Cerebral haemodynamic changes during propofol–remifentanil or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring

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Background. Sevoflurane or propofol–remifentanil-based anaesthetic regimens represent modern techniques for neurosurgical anaesthesia. Nevertheless, there are potential differences related to their activity on the cerebrovascular system. The magnitude of such difference is not completely known.

Methods. In total 40 patients, treated for spinal or maxillo-facial disorders, were randomly allocated to either i.v. propofol–remifentanil or inhalational sevoflurane anaesthesia. Transcranial Doppler was used to assess changes in cerebral blood flow velocity, carbon dioxide reactivity, cerebral autoregulation and the bispectral index to assess the depth of anaesthesia.

Results. Time-averaged mean flow velocity (MFV) was significantly reduced after induction of anaesthesia in both sevoflurane and propofol–remifentanil groups (P<0.001). At deeper levels of anaesthesia, MFV increased in the sevoflurane group, suggesting an uncoupling flow/metabolism, whereas it was further reduced in the propofol–remifentanil group (P<0.001). Indices of cerebral autoregulation were reduced in patients with high-dose sevoflurane whereas autoregulation was preserved in patients anaesthetized with propofol–remifentanil (P<0.001). Higher CO₂ concentrations impaired cerebral autoregulation in the sevoflurane group but not in patients anaesthetized with propofol–remifentanil.

Conclusions. Propofol–remifentanil anaesthesia induced a dose-dependent low-flow state with preserved cerebral autoregulation, whereas sevoflurane at high doses provided a certain degree of luxury perfusion.

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Sevoflurane and propofol are widely used as anaesthetic agents for neurosurgery and demonstrate similar characteristics for anaesthetic induction, maintenance, emergence time and early cognitive function. Sevoflurane is currently considered the inhalational agent of choice in neuroanaesthesia. Despite being less evident when compared with other halogenated anaesthetics, sevoflurane demonstrated an intrinsic cerebral vasodilatory effect, with a dose-dependent increase in cerebral blood flow and similar decrease in cerebrovascular resistance.

Propofol has been recommended as an ideal hypnotic during neurosurgical procedures. It is not associated with significant modification of cerebral haemodynamics. It can be used in total intravenous anaesthesia (TIVA) in association with remifentanil, an ultra-short-acting mu-opioid receptor agonist. Target-controlled infusion (TCI) of propofol–remifentanil allows for titration of the hypnotic–analgesic effect along with rapid recovery and early assessment of postoperative neurological function. Despite the fact that sevoflurane and propofol–remifentanil based anaesthesia represent modern techniques for neurosurgery, they display potential differences related to the effects on the cerebrovascular system. The magnitude of such differences is not completely known.
In this study, two different anaesthetic techniques, propofol–remifentanil TCI and sevoflurane inhalation anaesthesia, were compared regarding changes in cerebral blood flow velocity, carbon dioxide reactivity, and cerebral autoregulation in a prospective randomized manner. Transcranial Doppler (TCD) was used to obtain data regarding changes in cerebral haemodynamics.

Methods

The study was designed to have an 80% chance of detecting a 20% difference between the two groups at the two-sided 5% level, with an assumed SD of 30% in the outcome variables. Two treatment groups of 20 patients each were required. After approval had been obtained from the local Ethics Committee, patients classified as ASA I or II, age ranging from 18 to 65 yr and undergoing routine spinal and oral–maxillo–facial surgical procedures, were recruited into the study. Written informed consent was obtained from all the patients.

Patients with intracranial pathological conditions were excluded. Also patients with a history of cerebral, cardiac or systemic vascular disorders, or those receiving medications that might influence the cerebrovascular function were excluded. Preoperative duplex imaging of the vessels in the neck was performed to detect any pathological finding.

No pre-anaesthetic medication was administered to any patient. The study was conducted in four stages, and all the stages were completed before patient’s positioning for surgical treatment.

In the first stage, awake patients were placed in supine position and the bispectral index (BIS) (BIS® XP monitor, Aspect Medical Systems, Nantick, MA) was monitored. Mean arterial blood pressure (MAP), heart rate, oxygen saturation and end-tidal carbon dioxide were obtained using the Julian anaesthesiology workstation, which was connected to the monitoring unit (Vitara PM 8060, Dräger, Lübeck, Germany). The TCD probes were fixed in place by applying a headband to maintain a constant angle of insonation. Two baseline measurements of TCD variables in awake patients, with BIS values of 90–100, were performed.

In the second stage of the study, anaesthesia was induced using a TCI of propofol (2.5–3.5 μg ml⁻¹) followed by cisatracurium (0.15–0.2 mg kg⁻¹) and subsequent tracheal intubation. After induction of anaesthesia, the patients were placed on a mechanical ventilation system (Julian Anesthesiology Workstation; Dräger, Lübeck, Germany) with an air and oxygen mixture (FiO₂ 0.4). Then, patients were allocated to one of two different treatment groups using random numbers generated by a computer software program available online (www.graphpad.com/quickcalcs/randomization1.cfm).

In the first group of patients (Group TIVA), anaesthesia was maintained with remifentanil 0.15–0.25 μg kg⁻¹ min⁻¹ and TCI of propofol using Terufusion Syringe Pumps TE-371 and TE-372 (TERUMO Europe, Leuven, Belgium) titrated to achieve BIS values of 50 (5). In the second group of patients (Group SEVO), anaesthesia was maintained with sevoflurane titrated to achieve BIS values of 50 (5). In this way, both groups had comparable levels of anaesthesia.

The TCD probes were repositioned in case a displacement occurred during the preliminary stage, and examination was started in all patients after 15 min of stable BIS values during anaesthesia maintenance. This interval turned out to be necessary also to achieve an adequate diffusion of sevoflurane, and to obtain, in the patients maintained with sevoflurane, a predicted propofol concentration of <1.5–2 μg ml⁻¹, a concentration that is presumed to have minimal effects on cerebral haemodynamics. MAP was maintained within 10% of the pre-induction values by administration of crystalloids, whereas heart rate was maintained by use of atropine, if required. Because of the potential influence of crystalloids on TCD measurements, the infusion was given slowly, and examination delayed until the MAP returned to pre-induction values. If an excessive crystalloid infusion was needed, or if MAP could not be maintained, the patient was excluded from the study.

End-tidal carbon dioxide was also maintained within 10% of the initial values [4.7 (0.4) kPa]. The second series of TCD examinations was performed in both groups of patients. In the third stage of the study, in 20 patients (Group TIVA), TCI of propofol associated with remifentanil was titrated to achieve BIS values of 35 (2). In the remaining 20 patients (Group SEVO), the concentration of sevoflurane was increased to achieve similar BIS values. The third series of TCD measurements was performed after 15 min to allow sufficient time for equilibrium to be reached in both the groups.

In the fourth stage of the study, ventilation parameters were changed by changing the ventilatory frequency with a constant tidal volume in both groups to obtain an end-tidal carbon dioxide of 6.0 (0.4) kPa. A supplementary series of TCD examinations was obtained to evaluate carbon dioxide reactivity and autoregulation at a different carbon dioxide concentration. Such parameters were maintained until MAP, which usually tended to increase at the beginning of hypercapnic challenge, returned within the range selected in the study protocol (greater or lesser than 10% of the basal values).

Transcranial Doppler ultrasonography

The middle cerebral artery (MCA) was insonated bilaterally through the temporal window by using two pulsed 2-MHz TCD ultrasound probes (Explorer CVS; Diagnostic Medical System, Perols, France). Identification of the MCA flow velocity was confirmed using standard criteria, at a depth of 45–55 mm. The transient hyperaemic response test was performed in a manner described in previous studies. The test is used to assess the hyperaemic response of MCA blood flow velocity after a brief (5–9 s) compression of the ipsilateral common carotid artery. It was considered...
reliable when the following occurred: (i) compression of the common carotid artery caused a sudden and maximum decrease in flow velocity; (ii) stability of the heart rate and signal power during the test; and (iii) compression lasting between 5 and 9 s.

Four tests were performed at each stage of the study, alternating the two MCAs. Systolic flow velocity was calculated using the mean value of systolic peaks from five heart cycles, ending with the one preceding compression. The hyperaemic response was calculated using the mean systolic value of two heart cycles after compression release, with the exception of the very first cycle (Fig. 1).

The values of all tests were averaged, obtaining two values for each stage: FV1, defined as the mean basal MCA systolic flow velocity; and FV3, defined as the mean hyperaemic MCA systolic flow response.

As an index of the actual changes in cerebral blood flow during the four different test series of the study (Awake, BIS 50, BIS 35, Hypercapnia), we recorded the time-averaged mean flow velocity (MFV) in both the TIVA and sevoflurane groups. The values obtained were indicated as MFVawake, MFV50, MFV35, or MFVhypercapnia. The changes in MFV, taken to represent changes in cerebral blood flow (CBF) at different stages were calculated as

\[
\Delta\text{CBF}_{50} = \text{MFV}_{\text{awake}} - \text{MFV}_{50}; \quad \Delta\text{CBF}_{35} = \text{MFV}_{50} - \text{MFV}_{35}; \quad \Delta\text{CBF}_{CO2} = \text{MFV}_{\text{normocapnia}} - \text{MFV}_{\text{hypercapnia}}.
\]

The transient hyperaemic response ratio (THRR), representing the hyperaemic response, was taken as the index of autoregulation, and was calculated as THRR=FV3/FV1.

To assess the quality of the test, the magnitude of the decrease in the flow velocity during compression, the compression ratio (CR) was calculated as CR% = (FV1–FV2)×100/FV1, where FV2 is defined as the mean MCA flow velocity immediately after compression.

**Statistical analysis**

Comparisons between the groups regarding MAP, heart rate and end-tidal carbon dioxide during different stages of the study were made using one-way ANOVA with the Bonferroni post hoc correction. Baseline MFV, FV1 and THRR were compared using the Student’s t-test with the Welch correction. The Wilcoxon matched-pairs test was used to compare within-group changes in MFV and THRR during different stages of the study. The unpaired Student’s t-test was used to compare the changes between the groups. We used a computer software program (INSTAT, version 3.0, GRAPHPAD, San Diego, CA) to perform statistical analysis. *P*<0.05 was considered statistically significant. All values are reported as mean (SD).

**Results**

In all, 46 patients were recruited. Four patients, in the sevoflurane group, were subsequently excluded because of protocol violation as sympathetic stimulant drugs and/or large amount of crystalloids had to be administered to maintain MAP. Two patients, one in each group, were excluded because of bradycardia after carotid compression. Because of the patients’ withdrawal, after the first 30 patients, who were randomized in equal proportion, a block randomization was continued allocating patients in proportion of 2 in the sevoflurane to 1 in the TIVA group.

Analysis was restricted only to the participants who completed the study protocol. A total of 40 patients, 23 men and 17 women completed the study. The characteristics of patients are shown in Table 1.
Table 2 Summary of physiological variables in the two groups during the different stages of the study

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP (mm Hg)</th>
<th>Heart rate (beats min⁻¹)</th>
<th>End-tidal CO₂ (kPa)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>SEVO 85 (7)</td>
<td>73 (8)</td>
<td>4.7 (0.4)</td>
<td>36.8 (0.2)</td>
</tr>
<tr>
<td></td>
<td>TIVA 85 (8)</td>
<td>75 (10)</td>
<td>4.7 (0.4)</td>
<td>36.8 (0.2)</td>
</tr>
<tr>
<td>BIS 50</td>
<td>SEVO 78 (6)</td>
<td>76 (7)</td>
<td>4.7 (0.4)</td>
<td>36.8 (0.2)</td>
</tr>
<tr>
<td></td>
<td>TIVA 77 (7)</td>
<td>79 (7)</td>
<td>4.7 (0.4)</td>
<td>36.8 (0.2)</td>
</tr>
<tr>
<td>BIS 35</td>
<td>SEVO 73 (6)</td>
<td>77 (5)</td>
<td>4.7 (0.4)</td>
<td>36.7 (0.2)</td>
</tr>
<tr>
<td></td>
<td>TIVA 74 (7)</td>
<td>81 (7)</td>
<td>4.7 (0.4)</td>
<td>36.7 (0.2)</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>SEVO 76 (5)</td>
<td>77 (5)</td>
<td>6.0 (0.4)</td>
<td>36.8 (0.2)</td>
</tr>
<tr>
<td></td>
<td>TIVA 75 (5)</td>
<td>80 (5)</td>
<td>6.0 (0.4)</td>
<td>36.7 (0.2)</td>
</tr>
</tbody>
</table>

Values are given as mean (sd). BIS 50, BIS 35 and Hypercapnia are the stages of study during anaesthesia at BIS value of 50, 35 and with hypercapnia, respectively. Differences between the groups were insignificant.

Table 2 summarizes values of physiological variables at the different stages of the study. In awake patients MFV was 55.0 (8.6) cm s⁻¹ in Group SEVO and 54.3 (7.6) cm s⁻¹ in Group TIVA (P > 0.05).

In the second stage of the study, i.e. BIS 50, sevoflurane concentration was 1.7 (0.4)% (Group SEVO), whereas the TCI of propofol was at 2.7 (0.5) μl ml⁻¹, and remifentanil was administered at 0.18 (0.06) μg kg⁻¹ min⁻¹ (Group TIVA). Sevoflurane reduced MFV to 42.4 (8.2) cm s⁻¹ (P < 0.001), and TIVA reduced it to 37.3 (12.1) cm s⁻¹ (P < 0.001). The change (∆CBF₅₀) was significantly different between the groups (P < 0.05).

At the third stage of the study, i.e. at BIS 35, the sevoflurane concentration was increased to 2–4% in Group SEVO, whereas the TCI of propofol was at 3.1 (0.6) μl ml⁻¹ and remifentanil was administered at 0.20 (0.07) μg kg⁻¹ min⁻¹ in Group TIVA. High doses of sevoflurane increased MFV to 50.3 (11.4) cm s⁻¹ whereas TIVA, at equipotent anaesthetic doses, decreased MFV to 32.9 (9.1) cm s⁻¹ (P < 0.001) (Fig. 2). These data suggested an uncoupling flow/metabolism in Group SEVO (Fig. 3).

In awake patients, THRR was 1.21 (0.06) in Group SEVO and 1.23 (0.09) in Group TIVA, and after induction of anaesthesia, at BIS 50, the values were 1.22 (0.1) and 1.27 (0.2), respectively; the values were not statistically different. At BIS 35, in Group TIVA, the THRR increased to 1.36 (0.2), whereas in Group SEVO it decreased to 1.10 (0.1) (P < 0.001), indicating a tendency for impaired cerebral autoregulation during high-dose sevoflurane anaesthesia (Fig. 4).

In the last stage of the study, in both groups of patients, ventilation parameters were changed to achieve end-tidal carbon dioxide of 6 kPa. On average 5 min were required for MAP, which usually tended to increase at the beginning of hypercapnia, to return within the range selected in the study protocol (greater or lesser than 10%). MFV increased in both groups, from 50.3 (11.4) to 56.1 (11.5) cm s⁻¹ in Group SEVO, and from 32.9 (9.1) to 39.1 (7.4) cm s⁻¹ in Group TIVA; the THRR was 1.07 (0.04) in Group SEVO and 1.22 (0.13) in Group TIVA (P < 0.001) (Fig. 4).

**Discussion**

Our data suggest that the TIVA with propofol–remifentanil induces a low-flow state preserving the pressure-flow autoregulation whereas high doses of sevoflurane administration may cause a certain degree of luxury perfusion.

Both sevoflurane and propofol-based anaesthetic regimens represent modern techniques for neurosurgical anaesthesia. Haemodynamic properties of these agents have been widely analysed. Nevertheless, the influence of combining
The vasodilatory properties of sevoflurane are confirmed by our data; at higher doses and deep anaesthesia, namely at BIS values of 35, we have shown a certain degree of uncoupling of flow-metabolism in patients with sevoflurane (Fig. 3).

The uncoupling of flow-metabolism as seen during use of inhalational anaesthetic agents actually demonstrates that cerebral vasodilation is a result of a direct action of these agents on vascular smooth muscle. This may cause an impairment of cerebral autoregulation.\textsuperscript{25} Cerebrovascular autoregulation was therefore assessed in the two groups of patients. Modelling of cerebral autoregulation using the THR test has been performed, and details published previously.\textsuperscript{9,11–14} Essentially, the decrease in MCA perfusion pressure at the onset of carotid artery compression provokes autoregulatory vasodilation in the MCA territory. Release of compression allows perfusion pressure to return to baseline but, because of the reduced resistance of the vascular bed, flow velocity in the MCA overshoots the baseline values (transient hyperaemic response).

In theory, the dose-dependent action of sevoflurane on cerebral vascular resistance may reflect on cerebral autoregulation in a dose-dependent manner. Actually, it has been shown that in healthy subjects with normal $P_{\text{aCO}_2}$ cerebral autoregulation was preserved with 1.2 MAC\textsuperscript{22} and 1.5 MAC\textsuperscript{20} sevoflurane. During normocapnia, 1.5 MAC sevoflurane marginally affected dynamic autoregulation in response to rapid deflation of thigh cuffs.\textsuperscript{20} In a previous study, we determined that the transient hyperaemic response to carotid artery compression was preserved with 2 MAC sevoflurane anaesthesia whereas it was impaired on adding nitrous oxide. Nevertheless, the values of the hyperaemic response recorded during sevoflurane anaesthesia were lower than those recorded in normocapnic awake patients.\textsuperscript{31}

In this study, it was recorded that when approximately 2 MAC sevoflurane concentrations were used, the hyperaemic response showed a tendency to reduce. Conversely, during propofol–remifentanil anaesthesia, the autoregulatory index increased significantly. This suggests that the low-flow state induced by propofol–remifentanil and the increase of CVR probably widens the autoregulatory plateau,\textsuperscript{27} whereas the intrinsic tendency of sevoflurane to reduce cerebral vascular resistance has an opposite effect. Our findings agree with a recent study that showed that in anaesthetized patients undergoing cardiopulmonary bypass, infusion of propofol could improve cerebral autoregulation that was previously impaired.\textsuperscript{28}

Carbon dioxide strongly influences cerebral autoregulation. Hypocapnia widens the plateau of the static pressure autoregulation curve.\textsuperscript{29} The opposite effect is observed in hypercapnia with an upward shift of the autoregulatory curve and disappearance of the plateau at very high levels of $P_{\text{aCO}_2}$. Recently, however, Panerai\textsuperscript{30} suggested that a more realistic representation of the effects of carbon dioxide are manifested as changes in the critical closing pressure instead of changes in resistance with a shift of the pressure-flow curve and only minor changes of the slope.
Interestingly, at the same anaesthetic doses and levels of anaesthesia as determined using BIS, an end-tidal carbon dioxide of 6 kPa impaired autoregulation in patients receiving sevoflurane, but not propofol–remifentanil TIVA. It is of note that an end-tidal carbon dioxide of 6 kPa is well within the range commonly seen with spontaneous ventilation during general anaesthesia.

The view that the opposite effects on cerebral vascular resistance observed with the two anaesthetic regimens can be translated into hyper- and hypo-regulatory states would hold true only according to a single-parameter model. Nevertheless, this cannot provide a realistic representation of pressure-flow/velocity relationship of the cerebral autoregulation. In particular, autoregulation should be regarded as a reflection of flow-metabolism coupling. Despite conflicting results, there are studies demonstrating that propofol reduces CBF to a greater extent than it reduces cerebral metabolism, indicating that propofol has direct vasoconstricting properties. Jansen and colleagues found that in patients undergoing brain tumour surgery there was a significantly lower jugular saturation in patients anaesthetized with propofol than in a matched group anaesthetized with nitrous oxide and isoflurane; Nandate and colleagues found that in patients undergoing brain tumour surgery there was a significantly lower jugular saturation in patients undergoing brain tumour surgery. The results of these studies demonstrate that propofol and sevoflurane have different effects on cerebral autoregulation.

How the luxury perfusion produced by sevoflurane and the low-flow state determined by propofol–remifentanil TIVA when administered at high doses may influence clinical outcome still needs to be determined. Actually, the low-flow state and the consequent reduced intracranial pressure determined by propofol–remifentanil are significantly advantageous for neurosurgery; however, an equivalent reduction in cerebral metabolism with maintenance of oxygen extraction fraction is paramount. Further studies addressing this issue are therefore necessary.

Accordingly, even if caution in using high doses of sevoflurane in patients with increased intracranial pressure or at risk for inadequate brain relaxation can be suggested, definitive and unequivocal data on the potential differences in neuroprotective activity of the two studied anaesthetic regimens are difficult to determine.

Finally, there are some considerations on the methods used in this study. One advantage of this study is represented by the effort to limit confounding factors, as much as possible. Pre-anesthetic medications were not administered, and sympathetic drugs, such as phenylephrine, were avoided given the potential action on cerebral haemodynamics during contemporaneous administration of volatile anaesthetic agents. Furthermore, instead of using qualitative parameters to provide a reasonable certainty of ensuring an equipotent hypnotic effect, neuronal depression and, consequently, metabolic activity in the two groups of patients, we used the BIS which has the advantage of not requiring patient stimulation and of providing a quantitative measure. In fact, several findings indicate that the use of BIS may be a valuable guide for intraoperative administration of propofol and sevoflurane. The use of this monitoring device decreases consumption of both propofol and sevoflurane and facilitates immediate recovery after propofol anaesthesia, whereas intraoperative course is not changed. BIS has been previously used to evaluate the level of anaesthesia when comparing inhalational sevoflurane and i.v. propofol anaesthesia. BIS has been used to keep a constant hypnotic depth throughout anaesthesia to quantify the effects of sevoflurane and propofol on CBF, metabolic rate of oxygen and blood volume using positron emission tomography. Boisseau and colleagues compared the effects of propofol and sevoflurane on cortical somatosensory evoked potentials adjusting the anaesthetic concentration to obtain a constant hypnotic depth by means of the BIS.

On the other hand, a potential disadvantage of the study is represented by the use of MFV as a surrogate measure of changes in CBF. This is problematic because any change in the diameter of the insonated vessel would alter the relation between flow velocity and actual blood flow. However, it was demonstrated by direct intraoperative measurement that the MCA diameter does not change significantly during variations in MAP or P\textsubscript{aCO\textsubscript{2}}. In the end, we accepted only tests in which the power of the Doppler spectrum remained constant. In fact, the acoustic intensity for each velocity is proportional to the volume of blood moving at that particular velocity and, thus, if the acoustic intensity (i.e. the TCD waveform spectrum) remains constant, flow velocities are linearly proportional to actual blood flow within the vessel segment, suggesting that no change in MCA diameter occurred.

In conclusion, propofol–remifentanil TIVA demonstrated advantageous preservation pressure-flow relationship by inducing a dose-dependent low-flow state, during deep anaesthesia and higher end-tidal carbon dioxide concentrations. With sevoflurane, cerebral autoregulation was preserved at lower concentrations; however, at higher concentrations, it provided a degree of luxury perfusion and impaired autoregulation with hypercapnia. Accordingly, even if caution in using high doses of sevoflurane in patients with increased ICP or at risk for inadequate brain relaxation can be suggested, definitive and unequivocal data on the neuroprotective activity of the two studied anaesthetic regimens still needs to be determined.

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