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Cerebral Blood Flow and CO₂ Reactivity Is Similar during Remifentanil/N₂O and Fentanyl/N₂O Anesthesia

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Background: Remifentanil, a rapidly metabolized μ-opioid agonist, may offer advantages for neurosurgical procedures in which prolonged anesthetic effects can delay assessment of the patient. This study compared the effects of remifentanil–nitrous oxide on cerebral blood flow (CBF) and carbon dioxide reactivity with those of fentanyl–nitrous oxide anesthesia during craniotomy.

Methods: After institutional approval and informed patient consent were obtained, 23 patients scheduled to undergo supratentorial tumor surgery were randomly assigned to remifentanil or fentanyl infusion groups in a double-blinded manner. Midazolam, thiopental, and pancuronium induction was followed by equipotent narcotic loading infusions of remifentanil ($1 \ \mu g \cdot kg^{-1} \cdot min^{-1}$) or fentanyl ($2 \ \mu g \cdot kg^{-1} \cdot min^{-1}$) for 5–10 min. Patients were ventilated with 2:1 nitrous oxide–oxygen, and opioid rates were reduced and then titrated to a stable hemodynamic effect. After dural exposure, CBF was measured by the intravenous ¹³³xenon technique at normocapnia and hypocapnia. Reactivity of CBF to carbon dioxide was calculated as the absolute increase in CBF per millimeters of mercury increase in the partial pressure of carbon dioxide (Pa_{CO_2}). Data were analyzed by repeated-measures analysis of variance, unpaired Student's *t* tests, or contingency analysis.

Results: In the remifentanil group (n = 10), CBF decreased from 36 ± 11 to $27 \pm 8 \ ml \cdot 100 \ g^{-1} \cdot min^{-1}$ as Pa_{CO_2} decreased from 33 ± 5 to 25 ± 2 mmHg. In the fentanyl group (n = 8), CBF decreased from 37 ± 11 to $25 \pm 6 \ ml \cdot 100 \ g^{-1} \cdot min^{-1}$ as Pa_{CO_2} decreased from 34 ± 3 to 25 ± 3 mmHg. Absolute carbon dioxide reactivity was preserved with both agents: $1 \pm 1.1 \ ml \cdot 100 \ g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$ for remifentanil and $1.5 \pm 0.8 \ ml \cdot 100 \ g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$ for fentanyl ($P = 0.318$).

Conclusion: Remifentanil and fentanyl have similar effects on absolute CBF, and cerebrovascular carbon dioxide reactivity is maintained. (Key words: Cerebral blood flow; CO₂ reactivity; fentanyl; remifentanil.)

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OPIOID – NITROUS oxide anesthesia is commonly used for neurosurgical procedures. It is important during neurosurgery to know the effects of anesthetic agents on cerebral blood flow and cerebrovascular reactivity to changes in the partial pressure of carbon dioxide (Pa_{CO_2}). It is also desirable for patients undergoing neurosurgery to be exposed to an anesthetic that will allow rapid postoperative assessment.

Remifentanil hydrochloride is a μ-opioid agonist that is metabolized by blood and tissue esterases. This esterase metabolism results in an ultrashort elimination half-life ($t_{1/2} \ \beta$) of less than 10 min and is characterized by lack of accumulation in the blood or tissue with repeated or prolonged administration.[1–3] In an open-label clinical trial, remifentanil did not appear to cause cerebral vasodilation or to impair patient responsiveness to carbon dioxide.[4]

Fentanyl – nitrous oxide is used frequently for anesthesia for treatment of supratentorial lesions, and much is known about its effects on cerebral hemodynamics.[5] However, fentanyl has a half-life ($t_{1/2} \ \beta$) of 219 min and depends on redistribution to terminate its effect, which may delay postoperative patient assessment.[6,7] This randomized double-blinded study was performed to directly compare the cerebral blood flow and carbon di-

oxide reactivity of remifentanil–nitrous oxide with fentanyl–nitrous oxide anesthesia in patients undergoing craniotomy for supratentorial lesions.

Methods

This protocol was part of a multicenter study to compare the safety and effectiveness of remifentanil and fentanyl in adult patients scheduled for craniotomy for elective resection of supratentorial mass lesions. Cerebral blood flow measurements were performed at our institution only, because of specialized data collection and analysis expertise. Patient medical histories were reviewed, and those with symptomatic cardiopulmonary, hepatic, or renal disease or obesity were excluded. No patient received opioid medication within 2 days before the planned operation. After Institutional Review Board approval and informed consent, 23 patients were enrolled and randomly assigned to receive either remifentanil (REMI; Ultiva; Glaxo-Wellcome, Research Triangle Park, NC) or fentanyl (FENT; Sublimaze; Janssen, Titusville, NJ) in a double-blinded manner. Preoperative computed tomographic or magnetic resonance images were reviewed for mass effect or significant midline shift. Blood pressure was recorded at the time of screening and on the morning of surgery.

After enrollment, the research pharmacist prepared the opioid infusion syringes according to the randomization schedule. Syringes were prepared for each phase of the procedure as described by Guy et al.[8] The drugs were diluted to result in similar volumes that would allow equipotent infusions on a micrograms-per-kilogram-per-minute basis, thereby keeping investigators blinded as to which opioid was being given.

When patients arrived in the operating room, standard perioperative monitors were applied. These included an automated blood pressure cuff, a radial artery catheter for blood pressure recording and blood gas analysis, an electrocardiogram, a pulse oximeter, an esophageal stethoscope/temperature probe, a bladder catheter, a peripheral nerve blockade monitor, anesthesia agent monitors, and a capnograph. The patient's blood pressure was again recorded. The lowest two preoperative systolic blood pressures were averaged and used as the baseline to evaluate systemic hemodynamic responses, and subsequently to titrate the opioid infusions.

Anesthesia was induced with midazolam (0.01–0.08 mg/kg) and thiopental (3–7 mg/kg). Pancuronium (0.11–0.14 mg/kg) was given to facilitate tracheal intubation.

Equipotent opioid loading infusions were administered (REMI, $1~\mu g \cdot kg^{-1} \cdot min^{-1}$; FENT, $2~\mu g \cdot kg^{-1} \cdot min^{-1}$) for 5–10 min. Chest wall rigidity, if present, was noted. If necessary, an additional 50–150 mg thiopental could be administered for laryngoscopy and intubation.

After tracheal intubation, patients were ventilated with nitrous oxide and oxygen (in a 2:1 ratio) to a Pa_{CO_2} of 28 mmHg, and the opioid infusion was decreased to the maintenance level (REMI, $0.2~\mu g \cdot kg^{-1} \cdot min^{-1}$; FENT, $0.03~\mu g \cdot kg^{-1} \cdot min^{-1}$). The infusion was subsequently titrated to hemodynamic effect, maintaining the systolic blood pressure within 15% of the baseline values and the pulse between 45 and 90 beats/min. Hemodynamic variables were recorded throughout the surgical procedure and during the immediate postoperative period.[8] Systemic hemodynamic responses suggestive of inadequate depth of anesthesia, defined as systolic blood pressure 15 mmHg higher than the calculated baseline or heart rate > 90 beats/min, lasting > 1 min, were treated with an opioid bolus (REMI, 1 µg/kg; FENT, 2 µg/kg) to a maximum of five administrations. The opioid infusion rate could also be increased to a maximum of $0.4~\mu g \cdot kg^{-1} \cdot min^{-1}$ for REMI or $0.06~\mu g \cdot kg^{-1} \cdot min^{-1}$ for FENT. If additional anesthesia was necessary, isoflurane was added to the inspired gas mixture. Phenylephrine, ephedrine, atropine, labetalol, and esmolol were also given as deemed necessary by the attending anesthesiologist to control hemodynamic variables. Pancuronium was administered to maintain paralysis. A spinal drain was placed as deemed necessary by the surgeon. After dural exposure, the surgeon assessed the quality of brain relaxation according to the following scale: (1) excellent, (2) minimal swelling, (3) serious swelling, and (4) severe swelling requiring intervention.

After dural exposure and a minimum of 15 min after the last opioid infusion adjustment, carbon dioxide was added to the inspired gas mixture to increase the Pa_{CO_2} by 10 mmHg to achieve relative normocapnia. Regional CBF was determined by the intravenous ^{133}xenon method using a Cerebrograph 10a (Novo Diagnostic Systems, Bagsvaerd, Denmark), which was described and validated previously.[9] Briefly, a sodium iodine scintillation detector was placed over the middle cerebral artery distribution contralateral to the operative site. The CBF was measured by injecting 15–20 mCi ^{133}Xe in saline into the saphenous vein, followed by a saline flush. Tracer washout was recorded for 11 min. The carbon dioxide was then discontinued, and, after equilibrium at mild hypocapnia, CBF was again measured. In both instances, CBF was measured during periods of minimal surgical stimulation. For each CBF measurement, an arterial blood sample was drawn

Table 1. Patient Demographics and Tumor Characteristics

	Remifentanil	Fentanyl
Number	10	8
Gender		
Male	5	5
Female	5	3
Age (yr)	48 ± 13	41 ± 12
Weight (kg)	79 ± 12	80 ± 21
Maximum tumor diameter (cm)	4.0 ± 1.3	4.2 ± 2.3
Midline shift (mm)	7 ± 9	8 ± 8
Mass effect (observed frequency)		
None	2	2
Mild	4	2
Moderate	1	1
Severe	3	3

Values are mean ± SD. There were no significant differences between groups.

for Pa_{CO_2} and hematocrit determinations. Hemodynamic parameters (mean arterial pressure and heart rate) were also recorded. The CBF was calculated using the Initial Slope Index.[10,11] Reactivity of CBF to carbon dioxide was calculated both as absolute increase in CBF per milliliter of mercury increase in Pa_{CO_2} and as a percentage increase in CBF per milliliter of mercury increase in Pa_{CO_2}.

At bone flap replacement, the opioid maintenance infusion syringe was replaced. Because of the differing half-lives of the opioids and to maintain the blinded nature of the study, the replacement syringe contained either the same concentration of remifentanil for the REMI group or a saline placebo for the fentanyl group. Infusion was continued at the maintenance rate. For prophylactic treatment against emergence hypertension, labetalol or hydralazine or both could be administered. At the end of the procedure, neuromuscular blockade was reversed, and the opioid infusion and nitrous oxide were discontinued simultaneously. The trachea was extubated when patients were able to follow commands and demonstrate adequate spontaneous ventilation.

Time from discontinuation of nitrous oxide and opioid infusion to extubation was recorded. The presence of emergence delirium, nausea, vomiting, or respiratory depression were noted. To assess intraoperative recall, on the first postoperative day patients were asked "Do you remember anything about your operation?"

Statistical Analysis

For parametric data, comparisons were made by repeated measures of analysis of variance or unpaired Student's *t* tests. Nonparametric data were compared using contingency analysis. Data are expressed as mean ± SD. Significance was taken at $P < 0.05$.

Results

Twenty-three patients were enrolled in the study. Four patients were excluded from the CBF analysis because of technical problems. One patient was excluded because of an acute hemorrhage with bone flap elevation and abortion of the surgical procedure. Thus, the data reflect 10 remifentanil and 8 fentanyl patients. There were no differences between anesthetic groups with respect to gender, age, or weight (table 1). There were no differences between groups with regard to tumor size, midline shift, or mass effect (table 1). No patient had chest wall rigidity during induction. Five patients (three REMI, two FENT) received additional thiopental (25–75 mg) during intubation.

In the patients analyzed, there were no difficulties with surgical exposure. Brain relaxation was comparable between groups (table 2), and was scored as either "excellent" or "minimal swelling" in most patients. Only one patient in each group had swelling rated as "serious" but not necessitating treatment. Only one patient, in the FENT group, had a spinal drain placed. Brain relaxation for this patient was scored as excellent. Before the normocapnic CBF measurement, 20 ml CSF was removed. This patient's absolute CBF and reactivity to carbon dioxide were similar to those of others in the FENT group.

Table 3 summarizes physiologic measurements for the normocapnic and hypocapnic CBF determinations. During the two CBF measurements in the REMI group there were no significant differences in mean arterial pressure, heart rate, hematocrit level, or esophageal temperature. The CBF was responsive to changes in Pa_{CO_2} (table 2). As the Pa_{CO_2} decreased from 33 ± 5 mmHg to 25 ± 2 mmHg there was a corresponding decrease in

Table 2. Brain Relaxation Scores

	Remifentanil	Fentanyl
Number	10	8
(1) Excellent	5	4
(2) Minimal swelling	4	3
(3) Serious swelling	1	1
(4) Severe swelling	0	0

There were no differences between groups.

Table 3. Cerebral Blood Flow Data

	Normocapnia		Hypocapnia	
	Remifentanil	Fentanyl	Remifentanil	Fentanyl
CBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	36 ± 11	37 ± 11	27 ± 8*	25 ± 6†
Pa_{CO_2} (mmHg)	33 ± 5	34 ± 3	25 ± 2*	25 ± 3†
Absolute CO_2 ($ml \cdot 100\ g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$)	1.0 ± 1.2	1.5 ± 0.5		
Relative CO_2 reactivity (%/mmHg)	2.6 ± 3.6	4.5 ± 2.2		
Maintenance infusion dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.22 ± 0.12	0.05 ± 0.02	0.22 ± 0.11	0.05 ± 0.02
MAP (mmHg)	91 ± 8	92 ± 9	92 ± 7	93 ± 12
HR (beats/min)	64 ± 7	70 ± 14	67 ± 11	70 ± 12
T_{eso} (°C)	34.9 ± 0.5	35.4 ± 0.4*	34.9 ± 0.7	35.0 ± 0.8
Hct (%)	35 ± 5	36 ± 6	35 ± 4	36 ± 4
Crystalloid infused‡ (ml)	1,335 ± 342	1,575 ± 431	1,405 ± 302	1,506 ± 235

Values are mean ± SD.

CBF = cerebral blood flow; Pa_{CO_2} = arterial partial pressure of carbon dioxide; MAP = mean arterial pressure; HR = heart rate; T_{eso} = esophageal temperature; Hct = hematocrit.

* Significantly different from remifentanil normocapnia.

† Significantly different from fentanyl normocapnia.

‡ Total crystalloid infused at start of CBF measurement.

CBF from $36 \pm 11\ ml \cdot 100\ g^{-1} \cdot min^{-1}$ to $27 \pm 8\ ml \cdot 100\ g^{-1} \cdot min^{-1}$ (fig. 1).

Similarly, in the FENT group there were no significant differences in mean arterial pressure, heart rate, hematocrit level, or esophageal temperature between CBF measurements. The CBF decreased from $37 \pm 11\ ml \cdot 100\ g^{-1} \cdot min^{-1}$ to $25 \pm 6\ ml \cdot 100\ g^{-1} \cdot min^{-1}$ as the Pa_{CO_2} decreased from 34 ± 3 mmHg to 25 ± 3 mmHg (fig. 1).

There were no significant physiologic differences between the REMI and FENT groups at normocapnia, except for esophageal temperature, which was higher in the FENT (35.4 ± 0.4°C) group than in the REMI group (34.9 ± 0.5°C; P = 0.04). For the hypocapnic measurement there were no differences between groups. No patient received isoflurane during the CBF measurements. The CBF determinations were separated by 32 ± 12 min in the REMI group and by 64 ± 76 min in the FENT group (P = 0.195).

Absolute carbon dioxide reactivity was preserved with both agents: $1 \pm 1.2\ ml \cdot 100\ g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$ for remifentanil and $1.5 \pm 0.5\ ml \cdot 100\ g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$ for fentanyl, P = 0.318). The relative CBF reactivity was 2.6 ± 3.6%/mmHg carbon dioxide for REMI and 4.5 ± 2.2%/mmHg carbon dioxide for FENT (P = 0.197).

Systemic hemodynamic responses suggestive of inadequate anesthesia, defined as a heart rate > 90 beats/min, systolic blood pressure > 15 mmHg above baseline, or patient movement, were similar between the groups. One patient in the FENT group reported being aware of the last few sutures but denied any distress or awareness of conversation during the head wrap. One patient in the REMI group had emergence delirium.
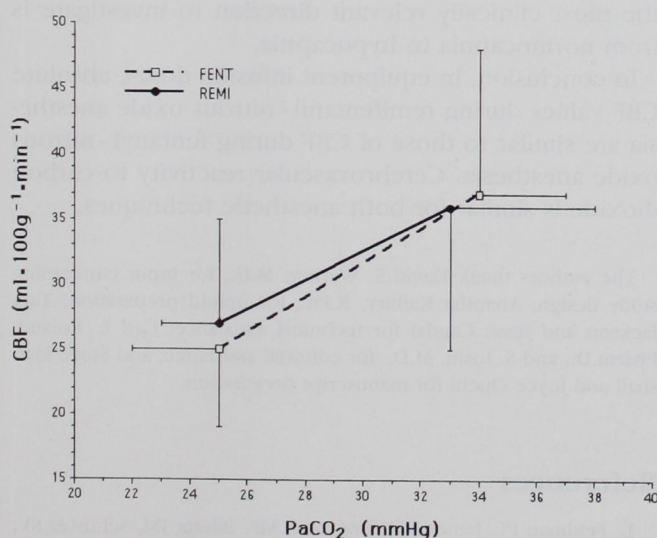

Fig. 1. Comparison of cerebral blood flow (CBF) for remifentanil (*closed circles*) and fentanyl (*open squares*) at normocapnia and hypocapnia. Error bars indicate SD. There was no significant difference between the two groups with changes in the carbon dioxide tension.

Discussion

This investigation shows that, in humans, absolute CBF values during remifentanil-nitrous oxide anesthesia are

similar to those of fentanyl–nitrous oxide anesthesia. These values are also similar to the historical values reported during neurosurgical anesthesia with sufentanil–nitrous oxide, isoflurane–nitrous oxide,[12] or desflurane,[13] and with our previous reports from an open-label study with remifentanil–nitrous oxide.[4] Furthermore, cerebrovascular carbon dioxide reactivity remained intact during remifentanil–nitrous oxide administration. The absolute carbon dioxide reactivity of 1 ± 1.2 ml $\cdot$ 100 $g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$ for remifentanil is similar to that of sufentanil (1.1 ± 0.2 ml $\cdot$ 100 $g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$), whereas the value for fentanyl (1.5 ± 0.5 ml $\cdot$ 100 $g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$) is slightly higher than the value for sufentanil, as previously reported by our group using the same method.[14] These CBF results correspond with those of Hoffman *et al.*,[15] who found that remifentanil did not cause cerebral vasodilation in dogs anesthetized with isoflurane–nitrous oxide. The small sample size of this CBF study was selected primarily based on the needs of the larger multicenter study. However, the CBF values and carbon dioxide reactivity observed with remifentanil–nitrous oxide anesthesia are within the ranges of other anesthetics and are comparable to the values for the fentanyl group.[4,12,13] Although this sample size was not sufficiently powered to detect a difference in the mean carbon dioxide reactivities of the magnitude reported, it is highly unlikely that, even if this difference existed, it would be clinically meaningful. The convention of reporting carbon dioxide reactivity is based on a linear model, when the carbon dioxide response curve is sigmoidal. Both of our drug groups could be hyperventilated to a clinically relevant Pa_{CO_2} with a corresponding appropriate reduction in CBF. The different slopes of the responses may be an artifact of where on the sigmoidal CBF–carbon dioxide response curve the patients were measured. Therefore, it is highly unlikely that a larger sample would yield further clinically useful information.

The surgical time requirements for dural exposure and opening resulted in variability in the timing of the CBF measurements. Although we cannot preclude the possibility of a time effect on CBF during narcotic infusion, previously our group documented a lack of a time effect of prolonged inhalational anesthesia on CBF in a similar patient population.[13] There was approximately a 0.5°C difference between the REMI and FENT groups at the normocapnic measurement. Based on previous reports concerning the effect of temperature on CBF, this could have resulted in an overestimation of CBF of some 4% or 5% for the FENT group compared with the REMI group.[16]

Knowledge of the cerebral hemodynamic profile of a drug facilitates the anesthetic management of a patient with compromised intracranial compliance. An anesthetic that causes cerebral vasodilation may cause difficulty with surgical exposure and necessitate greater brain retraction pressure and increase the potential for ischemia. Cerebral vasodilation can also theoretically increase intracranial pressure and lead to herniation, although vasodilating anesthetics (particularly isoflurane and nitrous oxide) have a long record of safe use. Nonetheless, an anesthetic with vasodilating properties may not be the most appropriate choice for a patient with neurologic compromise from increased intracranial pressure. Cerebral blood flow responses to differing levels of carbon dioxide are important to document. Hyperventilation remains an important therapeutic intervention to decrease cerebral blood volume, brain bulk, and intracranial pressure. Agents that impair the CBF effects of hyperventilation would have limited clinical use. We tested decreasing Pa_{CO_2} and found that carbon dioxide responsiveness associated with decreasing Pa_{CO_2} was similar in the FENT and REMI groups, with values that are comparable to historical controls for other anesthetics. It is reasonable to assume that the reverse maneuver (hypocapnia to normocapnia) generally should be intact in the range studied. We doubt that the order of Pa_{CO_2} level could introduce any meaningful error into the CBF measurements; however, any error should be similar in both groups. In any event, the most clinically relevant direction to investigate is from normocapnia to hypocapnia.

In conclusion, in equipotent infusion doses, absolute CBF values during remifentanil–nitrous oxide anesthesia are similar to those of CBF during fentanyl–nitrous oxide anesthesia. Cerebrovascular reactivity to carbon dioxide is similar for both anesthetic techniques.

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