

Comparison of the effects of sevoflurane and propofol on cooling and rewarming during deliberate mild hypothermia for neurosurgery[†]

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Background. Because the time available for cooling and rewarming during deliberate mild hypothermia is limited, studies of the rate of the cooling and rewarming are useful. The decrease in core hypothermia caused by heat redistribution depends on the anaesthetic agent used. We therefore investigated possible differences between sevoflurane and propofol on the decrease and recovery of core temperature during deliberate mild hypothermia for neurosurgery.

Methods. After institutional approval and informed consent, 26 patients were assigned randomly to maintenance of anaesthesia with propofol or sevoflurane. Patients in the propofol group ($n=13$) received propofol induction followed by a continuous infusion of propofol 3–5 mg kg⁻¹ h⁻¹. Patients in the sevoflurane group ($n=13$) received propofol induction followed by sevoflurane 1–2%. Nitrous oxide and fentanyl were also used for anaesthetic maintenance. After induction of anaesthesia, patients were cooled and tympanic membrane temperature was maintained at 34.5°C. After surgery, patients were actively rewarmed.

Results. There was no difference in the rate of decrease and recovery of core temperature between the groups. There was also no difference in skin surface temperature gradient (forearm to fingertip), heart rate and mean arterial blood pressure between the groups.

Conclusions. Sevoflurane-based anaesthesia did not affect cooling and rewarming for deliberate mild hypothermia compared with propofol-based anaesthesia.

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Deliberate mild hypothermia may provide cerebral protection against ischaemia during neurosurgery for cerebral aneurysm or resection of arteriovenous malformation. Although the effect of mild hypothermia on outcome is unknown,^{1–3} research into techniques that allow safe management of deliberate mild intraoperative hypothermia seems warranted. This is particularly true because the time available to provide the cooling and rewarming is limited. Cooling to the target temperature should be completed by the time that intracranial manipulation starts, and rewarming should be completed as soon as possible. Early emergence is required to allow neurological assessment.

Thus, the ideal anaesthetic agent for neurosurgery under deliberate mild hypothermia should allow rapid control of body temperature and early emergence from anaesthesia.

Sevoflurane and propofol both fulfil the requirements of a safe neuroanaesthetic agent, although their cerebral effects are still matters of debate.^{4–7} Recently, Ikeda and colleagues^{8,9} reported that the decrease in core temperature caused by redistribution of heat during anaesthetic induction depends on the type of anaesthetic. These authors found that

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core temperature decreased more after induction of anaesthesia with propofol than when anaesthesia was induced with sevoflurane. Although both sevoflurane and propofol are used for anaesthesia during deliberate mild hypothermia, there are no data comparing the effects of these anaesthetics on temperature during mild hypothermia.

In previous studies^{10 11} we found a cooling rate of 0.8–0.9°C h⁻¹ (SD ≈0.2) during propofol-based anaesthesia. We considered that if the cooling rate was slowed by 0.3–0.4°C h⁻¹ when sevoflurane was used, this would be important clinically. An extra hour for cooling by 2°C would result. In the present work we investigated whether sevoflurane-based anaesthesia reduces the rate of decrease of core temperature when inducing hypothermia for neurosurgery, compared with propofol-based anaesthesia.

Materials and methods

After institutional approval and informed consent, 26 patients scheduled to undergo elective neurosurgical procedures were enrolled. The study size was based on previous study data.^{10 11} For a mean cooling rate of 0.9°C h⁻¹ (SD 0.2) and a clinically important difference of 0.3–0.4°C h⁻¹, a significance value of 0.05 and a power of 0.95, eight to 13 patients would be needed in each of the two groups. We excluded patients with symptomatic ischaemic heart disease, hepatic or renal disease or coagulopathy, and patients who received vasodilators. When active cooling started, we excluded patients with tympanic temperature greater than 37.0°C or less than 36.0°C.

All patients were premedicated with roxatidine (H2 blocker) 75 mg orally 2 h before surgery. Thereafter, we randomly allocated 26 patients to the propofol or the sevoflurane group using computer-generated random numbers. Anaesthesia was induced with propofol 1.5–2.5 mg kg⁻¹, fentanyl 1–2 µg kg⁻¹ and vecuronium 0.15 mg kg⁻¹. The trachea was intubated, and the lungs were mechanically ventilated. Anaesthesia was maintained with nitrous oxide 50% in oxygen and propofol 3–5 mg kg⁻¹ h⁻¹ i.v. in the propofol group and sevoflurane 1–2% inspired in the sevoflurane group, supplemented with doses of fentanyl and vecuronium. Additional vecuronium was administered as required to maintain one or two twitches in response to supramaximal electrical stimulation of the ulnar nerve at the wrist. Routine monitoring included electrocardiogram, a radial arterial catheter, non-invasive blood pressure cuff, pulse oximetry and capnogram. The expired concentration of sevoflurane was monitored using a multi-gas monitor (Capnomac Ultima; Datex, Helsinki, Finland) in the sevoflurane group. A tympanic membrane probe was inserted in the external auditory meatus on the side opposite surgery for temperature monitoring using sterile copper–constantin thermocouple sensors (Mon-a-Therm thermocouples; Mallinkrodt Medical, St Louis, MO,

USA). The probe was taped in place, the aural canal occluded with cotton, and the external ear covered with a gauze pad. Skin temperature probes equipped with adhesive thermocouples (Mon-a-Therm) were placed on the surfaces of the forearm thenar eminence and the index fingertip. These probes were connected to Mon-a-Therm thermometers (Mallinkrodt Medical).

A water blanket (Blanketrol II Hyper-Hypothermia; Cincinnati Sub-Zero Products, Cincinnati, OH, USA) was placed under each patient. A polyurethane-formed pad covered with a cotton sheet (S-K pad; Asahi Medical Co., Osaka, Japan) protected the patient from direct contact with the water blanket. A convective device blanket (Warm Touch; Mallinckrodt Medical) was applied directly to the ventral body surface. After the induction of anaesthesia, active cooling was started. The temperature of the water blanket was set at 5°C and room temperature air was circulated by the convective device. Active cooling was stopped when tympanic membrane temperature was 35°C, and the body temperature was then allowed to decrease. The temperature setting on both the water blanket and the convective device was then adjusted to maintain a target of 34.5°C (passive cooling). After surgery, such as aneurysm clipping or tumour removal, active rewarming was started with the water blanket set at 41°C and the convective device at its highest setting (43°C). Active rewarming was stopped when tympanic membrane temperature was 35.5°C, and the body temperature was then allowed to increase. The temperature setting on both the water blanket and the convective device was then adjusted to maintain a target temperature of 36°C (passive rewarming). The arm used to monitor the skin temperature was excluded from the forced-air cover.

Temperatures were recorded at 15-min intervals, starting immediately after induction of anaesthesia, when active cooling was started (initial values). Forearm to fingertip skin-surface temperature gradients were calculated. As in the previous study, we considered a temperature gradient of <0°C to indicate vasodilation.¹² PaO₂, PaCO₂, pH, base excess, haemoglobin, sodium, potassium and glucose were determined in arterial blood samples using a commercial blood gas analyser (Bayer 860; Bayer Diagnostic Manufacturing, Bury St Edmunds, UK). Blood samples were collected at the start of active cooling and near the target temperature and analysed immediately.

Blood was sampled for plasma propofol concentration at the following times: (i) 15 min after the start of active cooling; (ii) at the target temperature; (iii) 15 min after starting active rewarming; and (iv) just before the completion of active rewarming. Each 5.0 ml of blood was drawn into a heparinized syringe, collected into a glass tube and centrifuged for 10 min at 3000 r.p.m.; 2.0 ml of each plasma sample was stored immediately at –20°C for propofol analysis. Plasma concentrations of propofol were determined by high-performance liquid chromatography. At the

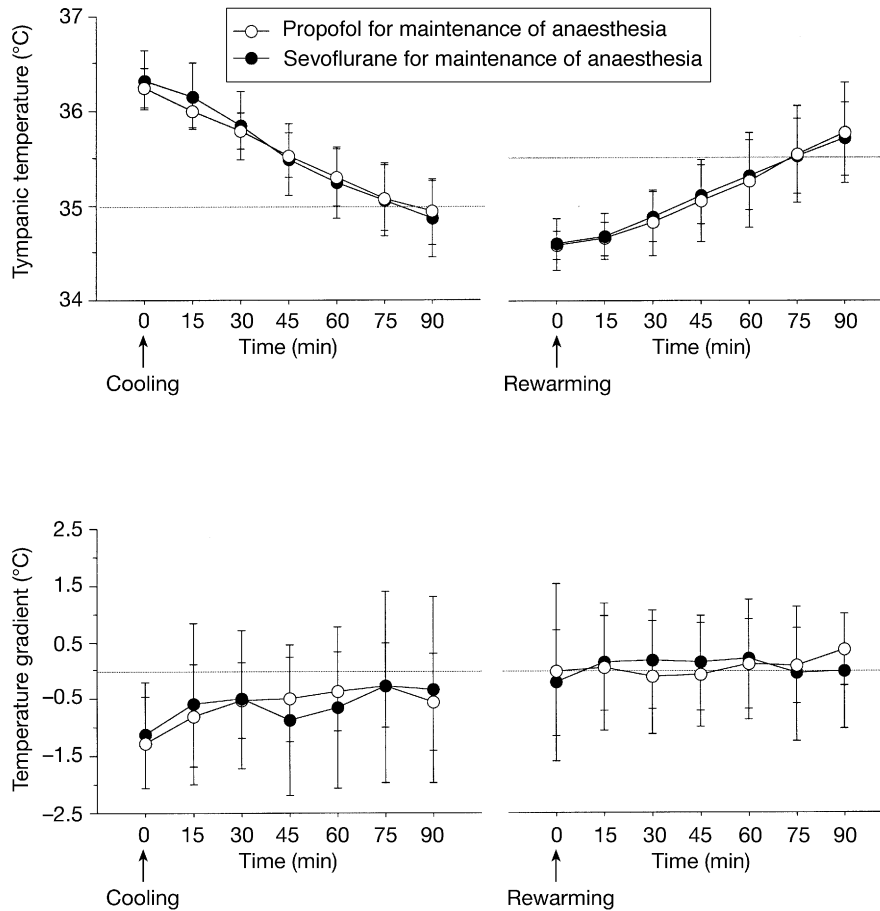


Fig 1 Changes in tympanic membrane temperature and forearm to fingertip skin-surface temperature gradients. Data are mean (SD). Cooling=start of active cooling; Rewarming=start of active rewarming.

same times, the expired concentration of sevoflurane was recorded in the sevoflurane group.

Data handling and statistical analysis

We calculated active cooling and rewarming rates of core temperature (tympanic membrane temperature) because these values changed in a linear fashion; active cooling and rewarming rates ($^{\circ}\text{C h}^{-1}$) were defined as the slopes of the simple regression lines calculated from core temperature values vs time from the beginning of cooling to the time when the temperature reached 35°C , and from the beginning of rewarming to the time when the temperature reached 35.5°C , respectively.^{10 11}

To reduce the number of tests, tympanic temperature changes during the cooling and rewarming periods were compared using a simple slope (cooling rate or rewarming rate), and changes in temperature gradient, heart rate, and mean arterial pressure were compared at defined temperature points (at the start of cooling, 35.5°C ; for the cooling period, 35.0°C ; at the start of rewarming, 35.0°C ; for the rewarming period, 35.5°C). The groups were compared using the paired *t*-test or analysis of variance (ANOVA) for repeated measures followed by Fisher's protected least

Table 1 Comparison of patient characteristics and intraoperative variables. Data are mean (SD)

| | Maintenance of anaesthesia | |
|--|----------------------------|--------------------|
| | Propofol (n=11) | Sevoflurane (n=10) |
| Age (yr) | 51 (32–70) | 52 (35–68) |
| Gender (F, M) | 6, 5 | 6, 4 |
| Weight (kg) | 58 (11) | 56 (9) |
| Height (cm) | 158 (8) | 159 (7) |
| Anaesthesia time (min) | 404 (132) | 369 (106) |
| Surgery time (min) | 311 (134) | 281 (89) |
| Infusion + transfusion (ml) | 3143 (725) | 2707 (818) |
| Urinary output + blood loss (ml) | 1652 (392) | 1405 (497) |
| Total dose of fentanyl (μg) | 405 (156) | 420 (98) |
| Total dose of vecuronium (mg) | 28 (5) | 26 (7) |
| Disease | | |
| Cerebral aneurysm | 4 | 4 |
| Brain tumour | 4 | 2 |
| OCVD | 2 | 2 |
| Others | 1 | 2 |

OCVD=occlusive cerebrovascular disease.

significant difference for continuous variables, and the χ^2 test for nominal data. The data are expressed as mean (SD); differences were considered significant when $P < 0.05$.

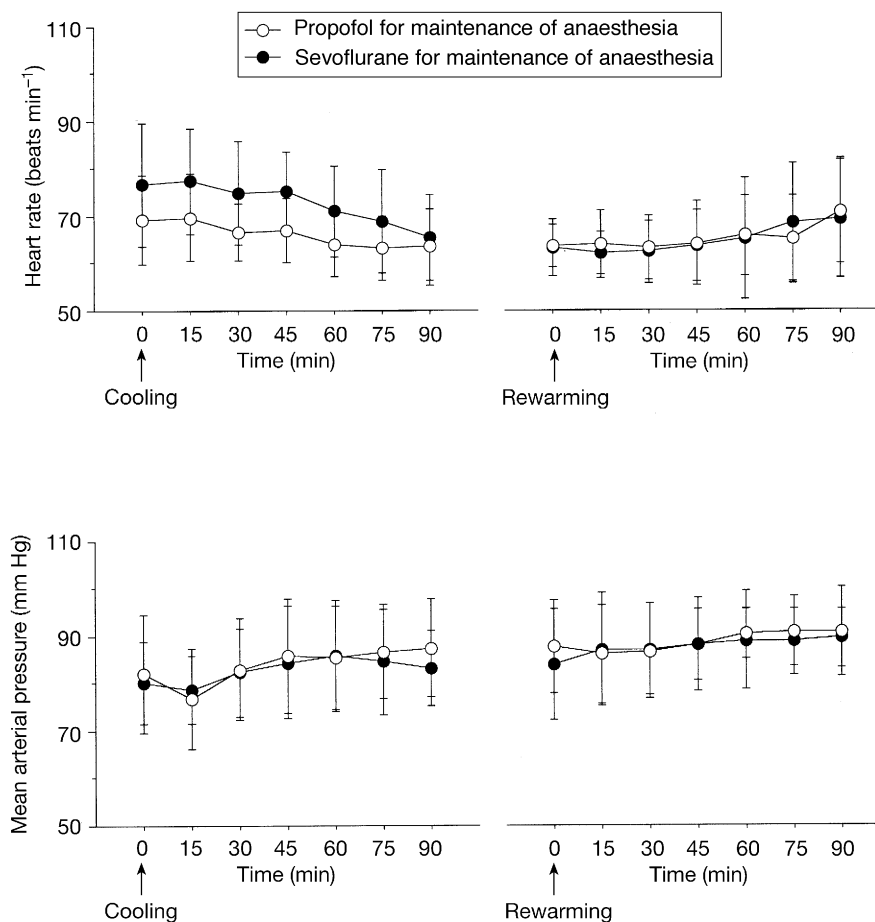


Fig 2 Heart rate and mean arterial blood pressure. Data are mean (SD). Cooling=start of active cooling; Rewarming=start of active rewarming.

Results

Two and three patients in the propofol and sevoflurane groups respectively were excluded because they had a tympanic temperature greater than 37.0°C at the start of active cooling.

Patient characteristics, anaesthesia and surgery time, balance, and total doses of fentanyl and vecuronium are shown in Table 1. Changes in tympanic membrane temperature are shown in Figure 1 and the cooling and rewarming data are given in Table 2. There was no difference in the active cooling and rewarming rates between the groups. Tympanic temperature at extubation and the lowest tympanic temperature were similar between the groups. The times taken for cooling and rewarming to each defined temperature were very similar for the two groups. There was also no difference in the time from the end of surgery to extubation between the two groups.

Figures 1 and 2 illustrate the changes in skin surface temperature gradient (forearm to fingertip), heart rate and mean arterial blood pressure. There was no difference in these values between the groups at each time.

Table 2 Temperature data given as mean (SD)

| | Maintenance of anaesthesia | |
|--------------------------------------|----------------------------|--------------------|
| | Propofol (n=11) | Sevoflurane (n=10) |
| Cooling rate (°C h ⁻¹) | -0.95 (0.36) | -1.04 (0.32) |
| Rewarming rate (°C h ⁻¹) | 0.84 (0.49) | 0.82 (0.35) |
| Lowest temperature (°C) | 34.5 (0.2) | 34.6 (0.2) |
| Temperature at extubation (°C) | 36.1 (0.6) | 36.0 (0.5) |
| Cooling to 35°C (min) | 83 (24) | 81 (27) |
| Cooling to lowest temperature (min) | 145 (48) | 132 (26) |
| Rewarming to 35.5°C (min) | 77 (27) | 75 (26) |
| Rewarming to extubation (min) | 126 (47) | 128 (49) |
| Surgery end to extubation (min) | 37 (18) | 29 (19) |

Figure 3 shows the changes in plasma propofol and expired sevoflurane concentrations. Plasma concentration of propofol was maintained around 3 µg ml⁻¹ and expired sevoflurane concentration was nearly 1.5%.

There were no significant differences between the groups in pH, PaCO₂, PaO₂, base excess, haemoglobin, sodium, potassium and glucose before or during mild hypothermia (data not shown).

Postoperative complications, such as myocardial ischaemia and rebound hyperthermia, were not observed.

Discussion

We found that cooling during sevoflurane-based anaesthesia was not different compared with a propofol-based method after the same method of induction with i.v. propofol.

During general anaesthesia, decreases in core temperature occur in three characteristic phases.^{13–15} An initial decrease in core temperature results from core-to-peripheral redistribution of body heat when anaesthesia inhibits tonic vasoconstriction. Subsequently, when heat loss exceeds metabolic heat production, core temperature decreases in a slow, linear fashion. Finally, a stable core temperature results when thermoregulatory vasoconstriction develops, which reduces cutaneous heat loss and keeps metabolic heat in the core. We considered the possibility that the redistribution of body heat and cutaneous heat loss and inhibition of the thermoregulatory vasoconstriction could be affected by the anaesthetic agent chosen, so affecting the cooling rate.

The temperature gradient indicates the state of the arteriovenous shunt vessels,¹⁶ and was used as an index of thermoregulatory vasoconstriction in this study. There were similar changes during cooling, so a sevoflurane-based anaesthetic has similar effects on arteriovenous shunt flow and thermoregulatory vasomotor tone during deliberate mild hypothermia, compared with propofol. We found no differences in heart rate and mean arterial pressure between the two groups, and conclude that the two anaesthetic regimens have similar effects on the cardiovascular system, although we did not measure variables such as cardiac output.

Previous investigators tested the hypothesis that thermoregulatory vasoconstriction reduces the transfer of applied heat and restricts peripheral-to-core flow of heat, thereby delaying and reducing the increase in core temperature.^{17–18} However, the increase in core temperature is not affected by vasodilation by anaesthetics.¹⁸ As in this previous report, we found no difference in the rate of rewarming for the two anaesthetics. Vasodilation by anaesthetics would not affect arteriovenous shunt flow and thermoregulatory vasomotor tone very much once hypothermia is achieved. During cooling, there were no differences in temperature gradient, heart rate and mean arterial pressure between the two groups, so the two anaesthetic regimens have similar thermoregulatory vasomotor effects.

Factors that can affect cooling and rewarming include patient size and shape, the presence or absence of vasoconstriction, and the method of temperature management.¹⁹ Intraoperative thresholds for thermoregulatory vasoconstriction are affected by the depth of anaesthesia, age and painful stimulation,^{20–24} and these might influence cooling and rewarming. Because the temperature management was standardized and the two groups were

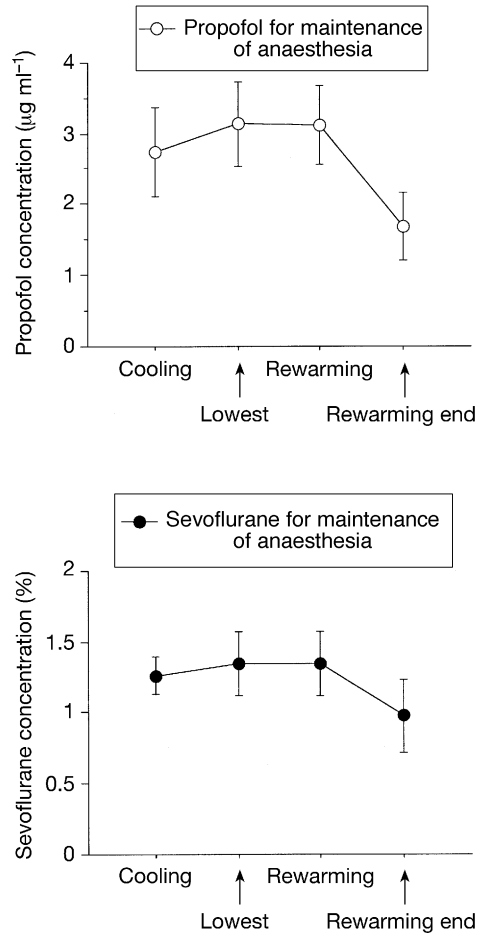


Fig 3 Plasma propofol and end-tidal sevoflurane concentrations. Data are mean (SD). Cooling=start of active cooling; Lowest=minimum tympanic temperature; Rewarming=start of active rewarming; Rewarming end=just before completion of active rewarming.

similar, any confounding effects from these factors would be small. H₂-blockers given for premedication can potentiate hypothermia,²⁵ but all patients were given the same dose. We obtained a plasma concentration of propofol of 3 µg ml⁻¹ or nearly 1.5% of sevoflurane during hypothermia. Several previous reports found similar thermoregulatory vasoconstriction thresholds (roughly 35°C).^{26–28} However, simple comparison of these anaesthetics with respect to thermoregulatory vasoconstriction may be difficult. The supplementary fentanyl or nitrous oxide could have affected thermoregulatory vasoconstriction, although the use of these agents was very similar in the two groups.

Does sevoflurane have cardiovascular effects that differ from those of propofol, such as less bradycardia and a different pattern of body heat transfer? This may occur during normothermia, but bradycardia is often observed during deliberate mild hypothermia.²⁹ Hypothermia seems to mask differences in the cardiovascular effects of the two

anaesthetics. Could induction of anaesthesia by inhalation have affected the results? Ikeda and colleagues^{8,9} reported that different methods and drugs for anaesthesia induction significantly affect temperature changes after induction. They suggested that even a very brief period of vasodilation during anaesthetic induction causes substantial redistribution hypothermia. However, an inhalation induction technique is not suitable for some neurosurgical patients, although this technique might have slowed the cooling rate. It might be worth trying different anaesthetic induction agents, which could cause more redistribution hypothermia, in future studies.

We found that sevoflurane was no worse or better than propofol for temperature management during intraoperative deliberate mild hypothermic therapy. Any difference would be trivial. We have found that amrinone, which is a phosphodiesterase inhibitor and has vasodilatory effects as well as inotropic effect because of its dual mechanism of action,³⁰ significantly accelerates both cooling and rewarming during propofol anaesthesia.^{10,11} Amrinone would have a greater effect on temperature than the choice of anaesthetics.

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