale 0–3 (none, mild, moderate, severe) and their level of pain noted using scores 0–5 (none, mild, moderate, severe, very severe, worst possible). When orientated fully, patients were asked to assess the acceptability of induction anaesthesia. They were asked about the smell of the volatile gas and also about pain of injection of the i.v. drug. Induction of anaesthesia was rated as ‘pleasant’, ‘neither pleasant nor unpleasant’ or ‘unpleasant’. Finally, patients were asked if they would be happy to receive the same anaesthetic again. The above observations were made by the same investigator who questioned all the patients.

Total costs of anaesthesia per operation were calculated based on the current UK list price of liquid sevoflurane (250 ml), 1% propofol prefilled syringe (50 ml), and disposables (cannulae, manometer lines and syringes) (Appendix).

Data were analysed using the Microsoft Excel (version 6.0) and Origin (version 4.1) statistical package. Parametric data were analysed using paired and non-paired t-tests with Bonferroni corrections for multiple comparisons. Discrete data were analysed using chi-square. All values are represented as mean (SD) with statistical significance determined at \(P<0.05\).
Table 1 Patient characteristics, duration of anaesthesia and drug requirements. Values are mean (sd) [95% CI]. *P<0.05 between groups

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>128</td>
<td>119</td>
</tr>
<tr>
<td>Age</td>
<td>52 (35–77)</td>
<td>[50.4–53.6]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 (13)</td>
<td>[76.4–79.6]</td>
</tr>
<tr>
<td>Surgical duration (min)</td>
<td>106 (39)</td>
<td>[103.3–108.7]</td>
</tr>
<tr>
<td>Anaesthetic duration (min)</td>
<td>137 (38)</td>
<td>[134.3–139.7]</td>
</tr>
<tr>
<td>Morphine (mg)</td>
<td>9.7 (1.1)</td>
<td>[9.1–10.3]</td>
</tr>
<tr>
<td>Alfen tamil (mg)</td>
<td>2.2 (1.3)</td>
<td>[1.7–2.7]</td>
</tr>
<tr>
<td>Temazepam</td>
<td>8/20</td>
<td>6/20</td>
</tr>
</tbody>
</table>

Table 2 Side effects during induction of anaesthesia. No differences between the groups were detected

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involuntary movements</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Coughing</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Breath holding</td>
<td>1 (5%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pain on injection</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Results

There was no significant difference between the two groups with respect to patient characteristics, mean duration of surgery or anaesthetic time. Similar amounts of morphine were administered to both groups, but patients in the propofol group received significantly more alfentanil intraoperatively (mean 2.2 (sd 1.3) mg vs 0.3 (0.8) mg, P<0.0001) (Table 1).

Time to loss of consciousness after induction with propofol was significantly shorter than sevoflurane (66.7 (20.1) s (95% CI (64.7–68.7)) vs 96.9 (38) s (94.2–99.6)) (P=0.004), although there was no marked difference in intubation times (5.2 (1.4) min (4.7–5.7) vs 6 (1.3) min (5.5–6.5)).

Following administration of propofol and sevoflurane, involuntary movements were relatively common, occurring in 30 and 15% of patients, respectively. Two patients (10%) receiving propofol complained of pain on injection. Inhaled induction with sevoflurane was not associated with laryngospasm. However, two patients (10%) experienced slight respiratory irritation eliciting coughing. Five patients (25%) in the sevoflurane group exhibited breath holding (not sufficient to cause a SaO2 of <97% as measured by the pulse oximeter) and two (10%) demonstrated restlessness. Side effects and complications occurring during induction of anaesthesia are summarized in Table 2. Ephedrine 9 mg was administered on one occasion in each group.

HR and MAP recorded immediately before induction of anaesthesia (baseline) were similar in both groups, along with the highest and lowest HR and MAP recorded perioperatively (Table 3).

Table 3 Haemodynamic variables. Values are mean (sd) [95% CI]. No differences between the groups were detected

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats min−1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>84 (13)</td>
<td>[82.4–85.6]</td>
</tr>
<tr>
<td>Highest (intraop.)</td>
<td>89 (16)</td>
<td>[87.2–90.8]</td>
</tr>
<tr>
<td>Lowest (intraop.)</td>
<td>63 (11)</td>
<td>[61.5–64.5]</td>
</tr>
</tbody>
</table>

Induction was associated with a significant decrease in HR and MAP (between 10 and 23%) (Fig. 1). Tracheal intubation produced a transient increase towards baseline values in both HR and MAP and, in the period prior to skin incision, there was a significant decrease in MAP, in both groups. HR also decreased, but significantly more so in the sevoflurane group both pre- and post-incision. During the
Table 4  Emergence times, emergence complications, and recovery events. Values are mean (SD) [95% CI]. No statistical significance between groups. †Nausea and vomiting scores (0–3); ‡pain scores (0–5)

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to eye opening (min)</td>
<td>11.5 (5.3) [10.5–12.5]</td>
<td>11.1 (3.3) [10.3–11.9]</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>13.2 (6.5) [12.1–14.3]</td>
<td>12.3 (3.0) [11.5–13.1]</td>
</tr>
<tr>
<td>Time to stating name (min)</td>
<td>15.5 (6.1) [14.5–16.5]</td>
<td>15.5 (3.1) [14.7–16.3]</td>
</tr>
<tr>
<td>Emergence side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>6 (30%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Breath holding</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Shivering</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Recovery events</td>
<td>Nausea and vomiting†</td>
<td>Pain‡</td>
</tr>
<tr>
<td></td>
<td>0 1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
</tbody>
</table>

Propofol 19 1 0 0 7 11 2 0 0 0
Sevoflurane 17 2 1 0 8 8 4 0 0

The remainder of the procedure, sevoflurane produced similar changes in HR and MAP values when compared with propofol (Fig. 1).

The time from discontinuation of the anaesthetic to spontaneous eye opening, extubation and to stating name and date of birth correctly were similar in both groups and there were no differences in subsequent recovery events (Table 4). The number of interventions made by the anaesthetist to adjust anaesthetic depth were 2.8 (0.9) (2.4–3.2) vs 6 (3.1) (5.2–6.8) for propofol and sevoflurane, respectively.

Two cases (10%) of mild and one case (5%) of moderate nausea were reported in the sevoflurane group, with only a single incidence reported in the propofol group. Pain scores were low with no difference between the two groups (Table 4).

Based on the amount of drug used, the cost of induction and maintenance of anaesthesia with sevoflurane was significantly cheaper than propofol (£28.06 (8.56) (£25.73–30.38) compared with £41.43 (18.85) (£39.53–43.33), respectively (P=0.001)). Additional costs (disposables) were only associated with the propofol group (£2.78).

The majority of patients (55% of the propofol group and 50% of the sevoflurane group) rated induction as ‘pleasant’. The others were indifferent (neither pleasant nor unpleasant), barring two cases (10%) where induction was described as unpleasant, one from each group. Finally, a large proportion of patients in both groups stated a willingness (95% in each group) for receiving the same anaesthetic in the future.

Discussion

A number of studies have compared single-agent anaesthesia with i.v. propofol (not TCI) and sevoflurane.5–7 This study demonstrates that for patients undergoing spinal surgery of up to 3 h duration, single-agent based anaesthesia with TCI propofol or sevoflurane is satisfactory when used together with opiates as in the normal clinical setting.

Previous investigations where either the maximum delivery of sevoflurane was 5% (limited by the vaporizer) or sevoflurane was administered in stepwise increments of 0.5% have reported induction times of between 109 and 186 s.5,6,8,9 The ability to administer up to 8% sevoflurane has allowed for a more rapid induction of 84 s.7 The induction time of the sevoflurane group reported in this study confirms this finding, having a similar time (97 s) despite using morphine at induction.

Induction with sevoflurane was associated with breath holding in 25% of the patients. However, this was not severe enough to cause hypoxaemia, as monitored by pulse oximetry, and a smooth induction was still attained, although breath holding may have prolonged induction. Two patients experienced coughing despite i.v. morphine pre-administration, and there were two cases of restlessness reported, which were not apparent in the propofol group.

Induction with both sevoflurane and propofol was well tolerated. Despite sevofluranes low blood:gas partition coefficient, inhalation induction was slower than i.v.-induction with propofol (67 s), although this is still clinically acceptable. Using the TCI system, with a target induction propofol concentration of 4–6 µg ml⁻¹, i.v.-induction time with propofol was not dissimilar to that previously reported (55 s).10

The increased incidence of involuntary movements noted in the propofol group was not significant and a trial of 134 patients in each group would be required to reach 5% statistical significance at 80% power. The use of propofol has been associated with an excitatory phenomenon.11 Although 10% of patients induced with propofol reported pain on injection, overall induction with propofol appeared marginally smoother compared with sevoflurane. These two side effects may however discourage the choice of propofol induction, despite the relative rapidity.

Previous investigations have shown a greater decrease in MAP after induction of anaesthesia with propofol than with sevoflurane.7,9 The effect of a bolus injection of propofol in producing a 15–30% decrease in MAP is well documented.12 We also found a similar decrease of MAP with propofol (using TCI) and sevoflurane just before intubation, with no difference demonstrated between the groups. This can be explained largely by the fact that both agents decrease systemic vascular resistance through endothelium-mediated vasodilation,13 which is further augmented when administered with an opioid.12

HR did not differ significantly between the groups during induction, but it did decrease significantly in both groups compared with baseline. Sevoflurane has been associated with slower HR,5 and in our study TCI propofol showed a similar effect. TCI propofol has been shown to have similar haemodynamics as non-target controlled infusion.10 The haemodynamic stability of propofol and sevoflurane during maintenance has also been demonstrated previously.6,9 In our study the haemodynamics differed between the two groups before and after incision, whereas the HR in the
sevoflurane group was considerably slower (10%) than that in the propofol group. This could be because sevoflurane has a greater effect on the resting HR. The remaining period of maintenance demonstrated generally good haemodynamic stability in both groups.

After admission to the recovery room, MAP and HR returned towards baseline levels for both groups. However, HR in the propofol group remained significantly decreased, possibly as a result of the larger administration of opioids in this group.

This study found that the number of interventions by the anaesthetist to adjust the anaesthetic depth of propofol was less than half that of sevoflurane (2.8 compared with 6 respectively). While similar amounts of morphine were used in each group, anaesthetists chose to administer more than seven times more alfentanil in the propofol group, which may have helped provide a more cardio-stable anaesthetic. Equally, patients receiving sevoflurane with nitrous oxide would require less opioid intraoperatively.

Freedman and colleagues\(^5\) and Lien and colleagues\(^8\) demonstrated eye opening times of between 8 and 10 min, extubation times of between 8.6 and 11 min, and times to stating names of between 11 and 15 min for both propofol and sevoflurane groups. The recovery times demonstrated in this study support these findings, despite the use of intraoperative morphine. In contrast, other investigators have found significant differences in recovery times, with sevoflurane recovery times almost half what has been reported in these studies.\(^7\)\(^9\)\(^15\) It is possible that the addition of morphine may have masked any potential difference in recovery between sevoflurane and propofol. However, with higher intraoperative opiate administration than in previous studies,\(^5\)\(^8\) it followed that postoperative pain scores were generally very low, with the majority of patients experiencing none to mild pain at most upon regaining consciousness. A pain free recovery and faster emergence is ideal, as earlier recovery but with pain, would mean a longer stay in recovery until the patients’ pain was controlled.

The recovery times after propofol administration seen here are similar to previous reports.\(^15\) Similarly, larger standard deviations were apparent, supporting the clinical impression that a more accurate prediction of emergence times was possible following sevoflurane than following propofol.

There is strong evidence to suggest that propofol has intrinsic antiemetic properties that may persist into the postoperative period even when it is used solely as an induction agent.\(^16\) In this study, despite the use of intraoperative opiates in both groups (with more opioid in the propofol group) nitrous oxide in the sevoflurane group and 1–3 h anaesthesia, there was a very low incidence of postoperative nausea and vomiting (PONV), with no difference between the groups. This may be because spinal surgery is associated with a low incidence of PONV.

The affordability of an anaesthetic technique may influence its usage. This study found induction and maintenance substantially cheaper with sevoflurane (£28.06) compared with propofol (£41.43) as previously reported.\(^17\)

The use of 66% nitrous oxide does not potentiate the anaesthetic agent, its effects are additive and thereby reduce the MAC of sevoflurane by up to 60%, thus decreasing the amount required to maintain anaesthesia. It is possible that nitrous oxide has a similar effect on propofol, being attributed to decrease EC\(_{50}\) (the effective concentration at which 50% of patients do not respond to a painful stimuli) by approximately 30%.\(^18\) Thus, adding nitrous oxide could reduce the maintenance dose of propofol, therefore decreasing cost. Maintenance with sevoflurane was based on a fresh gas flow of 3 litre min\(^{-1}\). A much lower fresh gas flow would reduce the amount of sevoflurane used.

On approaching patients preoperatively, inhalational induction was not as popular as the use of i.v.-induction agents, but this could be attributed to previous experiences. However, postoperatively, the majority described either technique as a ‘pleasant’ experience, and would choose the same anaesthetic again. In this study there were only two cases (one from each group) where induction was reported as ‘unpleasant’. Previous evaluations have reported the odour of sevoflurane to be pleasant and popular with almost all patients.\(^5\)\(^10\) In contrast, it has also been reported that significantly more patients (although a minority) who have received sevoflurane have been noted to prefer a different technique in future compared with propofol.\(^7\)

Acknowledgements

We gratefully acknowledge the assistance of the neuroanaesthetists of Leeds General Infirmary regarding data collection and comments regarding the study design, and Ms V. Allgar, Medical Statistics, St James’s Hospital for help with statistical analysis.

References

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Appendix

The total volume of propofol was as stated on the TCI unit at the conclusion of anaesthetic, and the total liquid volume of sevoflurane was calculated from the volume of vapour produced per ml of liquid (182.7 ml), fresh gas flow, per cent concentration and duration of anaesthetic.

The list prices (BNF 38; September 1999) used for this study were as follows.

Propofol: £10.67 for a 50 ml propofol prefilled syringe 1%
Sevoflurane: £123.00 for a 250 ml bottle.

The cost of propofol was calculated using the formula
Cost (£) = (List price of propofol prefilled syringe 1% / 50) × total dose (ml)

The cost of sevoflurane was calculated using the formula
Cost (£) = (fresh gas flow (ml) ×% sevoflurane / ml vapour per ml liquid anaesthetic (182.7)) × time (min) × (price of bottle / 250)