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Intracranial Pressure and Cerebral Hemodynamic in Patients with Cerebral Tumors

A Randomized Prospective Study of Patients Subjected to Craniotomy in Propofol–Fentanyl, Isoflurane–Fentanyl, or Sevoflurane–Fentanyl Anesthesia

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Background: **A critical point during craniotomy is opening of dura, where a high intracranial pressure (ICP) results in swelling of cerebral tissue. Controlled studies concerning ICP, degree of dural tension, and degree of cerebral swelling are therefore warranted.**

Methods: **In an open-label study, 117 patients with supratentorial cerebral tumors were randomized to propofol–fentanyl (group 1), isoflurane–fentanyl (group 2), or sevoflurane–fentanyl anesthesia (group 3). Normo- to moderate hypocapnia was applied, with a target level of arterial carbon dioxid tension of 30–40 mmHg. Mean arterial blood pressure was stabilized with intravenous ephedrine (2.5–5 mg) if necessary. Subdural ICP, mean arterial blood pressure, cerebral perfusion pressure (CPP), arteriovenous oxygen difference ($AVDo_2$), internal jugular vein oxygen saturation were monitored before and after a 10-min period of hyperventilation, and the carbon dioxide reactivity was calculated. Furthermore, the tension of dura before and during hyperventilation and the degree of cerebral swelling during hyperventilation and after opening of the dura were estimated by the neurosurgeon.**

Results: **No differences were found between groups with regard to demographics, neuroradiologic examination, positioning of the head, and time to ICP measurement. Before and during hyperventilation, ICP was significantly lower and mean arterial blood pressure and CPP significantly higher in group 1 compared with groups 2 and 3 ($P < 0.05$). The tension of dura before and during hyperventilation was significantly lower in group 1 compared with group2 ($P < 0.05$), but not significantly different from group 3. In group 1, cerebral swelling after opening of dura was significantly lower compared with groups 2 and 3 ($P < 0.05$). Furthermore, $AVDo_2$ was significantly higher and jugular vein oxygen saturation and carbon dioxide reactivity were significantly lower in group 1 compared with groups 2 and 3 ($P < 0.05$). No significant differences with regard to ICP, CPP, $AVDo_2$, carbon dioxide reactivity, and jugular vein oxygen saturation were found between patients anesthetized with isoflurane and sevoflurane.**

Conclusions: **The study indicates that before as well as during hyperventilation, subdural ICP and $AVDo_2$ are lower and CPP higher in propofol-anesthetized patients compared with patients anesthetized with isoflurane or sevoflurane. These findings were associated with less tendency for cerebral swelling after opening of dura in the propofol group. The carbon dioxide reactivity in patients anesthetized with isoflurane and sevoflurane was significantly higher than in the propofol group. The differences in subdural ICP between the groups are presumed to be caused by differences in the degree of vasoconstriction elicited by the anesthetic agents, but autoregulatory mechanisms caused by differences in CPP cannot be excluded.**

ANESTHESIA for craniotomy must be conducted with emphasis on hemodynamic stability, a sufficient cerebral perfusion pressure (CPP), and avoidance of agents or procedures that increase the intracranial pressure (ICP). Experimental and clinical studies of cerebral hemodynamics, including cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRo_2$), and ICP have been conducted during isoflurane,[1–8] sevoflurane,[8–11] and propofol anesthesia.[12–16] Clinical studies indicate that when isoflurane[2,3,6,7] or sevoflurane[8,10,17] are administered, CBF and $CMRo_2$ are reduced as compared with values obtained in awake normocapnic subjects. An increase in ICP has been found during anesthesia with isoflurane[1,5] and sevoflurane,[11] and an increase in CBF has been disclosed during isoflurane[7] and sevoflurane anesthesia.[10] However, in other studies of isoflurane[2,3,8] and sevoflurane,[8,9] CBF and ICP were unchanged. In contrast, a dose-related decrease in CBF, $CMRo_2$, and ICP has been found during propofol anesthesia.[12–15]

Only few comparative studies of ICP are available. In a prospective trial of three anesthetic techniques for elective supratentorial craniotomy (isoflurane–nitrous oxide, nitrous oxide–fentanyl, and propofol–fentanyl), epidural ICP measured through the first burr hole did not differ significantly, but more patients in the isoflurane–nitrous oxide group had ICP 24 mmHg or greater compared with the other two groups.[18] Other studies of lumbar cerebrospinal fluid (CSF) pressure for neurosurgical anesthesia disclosed contrasting results, no difference during propofol *versus* thiopental–isoflurane,[19] but significantly lower ICP during propofol anesthesia compared with isoflurane and sevoflurane.[5,11]

Subdural ICP monitoring after removal of the bone flap was recently introduced.[20,21] Subdural ICP correlates with dural tension as estimated by the neurosurgeons. If subdural pressure is 10 mmHg or greater, some degree of brain swelling occurs after opening of dura.[21] To our

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knowledge, comparable studies concerning the effects of propofol, isoflurane, and sevoflurane upon ICP and cerebral hemodynamics are not available. In the current study, patients with supratentorial cerebral tumors were randomized to receive either propofol–fentanyl, isoflurane–fentanyl, or sevoflurane–fentanyl anesthesia in an open-label study. The primary aims of the current study were (1) to investigate whether difference in subdural ICP existed before and during applied hyperventilation, and (2) to study the incidence of cerebral swelling after opening of the dura. Furthermore, as secondary aims we investigated whether CPP, arteriovenous oxygen difference ($AVDo_2$), carbon dioxide reactivity, and the neurosurgeons' estimate of dural tension differed between groups.

Materials and Methods

The investigation was a Danish multicenter study with three participating hospitals (Aarhus University Hospital, Rigshospitalet, and Glostrup University Hospital). The patients were enrolled between March 1998 and December 1999. The protocol was approved by the local ethics committee and fulfills the Helsinki Declaration. Oral and written informed consent was obtained from all patients.

Patients scheduled for elective craniotomy for supratentorial cerebral tumors were included and were randomized to one of three anesthetic groups: propofol–fentanyl, isoflurane–fentanyl, or sevoflurane–fentanyl. The patients were randomized in blocks of 21 in sealed numbered envelopes. Seven numbers representing each anesthetic technique were included in each block of 21 patients. These blocks were distributed to the three hospitals.

Elective patients (ages 18–70 yr) without clinical sign of arterial hypertension or chronic pulmonary insufficiency were eligible to be included in the study. All patients underwent a cerebral computed tomography–magnetic resonance scanning preoperatively and a had diagnosis of cerebral tumor with shift of the midline less than 10 mm.

Anesthesia and Monitoring

The patients were premedicated with 5 mg/25 kg oral diazepam 1 h before induction of anesthesia. If preoperative corticosteroid or anticonvulsant treatment were instituted, they were given together with diazepam.

Monitoring before induction consisted of automated noninvasive blood pressure (oscillometric blood pressure), continuous electrocardiogram, and pulse oximetry. After induction of anesthesia, end-tidal carbon dioxide and concentration of inspired and expired anesthetic gas were monitored continuously (Datex AS3; Helsinki, Finland). Controlled ventilation (fraction of inspired oxygen 50–60% by oxygen–air) was applied at an arterial carbon dioxide tension ($Paco_2$) between 30 and 40 mmHg, inspiratory peak pressure less than 20 cm H_2O, and a respiratory frequency between 10 and 20 breaths/min. The level of $Paco_2$ was achieved by continuous monitoring of pulmonary ventilation and end-tidal carbon dioxide and verified by arterial blood gas analysis. A Foley catheter was placed in the urinary bladder, and rectal temperature was continuously monitored. A radial artery catheter was inserted for continuous blood pressure monitoring and blood sampling. A catheter was introduced into the bulb of the internal jugular vein for pressure monitoring and blood sampling. Location of catheter was checked by radiograph. Bupivacaine (2.5 mg/ml) with epinephrine was used for infiltration of the scalp. Train-of-four stimulation was used to monitor muscular relaxation, which was achieved by a continuous infusion of atracurium.

After informed consent was obtained and before premedication, the sealed numbered envelope indicating anesthetic procedure was opened. The anesthetic procedures were as follows.

Group 1: Propofol–Fentanyl. Anesthesia was induced with 1–3 mg/kg propofol given over 1 min and 3–4 μg/kg fentanyl. Lidocaine (1 mg/kg) was administered over 1 min followed by muscular relaxation by 0.5 mg/kg atracurium. Anesthesia was maintained with infusions of propofol (6–10 $mg \cdot kg^{-1} \cdot h^{-1}$) and fentanyl (2–3 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Just before incision of the scalp, doses of propofol (1 mg/kg) and/or fentanyl (1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) were supplemented, if necessary. The infusion rates of propofol and fentanyl were unchanged during the ICP measurements and during the estimate of dural swelling.

Group 2: Isoflurane–Fentanyl. Anesthesia was induced with 1–3 mg/kg propofol given over 1 min and 2–3 μg/kg fentanyl. Lidocaine and atracurium were administered as in group 1. Anesthesia was maintained with isoflurane (maximally 1.5 minimum alveolar concentration [MAC]) and fentanyl (2–3 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Just before incision of the scalp, fentanyl (1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) was supplemented, if necessary. The infusion rates of propofol and fentanyl were unchanged during the ICP measurements and during the estimate of dural swelling.

Group 3: Sevoflurane–Fentanyl. Anesthesia was induced with 1–3 mg/kg propofol given over 1 min and 2–3 μg/kg fentanyl. Lidocaine and atracurium were administered as in group 1. Anesthesia was maintained with sevoflurane (maximally 1.5 MAC) and fentanyl (2–3 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Just before incision of the scalp, fentanyl (1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) was supplemented, if necessary. The infusion rates of propofol and fentanyl were unchanged during the ICP measurements and during the estimate of dural swelling.

With the exception of three patients who underwent surgery in the lateral position, the supine position was used in all patients. After positioning of the patient, the degree of neck rotation was registered as neutral, 45° or

less, and greater than 45°. The operating table was in neutral position in all patients.

Subdural Intracranial Pressure and Cerebral Hemodynamic

Subdural ICP was measured as previously described.[20] After removal of the bone flap, ICP was measured subdurally by an intravenous needle (22 gauge, 0.8 mm) that was connected to a pressure transducer *via* a polyethylene catheter. Zero-point adjustment was performed with the tip of the needle placed at the point of intended insertion of the dura. The needle was introduced through the dura until a continuous recording of ICP with typical cardiac and respiratory waves appeared. After 1 min of stabilization, the integrated mean value of subdural pressure was used as an estimate of ICP. The needle was left *in situ* until hyperventilation was accomplished. Simultaneously, the integrated value of mean arterial blood pressure (MABP) was recorded with zero-point adjustment at the mid-axillary line. CPP was calculated as the difference between MABP and ICP. The jugular bulb catheter, with zero-point adjustment to the mid-axillary line, was connected to a pressure transducer for continuous pressure measurement. The surgeons were blinded with regard to the values of ICP, MABP, and jugular bulb pressure.

Blood was withdrawn simultaneously from the arterial and jugular catheter for measurement of arterial oxygen tension and $Paco_2$, arterial and internal jugular vein oxygen saturation ($S_{jv}o_2$), jugular venous oxygen tension, and arterial and venous oxygen content (Radiometer®, Copenhagen, Denmark). The $AVDo_2$ was calculated as the difference between arterial and jugular venous oxygen content. In eight patients (one in the propofol group, three in the isoflurane group, and four in the sevoflurane group), withdrawal of blood from the jugular catheter was impossible or it was impossible to insert a jugular catheter.

After the initial ICP measurement, the pulmonary ventilation was increased by 30% for 10 min. The measurements were repeated about 11 min after the first measurements. Carbon dioxide reactivity was calculated as percent change $AVDo_2/\Delta Paco_2$ (in millimeters of mercury).

Fluid Administration and Regulation of Blood Pressure

During the first hour of anesthesia, 15 ml/kg isotonic saline and was administered, followed by 2–4 $ml \cdot kg^{-1} \cdot h^{-1}$. If systolic blood pressure decreased greater than 20 mmHg, colloids Haes-Steril® 6% (hydroxyethyl-starch; Fresenius Kabi AB, Uppsala, Sweden) was administered, eventually supplemented with 5–10 mg intravenous ephedrine. Mannitol or packed erythrocytes were not given before the ICP measurements.

Neuroradiologic Examination

From the latest computed tomography or magnetic resonance scanning, the localization of the tumors and midline shifts were registered. The maximum tumor area was calculated using the formula for area of an ellipse (area = $ab\pi$, where a is half length and b half width of the tumor).

Estimation of Dural Tension and Cerebral Swelling

Before subdural ICP measurement, the surgeon made a tactile evaluation of the dural tension. The neurosurgeons were blinded to choice of anesthesia and the ICP value obtained. The tensions were categorized as follows: (1) very slack; (2) normal; (3) increased tension; and (4) pronounced increased tension.

The degree of brain swelling during hyperventilation was evaluated by the neurosurgeon after opening of the dura. Swelling was estimated as follows: (1) no swelling; (2) moderate swelling of the brain; and (3) pronounced swelling of the brain.

Statistical Analysis

Based on a previous nonrandomized study of ICP during three different anesthetic techniques, given a minimum detectable difference of 3.6 mmHg, expected SD 5.0 mmHg, power of 0.80, and a significance level of $P < 0.05$, the total number of patients was calculated to be 114. Data within groups were tested for normal distribution. Normality test and equal variance test were applied. One-way analysis of variance was used if these tests were passed, and Tukey test was used for pairwise multiple comparison procedures. Kruskal–Wallis one-way analysis of variance on ranks and multiple comparisons *versus* control groups (Dunn method) were used for statistical analysis when normality test or equal variance test were not passed. These data included subdural ICP, MABP, and $AVDo_2$. The Bonferroni test was applied for statistical analysis. Chi-square test was used for statistical analysis of demographic data, localization, size and histopathologic diagnosis of the tumors, preoperative corticosteroid administration, and position of the head between the groups. Difference in tension of dura and the degree of cerebral swelling were tested by chi-square test in 2×4 or 2×3 tables. For correlation studies, Pearson product moment correlation and linear regression were performed. Mean values ± SD were calculated. $P < 0.05$ was considered statistically significant.

Results

A total of 117 patients were enrolled in the study. Eighty-nine patients were included in Aarhus versus 12 and 14 patients in Glostrup and Rigshospitalet, respectively. Forty-one patients were allocated to the propofol–

Table 1. Demographic Data, Biochemical Data, Localization of Tumor, and Pathohistologic Diagnosis

	Propofol–Fentanyl	Isoflurane–Fentanyl	Sevoflurane–Fentanyl
Number of patients	41	38	38
Sex (M/F), n	20/21	16/22	20/18
Age, yr	55 ± 14	55 ± 10	53 ± 11
Height, cm	171 ± 8	172 ± 8	172 ± 9
Body weight, kg	73 ± 12	72 ± 13	76 ± 13
Sodium, mm	140 ± 4	140 ± 3	139 ± 3
Potassium, mm	4.0 ± 0.4	4.0 ± 0.4	4.1 ± 0.4
Creatinine, μm	77 ± 13	74 ± 14	81 ± 17
MABP at admittance, mmHg	102 ± 14	103 ± 12	103 ± 14
MABP before induction, mmHg	102 ± 14	103 ± 12	103 ± 14
Localization of tumor, n			
Frontal	19	18	12
Parietal	6	7	7
Temporal	11	6	12
Occipital	3	2	4
Other	2	5	3
Midline shift, mm	5.5 ± 5.4	4.2 ± 4.0	4.4 ± 4.1
Maximal area of tumor, cm^2	13.7 ± 3.4	13.9 ± 14.7	14.8 ± 13.7
Pathohistologic diagnosis, n			
Glioblastoma	16	10	16
Meningioma	8	12	12
Glioma	10	8	3
Metastasis	4	5	6
Other	3	3	1

Data are shown as number of patients or mean ± SD. No significant intergroup differences were observed.

MABP = mean arterial blood pressure.

fentanyl and 38 patients were allocated to the isoflurane–fentanyl and sevoflurane–fentanyl, respectively.

Demographic and neuroradiologic data are summarized in table 1. In table 2, data concerning anesthesia are summarized. Induction doses of propofol and fentanyl were statistically different with the lowest dose of propofol and the highest dose of fentanyl during propofol–fentanyl as compared with isoflurane and sevoflurane. These differences were in accordance with the study set-up. The number of patients achieving blood pressure support by ephedrine did not differ between groups, but the total dose of ephedrine used was significantly higher in the isoflurane and sevoflurane groups.

Data obtained before and after hyperventilation are summarized in table 3. Before hyperventilation, subdural ICP and $S_{jv}O_2$ were significantly lower, while MABP and CPP were significantly higher during propofol–fentanyl compared with isoflurane–fentanyl and sevoflurane–fentanyl.

During hyperventilation, ICP decreased significantly in all groups. ICP was significantly lower, while MABP and CPP were significantly higher during propofol–fentanyl compared with isoflurane–fentanyl and sevoflurane–fen-

Table 2. Data concerning Premedication, Anesthesia, Time Interval between Induction of Anesthesia and First ICP Measurement, and Ephedrine Administration

	Propofol–Fentanyl	Isoflurane–Fentanyl	Sevoflurane–Fentanyl
Premedication			
Diazepam, mg	11 ± 4	10 ± 4	12 ± 4
Anesthesia			
Propofol induction, mg/kg	1.8 ± 0.6	2.4 ± 0.7*	2.2 ± 0.4*
Propofol maintenance, $mg \cdot kg^{-1} \cdot h^{-1}$	9.2 ± 1.8	—	—
Fentanyl induction, μg/kg	3.4 ± 1.0	2.9 ± 1.0*	2.6 ± 0.8*
Fentanyl maintenance, $\mu g \cdot kg^{-1} \cdot h^{-1}$	2.2 ± 0.7	1.9 ± 0.4*	2.0 ± 0.4
MAC of volatile agent	—	0.9 ± 0.1	1.0 ± 0.0
Time between induction and ICP measurement, min	100 ± 19	102 ± 18	105 ± 18
Ephedrine administration			
Number of patients	10	15	15
Total dose, mg	9 ± 3	15 ± 2*	14 ± 3*

Data are shown as number of patients or mean ± SD. The maintenance doses of propofol and fentanyl refer to the conditions at the time of intracranial pressure (ICP) measurement.

* $P < 0.05$ compared with propofol. No significant differences were observed between the isoflurane and sevoflurane groups.

MAC = mean alveolar concentration.

Table 3. Data Obtained Before and during Hyperventilation, Changes in Parameters before and during Hyperventilation, and Carbon Dioxide Reactivity

	Propofol–Fentanyl	Isoflurane–Fentanyl	Sevoflurane–Fentanyl
Data obtained before hyperventilation			
Mean arterial pressure, mmHg	86 ± 14	73 ± 10	76 ± 10
Subdural pressure, mmHg	7.5 ± 4.9	13.0 ± 7.5*	13.2 ± 7.1*
Cerebral perfusion pressure, mmHg	78 ± 15	60 ± 12*	63 ± 8*
Jugular bulb pressure, mmHg	7.0 ± 3.5	8.5 ± 4.3	8.9 ± 3.9
$Paco_2$, mmHg	34.5 ± 3.0	34.5 ± 3.0	36.0 ± 3.0
Pao_2, mmHg	203 ± 68	197 ± 66	179 ± 67
Jugular venous oxygen saturation, %	57 ± 10	65 ± 11*	65 ± 12*
Jugular venous oxygen tension, mmHg	32 ± 4.5	35 ± 6.8	36 ± 6.8*
$AVDo_2$, mm	3.1 ± 0.8	2.5 ± 0.8*	2.5 ± 0.8*
Hemoglobin, mm	7.2 ± 0.8	7.2 ± 0.6	7.2 ± 0.7
Rectal temperature, °C	35.8 ± 0.4	36.0 ± 0.6	35.9 ± 0.7
Data obtained during hyperventilation			
Mean arterial pressure, mmHg	87 ± 13	71 ± 12	74 ± 11
Subdural pressure, mmHg	5.8 ± 4.6	9.8 ± 6.3*	9.4 ± 6.6*
Cerebral perfusion pressure, mmHg	82 ± 14	61 ± 11*	64 ± 10*
Jugular bulb pressure, mmHg	6.3 ± 3.4	8.1 ± 4.0	8.4 ± 4.2
$Paco_2$, mmHg	28.5 ± 3.0	29.3 ± 2.3	30.8 ± 3.0*
Jugular venous oxygen saturation, %	52 ± 11	57 ± 12*	56 ± 12*
$AVDo_2$, mm	3.6 ± 0.9	3.0 ± 0.9*	3.2 ± 0.8
Changes in parameters before and during hyperventilation			
Change in subdural pressure (ΔICP), mmHg	1.7 ± 2.2	3.2 ± 3.7*	3.4 ± 3.7*
Change in $Paco_2$ ($\Delta Paco_2$), mmHg	6.1 ± 2.0	5.0 ± 2.0*	4.9 ± 2.2*
Change in cerebral perfusion pressure, mmHg	3.3 ± 6.1	1.5 ± 7.4	0.2 ± 8.7
Carbon dioxide reactivity (% change in $AVDo_2$, $\Delta Paco_2$), mmHg	2.0 ± 1.4	3.6 ± 2.6*	4.6 ± 3.2*

Data are shown as mean ± SD.

* $P < 0.05$ compared with the propofol group. No significant differences were observed between the isoflurane and sevoflurane groups.

$AVDo_2$ = arteriovenous oxygen content difference; ICP = intracranial pressure.

tanyl. Hyperventilation was accompanied by a significant increase in $AVDo_2$ in all groups. During propofol–fentanyl anesthesia, $AVDo_2$ was significantly higher compared with isoflurane–fentanyl, but not significantly different from sevoflurane–fentanyl. $Paco_2$ was significantly higher in the sevoflurane group compared with the propofol group.

The carbon dioxide reactivity was significantly lower during propofol–fentanyl anesthesia compared with isoflurane–fentanyl and sevoflurane–fentanyl anesthesia, respectively. Although the difference in $Paco_2$ was significantly greater during propofol–fentanyl anesthesia, the reduction in ICP during hyperventilation was significantly smaller compared with the isoflurane–fentanyl and the sevoflurane–fentanyl groups, respectively (table 3).

The distributions of the tactile estimate of dural tension, before and during hyperventilation, and the estimates of brain swelling after opening of dura are indicated in table 4. Before and during hyperventilation, dural tension was significantly lower in the propofol–fentanyl group compared with isoflurane–fentanyl group. After opening of the dura, the degree of cerebral swelling was found to be more prominent in the isoflurane–fentanyl and sevoflurane–fentanyl groups compared with the propofol–fentanyl group.

Correlation Studies

No significant correlations were found between $Paco_2$ and ICP, between $\Delta Paco_2$ and ΔICP, or between MABP and ICP in the respective groups. We also found no significant correlation between neuroradiologic data (tumor size, midline shift) and subdural ICP obtained before hyperventilation, or between anesthetic maintenance dose of fentanyl and subdural ICP.

Discussion

In the current study, we found that subdural ICP and the incidence of brain swelling after opening of dura were significantly lower during propofol–fentanyl anesthesia compared with isoflurane–fentanyl and sevoflurane–fentanyl anesthesia.

Subdural ICP is a regional estimate of ICP and as such influenced by the presence of space-occupying processes[22] and gravity.[23] As a consequence, complete identical ICP levels are not found when subdural ICP and intraventricular pressure are compared. In recent studies, the level of subdural ICP correlated better with the degree of cerebral swelling after opening of dura compared with the neurosurgeons' estimate of dural tension performed blinded with regard to ICP level.[20–22]

In comparative studies of lumbar CSF pressure in patients without space-occupying lesion subjected to desflurane, isoflurane, sevoflurane, or propofol anesthesia, a higher CSF pressure was found during volatile anesthesia compared with propofol anesthesia.[1,11] However, in a

Table 4. Degree of Dural Tension Before Hyperventilation, during Hyperventilation, and the Degree of Brain Swelling After Opening of Dura

	Propofol–Fentanyl	Isoflurane–Fentanyl	Sevoflurane–Fentanyl
Dural tension before hyperventilation			
Dura very slack, n (%)	4 (9.8)	1 (2.6)	1 (2.6)
Normal tension of dura, n (%)	22 (53.7)	11 (28.9)	14 (36.8)
Increased tension of dura, n (%)	13 (31.7)	20 (52.6)	21 (55.3)
Pronounced increased tension, n (%)	2 (4.9)	6 (15.8)	2 (5.3)
Significant difference compared with propofol	—	$P < 0.05$	NS
Dural tension during hyperventilation			
Dura very slack, n (%)	7 (17.1)	2 (5.3)	2 (5.3)
Normal tension of dura, n (%)	24 (58.5)	16 (42.1)	23 (60.5)
Increased tension of dura, n (%)	8 (19.5)	14 (36.8)	13 (34.2)
Pronounced increased tension, n (%)	2 (4.9)	6 (15.8)	0 (0.0)
Significant difference compared with propofol	—	$P < 0.05$	NS
Degree of brain swelling after opening of dura			
No brain swelling, n (%)	30 (73.2)	16 (42.1)	21 (53.3)
Moderate brain swelling, n (%)	11 (26.8)	16 (42.1)	14 (36.8)
Pronounced brain swelling, n (%)	0 (0.0)	6 (15.8)	3 (7.9)
Significant difference compared with propofol	—	$P < 0.05$	$P < 0.05$

Data are shown as number and percentage. Chi-square tests (2×4 and 2×3 tables) were used for comparative analysis. No significant differences between the isoflurane and sevoflurane groups were observed.

study of lumbar CSF pressure in neurosurgical patients subjected to either propofol–fentanyl or thiopental–isoflurane–fentanyl anesthesia, no significant difference in lumbar CSF pressure was disclosed.[19] We suppose that subdural ICP measurement is more relevant as a regional estimate compared with lumbar CSF measurement, because tumor or cerebral edema localized close to the craniectomy increases subdural pressure more than lumbar CSF pressure. In addition, obliteration of the CSF pathway caused by transcranial herniation makes CSF pressure measurement less reliable. In another comparative study, epidural ICP was recorded through the first burr hole. A nonsignificant difference in epidural ICP, averaging 12 and 15 mmHg, in the propofol and isoflurane–nitrous oxide anesthetized patients, and significantly higher CPP and MABP in the propofol group were found. In principle, these findings corroborate with those of the current study, where a significantly lower value of subdural ICP of 7.5 mmHg and a significant higher CPP were observed in patients who received propofol in contrast to isoflurane. Methodologic differences in ICP monitoring might explain the difference in ICP. We suggest that removal of the bone flap might provide a certain degree of cerebral decompression. Similarly, our findings, indicating no significant difference between ICP in patients subjected to isoflurane compared with those subjected to sevoflurane, are in agreement with another study implicating intraparenchymal ICP measurement.[8]

In the current study, cerebral swelling after opening of the dura was more pronounced in isoflurane- and sevoflurane-anesthetized patients. The neurosurgeons were blinded to the anesthetic technique. In another study, no difference with regard to degree of cerebral swelling was disclosed between isoflurane- and propofol-anesthetized patients. However, a significant correlation between swelling score and ICP was found.[18] Time-related difference in protocols might explain the discrepancy. In the current study, ICP recording and estimation of swelling were performed simultaneously, while swelling score was assigned about 30 min after the ICP recording in the other study.

In the current study, the $S_{jv}O_2$ was significantly higher and the $AVDO_2$ significantly lower during anesthesia with isoflurane and sevoflurane compared with propofol. In accordance with recent studies in patients with supratentorial tumors where $AVDO_2$ or $S_{jv}O_2$ were similar during sevoflurane–nitrous oxide and isoflurane–nitrous oxide anesthesia,[8,24] we did not find any significant difference in $AVDO_2$ between isoflurane- and sevoflurane-anesthetized patients. The lower $AVDO_2$ during anesthesia with isoflurane or sevoflurane is in agreement with the conception that isoflurane[7] and sevoflurane[10] produce a dose-related increase in CBF, but disagree with other studies where an increases in CBF was not disclosed during isoflurane[2,3,8] or sevoflurane[8,9] anesthesia. In contrast, propofol elicits a dose-dependent correlated decease in CBF and $CMRO_2$.[14–16] In the current study, however, differences in $CMRO_2$ between propofol and inhalation anesthetics should be taken into consideration, as suggested by the equation: $AVDO_2 = CMRO_2/CBF$. During 0.7 or 1.3 MAC sevoflurane anesthesia supplemented with fentanyl for patients with supratentorial tumors, $CMRO_2$ was unchanged, averaging 1.3 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$.[10] $CMRO_2$ during propofol anesthesia administered as 6 or 12 mg $\cdot kg^{-1} \cdot h^{-1}$ was 1.9 and 1.4 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, respectively.[25] These findings suggest that $CMRO_2$ during sevoflurane and propofol anesthesia was decreased to the same level in our investigation. We therefore suggest that the differences in

jugular bulb saturation and $AVDo_2$ values between propofol and the two volatile anesthetics are caused by a higher CBF in the isoflurane and sevoflurane groups. Whether the difference in $AVDo_2$ between propofol and isoflurane–sevoflurane also influences the level of ICP is, however, a question. It has been argued that ICP probably is more related to changes in cerebral blood volume than to changes in CBF.[26–28] Furthermore, differences in resistance against reabsorption of CSF during propofol, sevoflurane, and isoflurane anesthesia potentially influence the level of ICP. While propofol and sevoflurane do not influence this parameter,[29,30] isoflurane decreases the resistance against reabsorption.[31]

In clinical studies, no changes in $AVDo_2$ or jugular oxygen tension were found during several hours of anesthesia with isoflurane, sevoflurane, or halothane.[32] In the current study, the time interval between induction of anesthesia and the ICP measurements averaged 100, 102, and 105 min, without intergroup differences. Thus, differences in adaptation of CBF between the isoflurane and sevoflurane groups are not supposed to influence CBF, cerebral blood volume, or ICP. Nor does difference in anesthetic depth in the volatile groups influence the findings, because no significant difference between the MAC values of isoflurane and sevoflurane groups was found.

Both before and after hyperventilation, a significantly higher CPP was found in the propofol group compared with the isoflurane and sevoflurane groups. Ephedrine was administered intravenously to treat decrease in blood pressure. No significant differences were found between the groups with regard to the number of patients subjected to ephedrine, but the total dose was significantly reduced during propofol anesthesia. In humans, ephedrine does not increase CBF.[33] The significant difference in total ephedrine dose found in the current study might be caused by an enhancement of pressure response to intravenous ephedrine during propofol in comparison with sevoflurane anesthesia.[34]

In clinical studies, cerebral autoregulation is preserved with propofol[35] but is impaired during 1.5 MAC isoflurane,[36] and studies of dynamic cerebral autoregulation with transcranial Doppler indicate that during 1.5 MAC sevoflurane, dynamic autoregulation is better preserved during sevoflurane than with isoflurane anesthesia.[37,38] These studies suggest that cerebral autoregulation is better preserved during propofol and sevoflurane anesthesia than during isoflurane anesthesia. As such, a higher CPP during propofol or sevoflurane anesthesia should elicit a decrease in ICP. In contrast, a low CPP during anesthesia with isoflurane might elicit a decrease in ICP if cerebral autoregulation is impaired. The question whether cerebral autoregulation influences ICP is further complicated by the fact that cerebral autoregulation might be impaired or abolished in patients with cerebral tumors.[39] In the current study, the administration of isoflurane and sevoflurane was restricted to well-defined and low MAC levels, and the maintenance doses of propofol and fentanyl were well defined. According to the protocol, we maximally accepted a 20% decrease in MABP. Otherwise, ephedrine was administered. Nevertheless, the difference in MABP between the three groups was not prevented. Consequently, it cannot be excluded that the higher ICP levels found with isoflurane and sevoflurane were influenced by autoregulatory mechanism.

In the current study, the decrease in ICP after hyperventilation averaged 1.7 mmHg in the propofol group, but 3.2 and 3.4 mmHg in the isoflurane and sevoflurane groups, respectively. The significantly greater decrease in ICP is reflected by a significantly higher carbon dioxide reactivity during anesthesia with volatile agents. This is in agreement with other clinical studies indicating a preserved carbon dioxide reactivity during anesthesia with isoflurane[3,24] or sevoflurane,[17,24,40] but decreased carbon dioxide reactivity during anesthesia with propofol.[41] Experimentally, it has been shown that carbon dioxide reactivity is at least partially determined by CPP. Reduced CPP seems to be followed by a decreased carbon dioxide reactivity.[42] Thus, the decreased carbon dioxide reactivity found in the propofol group cannot be explained by a low CPP, because CPP was significantly higher in this group. It could be argued that the differences in ΔICP, although significant statistically, are of no clinical relevance. Before hyperventilation we noticed a high ICP ($>$ 20 mmHg) in five patients in the isoflurane group and six in the sevoflurane group, while no patients in the propofol group had ICP exceeding this level. In these patients, the average decrease in ICP after hyperventilation was 6.4 mmHg for isoflurane anesthesia and 6.2 mmHg for sevoflurane anesthesia, suggesting a substantial decrease in ICP when intracranial hypertension is present. In another randomized study, ICP of 24 mmHg or greater was also found during isoflurane- in comparison with propofol-anesthetized patients.[18]

In awake healthy humans, $S_{jv}O_2$ averages 62% (range, 55–75%). In acute head injury, $S_{jv}O_2$ less than 50% suggests hypoperfusion, and readings less than 40% are supposed to be associated with cerebral ischemia.[43] In comparison with isoflurane and sevoflurane, low values of $S_{jv}O_2$ were disclosed during propofol anesthesia in patients undergoing coronary bypass,[44] and during craniotomy, a 50% incidence of $S_{jv}O_2$ less than 50% was found in patients subjected to propofol–fentanyl anesthesia but not in those anesthetized with isoflurane–nitrous oxide.[45,46] Before hyperventilation, $S_{jv}O_2$ less than 50% was found in 15% of propofol-anesthetized patients as compared with 9% and 12% in the isoflurane and sevoflurane groups. After hyperventilation, the incidences were 47%, 23%, and 33% in the respective groups. The differences in $S_{jv}O_2$ between the respective groups were not explained by difference in the level of

blood pressure or CPP, the latter being higher in the propofol group. It must be stressed that a threshold value of $S_{jv}O_2$ indicating impeding cerebral ischemia has not been defined during clinical anesthesia. Propofol is generally accepted as an agent with neuroprotective properties, and propofol-induced neurologic deterioration has never been described.

In summary, the current study indicates that, during craniotomy for cerebral tumors, subdural ICP is lower, the degree of cerebral swelling is less pronounced, and CPP is higher in patients anesthetized with propofol compared with isoflurane or sevoflurane. These differences support the view that operating conditions are better during propofol compared with isoflurane or sevoflurane anesthesia.

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