Neuroanesthesia and Intensive Care

Sevoflurane for interventional neuroradiology procedures is associated with more rapid early recovery than propofol

[Le sévoflurane, comparé au propofol, est associé à une récupération plus rapide en neuroradiologie interventionnelle]

Hugo E. Castagnini MD,* Frank van Eijs MD,† Frederick C. Salevsky MD,‡ Michael H. Nathanson FRCA§

Purpose: Sevoflurane and propofol are both suitable for neuroanesthesia but have not previously been compared as maintenance agents for long duration (one to five hours) procedures.

Methods: Using a multicentre international study protocol, 103 patients were randomized to receive either sevoflurane or propofol for maintenance of anesthesia during interventional neuroradiology procedures. After a standardized induction of anesthesia with propofol, 53 patients received sevoflurane 1 to 3% with 60% nitrous oxide (N₂O) in oxygen (O₂), and 50 patients received propofol 4 to 10 mg·kg⁻¹·hr⁻¹ with 60% N₂O in O₂. Maintenance agents were titrated against systemic arterial blood pressure (baseline mean arterial pressure ± 20%). Recovery times, changes in sedation, pain, nausea and vomiting and psychomotor function during recovery and use of rescue medication were recorded.

Results: The group receiving sevoflurane had a more rapid recovery to spontaneous ventilation, extubation, eye opening and orientation compared to the group receiving propofol (3 vs 4 min, $P = 0.01$; 5 vs 6 min, $P = 0.015$; 7 vs 10 min, $P < 0.001$; 13 vs 17 min, $P = 0.028$; respectively). Sedation, pain, nausea and vomiting, and psychomotor function scores were similar in the two groups. Use of opioid boluses and vasopressors were similar.

Conclusion: The use of sevoflurane for maintenance of anesthesia for prolonged neuroradiological procedures is associated with more rapid early recovery than propofol and is associated with similar side effects. Sevoflurane and propofol can both be recommended for these procedures. The clinical benefit of the more rapid recovery with sevoflurane is unknown.

Objectif: Le sévoflurane et le propofol conviennent tous les deux à la neuroanesthésie, mais n'ont jamais été comparés comme agents de maintien lors d'opérations de longue durée, soit de une à cinq heures.

Méthode : Nous avons étudié 103 patients, selon un protocole international multicentrique, qui ont reçu du sévoflurane ou du propofol pour maintenir l'anesthésie en neuroradiologie interventionnelle. À la suite d'une induction normalisée de l'anesthésie avec du propofol, 53 patients ont reçu du sévoflurane de 1 à 3 % avec 60 % de protoxyde d'azote (N₂O) dans de l'oxygène (O₂) et 50 patients ont reçu de 4 à 10 mg·kg⁻¹·h⁻¹ de propofol avec 60 % de N₂O dans de l'O₂. Les agents de maintien ont été titrés en regard de la tension artérielle générale (moyenne de la tension artérielle de base ± 20 %). Le temps nécessaire pour récupérer de l'anesthésie, les modifications de la sédation, la douleur, les nausées et les vomissements et l'état de la fonction psychomotrice pendant la récupération ainsi que l'usage de médication de secours ont été les paramètres notés.

Résultats : On a observé qu'avec le sévoflurane la reprise de la respiration spontanée, l'extubation, l'ouverture des yeux et le retour de l'orientation ont été plus précoces qu'avec le propofol (3 vs 4 min, $P = 0,01$; 5 vs 6 min, $P = 0,015$; 7 vs 10 min, $P < 0,001$; 13 vs 17 min, $P = 0,028$; respectivement). Les scores de sédation, de douleur, de nausées et de vomissements et de fonction psychomotrice ont été similaires chez les patients des deux groupes. L'usage de bolus d'opioïdes et de vasopresseurs a aussi été similaire.

Conclusion : L'usage du sévoflurane, comparé au propofol, pour maintenir l'anesthésie pendant les interventions neuroradiologiques prolongées, est associé à une récupération plus rapide, mais à des effets secondaires similaires. On peut donc recommander les deux

From the Neuroradiology Research Institute FLENI,* Buenos Aires, Argentina; the Saint Elisabeth Hospital,† Tilburg, Netherlands; the Montreal Neurological Hospital,‡ Montreal, Quebec, Canada; and the Queen's Medical Centre,§ Nottingham, UK.

Address correspondence to: Dr. Michael Nathanson, Department of Anaesthesia, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK. Phone: 44 115 970 9195; Fax: 44 115 978 3891; E-mail: mike.nathanson@nottingham.ac.uk
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médicaments pour ce type d'opérations. L'avantage clinique de la récupération précoce reliée au sévoflurane n'est pas connu.

ONE requirement of good neuroanesthetic practice both for traditional (open) surgical procedures and for interventional neurological procedures is the use of techniques and drugs that permit rapid recovery of consciousness and allow early assessment of the neurological status of the patient. It is also essential for the anesthetic agents used not to significantly alter the major parameters of cerebral circulation, such as carbon dioxide reactivity, intracranial pressure, cerebral blood flow and autoregulation. Sevoflurane has been shown to have a pharmacological profile suitable for neuroanesthesia,¹ and has been associated with a short recovery profile, which supports its use for neuroanesthesia.² Propofol is also associated with a rapid recovery and is suitable for use as a neuroanesthetic agent.³

This study is the first to compare recovery from sevoflurane and propofol for maintenance anesthesia during neurological procedures of one to five hours duration, for which the speed and quality of recovery are critical. Previous studies comparing these agents have predominantly examined their use during short procedures, particularly in ambulatory surgery. Few clinical studies have compared different anesthetic techniques for neuroanesthesia.^{4,5}

We conducted a phase IV, single-blind, randomized, multicentre study to compare sevoflurane and propofol when used for maintenance of anesthesia for prolonged interventional neuroradiological procedures. The primary objective of the study was to determine if there is a difference in the early recovery profiles after the use of these agents. We also assessed their acceptability for these procedures.

Methods

Four centres in four countries (Argentina, the United Kingdom, the Netherlands and Canada) participated in the study. Institutional Review Board approval was obtained for each site. After obtaining informed consent, 108 patients were recruited into the study.

Inclusion criteria were: adult patients (aged 18–75 yr), able to give informed consent, ASA physical status I to III, and scheduled to undergo an interventional neuroradiology procedure (including embolization of an intracranial tumour, embolization of an arteriovenous malformation, embolization of an intracranial

aneurysm) with an expected duration between one and five hours. Exclusion criteria included: pre-procedure Glasgow coma scale (GCS) less than 13, concurrent use of sedative medication, preexisting renal or hepatic dysfunction, and risk of pulmonary aspiration.

Patients were randomly assigned (by use of sealed envelopes) to one of two groups: group P = propofol for induction and propofol with 60% nitrous oxide (N₂O) in oxygen (O₂) for maintenance of anesthesia; group S = propofol for induction and sevoflurane with 60% N₂O in O₂ for maintenance of anesthesia. Of the 108 enrolled patients, 103 completed the study. Fifty of these patients were assigned to group P, and 53 patients were assigned to group S.

The following baseline variables were recorded prior to induction of anesthesia: heart rate (HR), mean arterial blood pressure (MAP; by a non-invasive method), peripheral blood oxygen saturation (SaO₂), baseline scores for GCS, Ramsay sedation scale (Appendix), four-point scales for nausea and vomiting (none, mild, moderate, severe – as determined by patient), 10 cm visual analogue scales (VAS) for pain and sedation and digit-symbol substitution test (DSST).

Induction of anesthesia was performed similarly in both groups by *iv* administration of propofol 2–3 mg·kg⁻¹, fentanyl 1 µg·kg⁻¹ or alfentanil 10 µg·kg⁻¹ and atracurium 0.5 mg·kg⁻¹ or vecuronium 0.1 mg·kg⁻¹. In both groups, either a laryngeal mask airway (LMA) or an endotracheal tube (ETT) was inserted (standardized for each centre). A circle system and ventilator were used to provide intermittent positive pressure ventilation. For the first five minutes of anesthesia, mechanical ventilation was performed with a fresh gas flow (FGF) rate of 6 L·min⁻¹ made up of 60% N₂O in O₂, maintaining an end-tidal carbon dioxide concentration (EtCO₂) of 30 to 37.5 mmHg. After five minutes, the FGF rate was reduced to 1 L·min⁻¹ of 60% N₂O in O₂.

For maintenance of anesthesia, patients in group P received a continuous infusion of propofol, initially at a rate of 10 mg·kg⁻¹·hr⁻¹. After the first ten minutes, the infusion rate was titrated between 4 and 10 mg·kg⁻¹·hr⁻¹ to maintain MAP within 20% of the baseline (pre-induction) level. Patients in group S received sevoflurane at an inspired concentration of 1 to 3%, titrated to maintain MAP within 20% of baseline levels.

Additional doses of fentanyl or alfentanil were used to control increases in MAP not responding to a 50% increase in the inspired concentration of sevoflurane (group S) or to a bolus dose of 20 to 50 mg of propofol followed by a 50% increase in the propofol infusion rate (group P). Use of ephedrine to manage hypotension not responding to a reduction in anesthetic agent

was recorded. During the maintenance period, atracurium or vecuronium was used to maintain one single twitch response to a train-of-four stimuli.

The following variables were recorded every two minutes for the first ten minutes of the procedure and every ten minutes thereafter: HR, MAP, SaO₂, EtCO₂. At the end of the procedure (as determined by the attending neuroradiologist), anesthesia was discontinued, residual neuromuscular blockade was reversed and the patient's lungs were ventilated with 100% O₂ at a FGF of 4 to 6 L·min⁻¹.

The following recovery times were recorded: time to return of spontaneous ventilation, time to recovery from anesthesia (purposeful movement or eye opening on verbal command), time to extubation (removal of LMA or ETT), time to orientation (able to recall time, place and person), and time to be judged suitable for discharge from the recovery area. To be considered fit for discharge the patient had to be awake, maintaining their own airway, comfortable, cardiovascularly stable, and the femoral artery puncture site had to be dry. The patient's neurological status had to be stable.

The following variables were recorded on admission to the recovery area and every 15 min thereafter for 60 min: GCS, Ramsay sedation scale, nausea and vomiting, VAS for pain and sedation, and DSST.

Continuous demographic variables were analyzed using an analysis of variance model. Recovery times were analyzed using the Wilcoxon rank-sum test. Hemodynamic and DSST data were analyzed using the general linear model for multiple comparisons. Categorical variables, including Ramsay scale score, GCS, and VAS for nausea and vomiting, were compared using Fisher's exact test. All statistical tests were two-tailed, with a *P* value of < 0.05 considered statistically significant.

Results

Of the 108 patients enrolled in the study, eight patients experienced adverse events in group P and 12 in group S. Three of the adverse events in group P and six in group S were clearly related to the procedure and not to the study drug and in five of these patients the adverse event led to the withdrawal of the patient from the study (Table I). Data from these withdrawn patients were excluded from further analysis. No differences were found in the incidence of adverse events between the two groups.

The types of neuroradiological procedures performed in the study were embolization of cerebral artery aneurysm (51%), embolization of arteriovenous malformation (38%), embolization of intracranial tumour (6%) and others (5%). There were no differ-

TABLE I Withdrawn patients

	Site	Reason for withdrawal
Group P	United Kingdom	Surgical misadventure – probable further bleeding from aneurysm
	Netherlands	Intracerebral hemorrhage
Group S	Argentina	Cerebral vessel occlusion
	Argentina	Intracerebral hemorrhage
	United Kingdom	Coil dislodged leading to thrombosis

TABLE II Demographic characteristics and duration of surgery and anesthesia

	Group S (<i>n</i> = 53)	Group P (<i>n</i> = 50)
Age (yr)	47.2 (14.4)	47.9 (14.8)
Male/female	18/35	25/25
Mean weight (kg)	69.4 (14.8)	72.1 (15.0)
ASA I/II/III	14/36/3	13/32/5
Duration of surgery (min)	142 (52)	129 (47)
Duration of anesthesia (min)	159 (53)	145 (50)

Data expressed as number or mean (± SD), as appropriate.

TABLE III Recovery times (minutes)

	Group S	Group P	<i>P</i> - value
Time to spontaneous ventilation	3 (0–11)	4 (0–16)	0.01
Time to extubation	5 (1–14)	6 (0–20)	0.015
Time to eye-opening	7 (0–14)	10 (3–20)	< 0.001
Time to orientation	13 (5–115)	17 (6–69)	0.028
Time to discharge from recovery room	38 (1–115)	27 (9–95)	0.43

Data expressed as median (range).

ences between the groups in the distribution of these procedures. No differences were found in demographics, duration of anesthesia or duration of procedure between the two groups (Table II).

There were no differences between the groups in requirements for ephedrine (seven in each group), opioid boluses during maintenance (two in group S, one in group P) or antiemetic therapy postprocedure (three in group S, zero in group P, *P* = 0.24). No differences were seen in MAP or HR during maintenance between the two groups.

Times to spontaneous ventilation, extubation, recovery from anesthesia (eye opening) and orientation were shorter in the patients receiving sevoflurane

FIGURE 1 Change from baseline in digit-symbol substitution test during recovery from sevoflurane and propofol anesthesia.

FIGURE 2 Visual analogue scale scores for sedation during recovery from sevoflurane and propofol anesthesia.

(Table III). Times to be judged fit for transfer from the recovery room were similar between the groups. A post-hoc power analysis has shown that the power of this study to detect a difference (where $\alpha = 0.05$) for time to spontaneous ventilation, time to extubation, time to eye opening and time to orientation is 79%, 98%, 98% and < 1% respectively.

The mean change from baseline in DSST scores is shown in Figure 1. Mean DSST scores were similar between the groups at all time points, with the exception of a small difference between the groups on admission to the recovery area. The two groups had similar VAS scores for sedation during the recovery period (Figure 2), as well as similar Ramsay sedation scale scores.

There were no differences in the GCS, VAS scores for pain, nausea scores or vomiting scores between the groups.

Discussion

The primary objective of this study was to compare the speed of recovery after prolonged anesthesia with sevoflurane or propofol. Our results demonstrate that in patients undergoing interventional neuroradiological procedures of one to five hours duration, the use of sevoflurane was associated with more rapid early recovery compared to propofol. The reductions in times to eye opening, return of spontaneous ventilation and extubation were between one and four minutes. Rapid recovery may be of benefit to neuroanesthesiologists and neuroradiologists who wish to see a rapid return to consciousness in order to permit early assessment of neurological function after these potentially high-risk procedures and, notwithstanding the differences in early recovery, this was achieved with both techniques. Early assessment of neurosurgical and neuroradiological patients is considered desirable although outcome data to support this belief are not available. To demonstrate that the more rapid early recovery we observed was of benefit would require a much larger study than this.

The difference in recovery measured in this study mirrors that seen in many of the studies that have looked predominantly at shorter duration (usually day-case) anesthesia.⁶ It is of interest that despite two to three hours duration of anesthesia, a difference was seen between sevoflurane and propofol. There is little published work on the comparison of these agents for prolonged procedures. Eger *et al.*⁷ found that increasing the duration of anesthesia up to eight hours is associated with longer recovery times for both desflurane and sevoflurane. Jellish *et al.*⁸ found that after elective surgical procedures lasting approximately two hours, sevoflurane anesthesia was associated with more rapid times to extubation, to obey commands and to orientation than propofol anesthesia (9 *vs* 13 min, 11 *vs* 14 min and 15 *vs* 20 min, respectively). Conversely, a study comparing single agent anesthesia with sevoflurane or propofol for spinal surgery lasting two to 2.5 hr found no difference in recovery times.⁹ However, all patients had received morphine intraoperatively, which may have masked any differences in recovery. When the results from a number of studies were pooled, it was found that increasing the duration of sevoflurane anesthesia (three to five hours) did not result in a reciprocal increase in recovery times.¹⁰ Todd *et al.* compared three techniques for maintenance of anesthesia for craniotomy surgery. They found very few differences in recovery from anesthesia in patients receiving either a propofol/fentanyl or an isoflurane/N₂O-based technique. Time to orientation was shorter (10 *vs* 20 min) in those patients who had received propofol/fentanyl.⁴ Talke *et al.* found no dif-

ference in recovery between a propofol-based and an isoflurane-based technique.⁵

We measured a small difference in psychomotor function at one time point only. The similarity in sedation scores and psychomotor scores suggests that there is little difference between these agents during the early recovery period once the patient is awake. There were no differences in the other outcomes - pain, nausea and vomiting - and the hemodynamic variables. These procedures are not usually associated with postprocedure pain. Similarly, the absence of a difference in nausea and vomiting scores might be expected after procedures that are not commonly associated with postoperative nausea and vomiting (PONV). Although some researchers have reported an increase in PONV associated with sevoflurane use,^{11,12} others have found no difference.^{8,9} Use of an anesthesia technique without the concomitant use of long-acting opioids may have contributed to the overall low rate of PONV in this study.

It may be argued that recovery from sevoflurane anesthesia was more rapid because of a different depth of anesthesia during the procedure and, in particular, during the period leading up to the end of the procedure. We might have used a 'depth-of-anesthesia' monitor, such as the bispectral index, which might also have prevented excessively deep anesthesia and led to shorter recovery times.¹³ Instead, we decided to titrate the depth of anesthesia against hemodynamic variables, particularly MAP. This technique may not ensure a similar depth of anesthesia, as the two agents may modify the blood pressure response to stimuli by different mechanisms. These procedures are not stimulating, however, and in the absence of a major intracranial catastrophe, blood pressure is a useful indicator of anesthesia depth. Furthermore, titrating the administration of maintenance agents against the MAP best mimics usual clinical practice.

Use of sevoflurane for prolonged procedures may raise concern regarding the total amount of sevoflurane administered (MAC-hours). A limit of the use of this drug at low flow rates exists in the United States and some other countries; however, many countries do not have this limitation. This subject remains at the centre of much controversy at present.¹⁴ Although interventional neuroradiological procedures can be prolonged, the amount of maintenance agent administered is often limited and the total dose administered remains low. Our protocol allowed administration of sevoflurane up to 3% inspired. However, for the majority of patients in the sevoflurane group, the average inspired concentration during the maintenance period was much less than the 3% inspired concentration allowed (Nathanson MH, unpublished observation).

In conclusion, we found that use of sevoflurane for maintenance of anesthesia for neuroradiological procedures of one to five hours duration was associated with more rapid early recovery (one to four minutes) than propofol. No differences were found in sedation, pain, PONV or psychomotor function. Sevoflurane and propofol can both be recommended for these procedures. The more rapid early recovery with sevoflurane may be an advantage, but the clinical significance of this difference is unknown.

APPENDIX

Ramsay sedation scale:

- 1 - Anxious, agitated or restless;
- 2 - Cooperative, orientated and tranquil;
- 3 - Responds to commands;
- 4 - Asleep, but with brisk response to light glabellar tap or auditory stimulus;
- 5 - Asleep, sluggish response to light glabellar tap or auditory stimulus;
- 6 - Asleep, no response.

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