British Journal of Anaesthesia **86 (1)**: 44–9 (2001)

Recovery and neurological examination after remifentanil–desflurane or fentanyl–desflurane anaesthesia for carotid artery surgery

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We studied 44 patients undergoing carotid endarterectomy (CEA) to compare recovery after general anaesthesia with desflurane supplemented with either remifentanil or fentanyl. Remifentanil was infused at 0.1 μg kg^{-1} min^{-1} and desflurane was adjusted at 2 vol% end-tidal. Fentanyl was given as a bolus dose of 2 μg kg^{-1} before induction and repeated at skin incision; desflurane was adjusted as needed. Times for early recovery and response to simple neurological tests (digit symbol substitution test (DSST) and Trieger dot test (TDT)) were measured 30, 60 and 90 min after operation. Emergence from remifentanil–desflurane anaesthesia was significantly quicker than that from fentanyl–desflurane anaesthesia: mean times to extubation were 4.1 (SD 1.7) and 8.2 (4.9) min, respectively; mean times for patients to state their name correctly were 6.0 (2.8) and 13.8 (9.0) min, respectively. Patients in the remifentanil–desflurane group successfully performed neurological tests significantly earlier than those in the fentanyl-desflurane group; for example, patients in the former group completed the arm holding test at 7.9 (3.0) min, while those in the latter group did this at 20.6 (19.7) min ($P \leq 0.01$). Intermediate recovery was less impaired at 30 min (DSST, TDT) and at 60 min (DSST). More rapid awakening and an earlier opportunity for neurological examination suggest that remifentanil–-desflurane is a suitable alternative to a standard fentanyl-based general anaesthetic technique in patients undergoing CEA.

Br J Anaesth 2001; **86**: 44–9

Keywords: analgesics opioid, remifentanil; analgesics opioid, fentanyl; anaesthetics volatile, desflurane; surgery, carotid endarterectomy; recovery, postoperative

Accepted for publication: August 30, 2000

Carotid artery surgery carries the risk of substantial complications; in some cases (such as dissection, thrombosis or haemorrhage), the damage can be reduced if complications are diagnosed early and treated promptly.[1–3] Therefore, rapid recovery and early neurological assessment are useful goals in the anaesthetic management of patients undergoing carotid endarterectomy (CEA). The combination of short-acting anaesthetics such as remifentanil and desflurane may be superior to a standard fentanyl general anaesthetic technique. We compared early and neurological testing of patients undergoing elective CEA who were randomly assigned to receive general anaesthesia with remifentanil–desflurane or fentanyl-desflurane.

Patients and methods

Preinduction

With institutional review board approval and written informed consent, we enrolled 44 adult male and female patients in a prospective randomized two-group study. All patients were classified as ASA physical status II or III and scheduled for elective CEA because of a narrowing of the carotid artery lumen of ⩾80% in asymptomatic or ⩾70% in symptomatic patients. Exclusion criteria were a history of any disabling central nervous disease, hypersensitivity to opioids or substance abuse, or a treatment with opioids or

any psychoactive medication. After enrollment patients were randomized by drawing lots from a closed box.

Induction and maintenance

On the morning of surgery, all patients were given 5 mg of diazepam orally 90 min before induction. In the operating room, two intravenous catheters were inserted and the radial artery was cannulated. Standard monitors were applied. Before induction, all patients were given 5 ml kg^{-1} of a 3% gelatin infusion intravenously.

In the fentanyl–desflurane group, induction started with a dose of fentanyl 2 μg kg^{-1}. Five minutes later etomidate was given for hypnosis, initially starting at 0.15 mg kg^{-1} and then at 2 mg every 10 s until the patient was unresponsive to verbal command. The desflurane vaporizer was then set to 3 vol% and ventilation with desflurane in oxygen was given as required. Patients were then given 0.1 mg kg^{-1} of cisatracurium, the trachea was intubated 3 min later and the lungs were ventilated to achieve normocapnia, using desflurane and 66% nitrous oxide in oxygen. Five minutes before skin incision, another 2 μg kg^{-1} bolus dose of fentanyl was injected and desflurane was added as needed for maintenance, starting at an end-tidal concentration of 4 vol% (=2/3 MAC).

In the remifentanil–desflurane group, all patients were given atropine 5 μg kg^{-1} followed by remifentanil 1 μg kg^{-1}, injected over 30 s, and an infusion of remifentanil was started simultaneously at 0.1 μg kg^{-1} min^{-1}. Five minutes later, etomidate was given, followed by desflurane and cisatracurium as described above. Five minutes after intubation remifentanil was reduced to 0.05 μg kg^{-1} min^{-1} and then readjusted to 0.1 μg kg^{-1} min^{-1} 3 min before skin incision. Maintenance of anaesthesia consisted of remifentanil infused at 0.1 μg kg^{-1} min^{-1}, with desflurane added to obtain an end-tidal concentration of 2 vol% (=1/3 MAC).

In both groups, according to our department's policy, nitrous oxide was discontinued 5 min before the carotid artery was cross-clamped; the lungs were then ventilated with desflurane in oxygen until the end of the operation.

Monitoring and haemodynamic control

Continuous monitoring included heart rate (HR), systemic arterial pressure, respiratory rate, oxygen saturation and end-tidal concentrations of carbon dioxide and desflurane. Arterial blood gases were analysed intermittently and the Pa_{CO_2} was maintained between 4.8–5.9 kPa (36–44 mm Hg). The oxygen saturation was measured by pulse oximetry and maintained above 95%. Transcranial Doppler ultrasound was continuously applied, by a neurologist (M.M.), to the ipsilateral middle cerebral artery to measure mean blood velocity during surgery and cross-clamping (for the exact technique see ref. 4).

Baseline systolic arterial pressure (SAP) was defined as the lower of the two measurements obtained the day before surgery and immediately before induction of anaesthesia. The definition of adverse haemodynamic responses was adapted from Garrioch and Fitch:[1] responses of ⩾1 min of duration were classified as 'hypertension' (SAP>40 mm Hg from baseline or >200 mm Hg), 'hypotension' (SAP<40 mm Hg from baseline or <100 mm Hg), 'tachycardia' (HR>100 beats min^{-1}) and 'bradycardia' (HR<45 beats min^{-1}). Inadequate anaesthesia was defined as hypertension, tachycardia or patient movement, eye opening, swallowing, grimacing, lacrimation or sweating.

In the fentanyl–desflurane group, if anaesthesia was inadequate the end-tidal desflurane concentration was increased in steps of 0.5 vol% as necessary. If this was judged insufficient, then an additional bolus dose of 0.5 μg kg^{-1} fentanyl could be injected. Hypotension was initially treated with i.v. fluid replacement; desflurane was then reduced in steps of 0.5 vol%, and finally, an i.v. vasopressor (cafedrine/theodrenaline) was given at a dose chosen by the investigator. In the remifentanil–desflurane group, if anaesthesia was inadequate the infusion rate was increased by 0.05 μg kg^{-1} min^{-1} or a bolus dose of 1 μg kg^{-1} was injected; both interventions were repeated as necessary. If this was insufficient, desflurane was increased by 0.5 vol% end-tidal. Hypotension was initially treated with i.v. fluids; the remifentanil infusion rate was then reduced to a permitted minimum of 0.05 μg kg^{-1} min^{-1}; finally, an i.v. vasopressor was used as described above. In both groups bradycardia was treated with 0.25 mg of atropine.

Recovery period

Fifteen minutes before the expected end of surgery, complete neuromuscular recovery was ensured by neuromuscular monitoring; all patients received a 100 ml infusion of 0.9% NaCl containing metamizol 25 mg kg^{-1} for postoperative pain relief. The end of surgery was defined as the final surgical suture, when anaesthetic delivery was stopped. During recovery, a post-anaesthetic recovery score (PARS), as defined by Aldrete and Kroulik,[5] was recorded continuously. Oxygenation was maintained by intermittent positive pressure ventilation using a fresh gas flow of 10 litres min^{-1} of 100% oxygen until spontaneous respiration returned. Emergence from anaesthesia was assessed by measuring the times to return of spontaneous ventilation, extubation, response to verbal command (opening eyes, stating name and date of birth) and when the Aldrete score became 9 or above.

All patients were then moved to the post-anaesthesia care unit (PACU), where observation was continued by an investigator and a PACU nurse, neither of whom was aware of the anaesthetic regimen. If further pain relief was requested, patients could be given bolus doses of 3 mg piritramide at the discretion of the attending nurse. Each patient was continuously observed for neurological deficits, and the times (expressed as minutes from end of surgery) taken for the patient to be able to perform the arm and the

leg holding tests were recorded. The depth of sedation was assessed for the first 60 min after the end of surgery using a five-point scale for observer assessment of alertness/sedation: 1=asleep, unarousable; 2=asleep, difficult to rouse; 3=asleep, easy to rouse; 4=awake and calm; 5=awake but anxious.

Intermediate recovery was assessed by the Trieger dot test (TDT), in which individuals are asked to connect a series of 50 dots of a geometrical figure,[6] and by the digit symbol substitution test (DSST), in which individuals are asked to match numbers with predefined symbols during a 120 s period (adapted from refs [7] and [8]). All patients had completed a first series of these tests on the day before surgery, with the results serving as baseline values. Thirty, 60 and 90 min after the end of surgery, both tests were repeated; the results are expressed as a percentage of baseline.

End-points and statistical analysis

The primary end-point of this study was defined as the time taken to respond to verbal command (state the correct name). Applying an *a priori* power analysis, at least 17 patients had to be enrolled in each treatment group to provide 80% power to detect a difference of 3 min at α=0.05. Statistical analysis was performed by means of the Mann–Whitney *U*-test for numerical data and Fisher's exact test for nominal data. All tests were two-tailed with statistical significance defined as $P<0.05$; data are presented as mean and standard deviation (SD) in the tables or standard error (SEM) in the figures. Statistical analysis was planned and performed in collaboration with a statistician of the Institute of Medical Biometrics, Epidemiology and Informatics, University of Saarland, using SPSS computer software (version 7.5.2G; SPSS Inc.).

Results

Forty-four patients were enrolled in this study (23 in the remifentanil group and 21 in the fentanyl group); the groups were similar with respect to age, weight, height, ASA physical status and duration of surgery (Table 1). With remifentanil, less etomidate was necessary to achieve a loss of consciousness during induction of anaesthesia. At the end of surgery, the mean end-tidal desflurane concentration was significantly lower (1.9 (SD 0.2) vol%) than with fentanyl (3.5 (1.4) vol%). Carotid artery cross-clamping times were similar in both groups but, by chance, significantly more patients with remifentanil–desflurane had surgery on the left (dominant hemisphere) side.

Overall, haemodynamic responses (i.e. the courses of HR and mean arterial pressure) were similar for both treatment groups: mean arterial pressure did not differ throughout surgery and was significantly less with remifentanil than with fentanyl only immediately before and 1 min after intubation (Table 2). Intervention with a vasopressor (cafedrine/theodrenaline) was used in 70% of all patients (78% with remifentanil, 62% with fentanyl (P=0.33)) and there was no difference in the amount of drug given per treated patient (0.92 (0.61) or 0.92 (0.43) ml).

Table 1 Patient, surgical, anaesthetic and neurological characteristics; values are mean (SD) or number of patients (% of total group). CXC=carotid artery cross-clamping. †End-tidal desflurane concentration at the end of surgery without tapering. *Significant difference between the two treatment groups ($P<0.05$)

	Remifentanil–desflurane	Fentanyl–desflurane
Number of patients	23	21
Gender (male/female)	16/7	12/9
Age (yr)	64.0 (44–76)	62.4 (43–77)
Height (cm)	168.2 (7.1)	167.6 (7.9)
Weight (kg)	73.5 (9.8)	77.6 (10.5)
ASA physical status, *n* (%)		
ASA II	4 (17%)	5 (24%)
ASA III	19 (83%)	16 (76%)
Duration of surgery (min)	100.9 (23.0)	110.4 (18.1)
Side of operation (left/right)	16/7	5/16*
Duration of anaesthesia (min)	138.5 (25.6)	148.8 (19.6)
Fentanyl (mg)	–	0.35 (0.1)
Etomidate (mg)	20.7 (5.5)	25.5 (7.3)*
Desflurane (vol%)†	1.9 (0.2)	3.5 (1.4)*
Duration of CXC (min)		
Without shunt	44.4 (13.1) (*n*=19)	49.8 (18.8) (*n*=18)
With shunt	9.8 (5.9) (*n*=4)	10.3 (5.7) (*n*=3)

Table 2 Mean (SD) cardiovascular variables before and after induction of anaesthesia and during carotid artery sugery; *$P<0.05$ and **$P<0.01$ between groups. CXC=carotid artery cross-clamping

	Mean arterial pressure (mm Hg)		Heart rate (bpm)	
	Remifentanil–desflurane	Fentanyl–desflurane	Remifentanil–desflurane	Fentanyl–desflurane
Baseline	111.7 (17.5)	116.4 (13.6)	74.7 (11.1)	78.0 (14.3)
Before intubation	82.7 (16.0)	92.7 (16.0)*	62.1 (13.3)	66.5 (11.6)
1 min after intubation	110.9 (23.1)	131.8 (24.9)**	76.3 (15.0)	86.2 (20.5)
5 min after intubation	95.7 (22.7)	93.4 (20.5)	67.3 (15.2)	69.0 (15.8)
Before CXC	93.7 (16.0)	92.1 (11.9)	64.3 (8.3)	73.1 (14.1)*
End of surgery	86.1 (17.4)	90.4 (12.7)	63.1 (8.7)	65.5 (11.3)

Table 3 Recovery times (min) after discontinuation of anaesthetics. PARS=Post-anaesthetic recovery score. Values are mean (SD); *n*=number of patients

	Remifentanil–desflurane (*n*=22)	Fentanyl–desflurane (*n*=20)	*P*
Spontaneous ventilation	3.9 (1.6)	6.4 (5.0)	0.09
Opening eyes	3.8 (1.6)	8.0 (5.3)	<0.01
Extubation	4.1 (1.7)	8.2 (4.9)	<0.01
Stating name	6.0 (2.8)	13.8 (9.0)	<0.001
Stating date of birth	6.2 (2.8)	14.9 (10.8)	<0.001
PARS ⩾9	6.4 (2.9)	16.4 (17.7)	<0.01
Arm holding test	7.9 (3.0)	20.6 (19.7)	<0.001
Leg holding test	12.2 (17.6)	33.9 (27.6)	<0.001

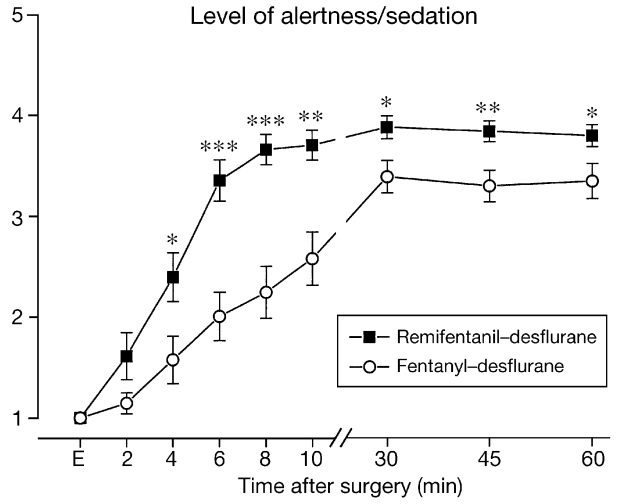

Fig 1 Mean (SEM) scores of an observer-assessed alertness/sedation scale (1=asleep, unarousable; 2=asleep, difficult to rouse; 3=asleep, easy to rouse; 4=awake and calm; 5=awake but anxious). E=End of surgery. Differences between the treatment groups were statistically significant: ***P<0.001, **P<0.01 and *P<0.05.

Recovery period

After awakening, a major stroke was found in one patient in each treatment group. Consequently, early recovery times were recorded for 22 patients in the remifentanil group and for 20 patients in the fentanyl group. Apart from the onset of spontaneous ventilation, recovery times were significantly shorter after remifentanil–desflurane: tracheal extubation was possible sooner and patients could open their eyes sooner and state their name and date of birth correctly sooner. Neurological tests could be carried out significantly earlier (Table 3).

The sedation score showed that patients after remifentanil–desflurane anaesthesia were significantly more alert than those after fentanyl–desflurane anaesthesia, and a significant difference was noted even 60 min after the end of surgery (Figure 1).

Psychomotor and cognitive performance was assessed by DSST and TDT scores in 20 patients in each group. Two patients in the remifentanil group could not be investigated: one patient underwent surgical treatment for superficial wound bleeding, and another refused to participate in that

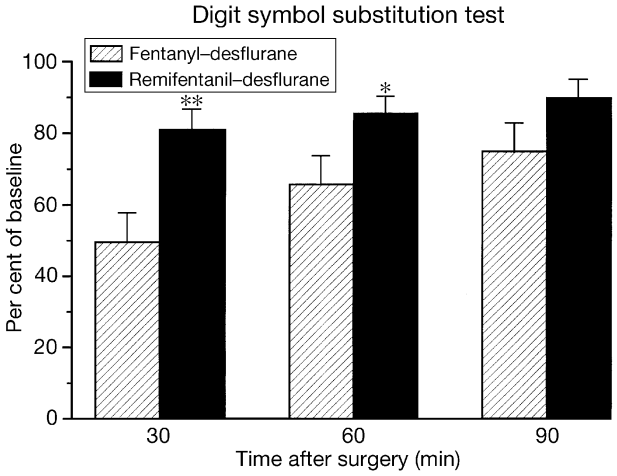

Fig 2 Mean (SEM) results of the digit symbol substitution test 30, 60 and 90 min after the end of surgery, expressed as percentage of baseline. Differences between the treatment groups were statistically significant: **P<0.01, *P<0.05.

part of the study. Both tests showed an initial decrease from baseline values and than progessively improved during the period of emergence. Following remifentanil–desflurane anaesthesia, DSST and TDT were impaired significantly less at 30 min (DSST, TDT) and 60 min (DSST) after anaesthesia (Figures 2 and 3).

Discussion

We found that patients undergoing carotid artery surgery after remifentanil–desflurane anaesthesia recovered more quickly than those given a 'traditional' general anaesthetic technique with intermittent bolus doses of supplemental fentanyl. This acceleration of recovery is not limited to the initial period of awakening from anaesthesia; it also allows earlier neurological examination and is still shown in the first hour after surgery with a more rapid return of psychomotor and cognitive functions.

These results are of current interest since CEA is increasingly being performed in patients with carotid stenosis, and randomized clinical studies have shown that strokes can be reduced.[9] However, CEA may cause postoperative neurological deficits, which should be diagnosed and treated promptly. In some techniques, the use of opioids is reduced whenever possible to allow rapid postoperative awakening and early neurological assessment.[2] Other techniques use an opioid-based anaesthetic because of the prevalence of co-existing coronary artery disease in these patients.[1]

Remifentanil is rapidly broken down by non-specific esterases to nearly inactive metabolites, so recovery from intraoperative opioid analgesia can be rapid.[10] After remifentanil, about 2 min elapsed from the onset of spontaneous ventilation to the moment that patients could state their name and date of birth correctly, and 2 min later

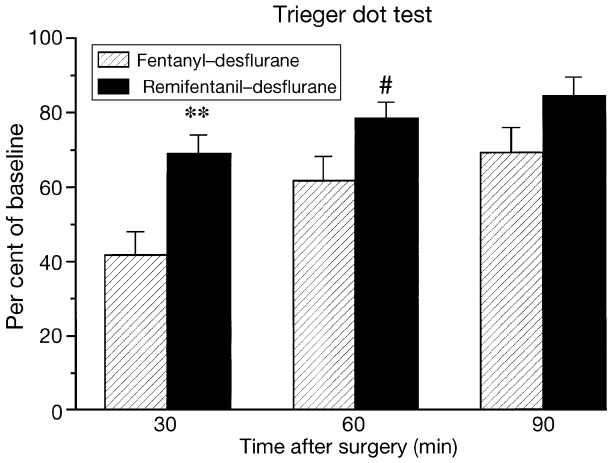

Fig 3 Mean (SEM) results of the Trieger dot test 30, 60 and 90 min after the end of surgery, expressed as percentage of baseline. Differences between the treatment groups: $^{**}P<0.01$, $^{\#}P=0.05$.

patients could be examined neurologically by the arm holding test. The sedation score, DSST and TDT results, showed that intermediate recovery was also shorter.

The properties of remifentanil allow high-dose opioid use throughout the operation, and reduce the amount of desflurane needed, which is a reason for the difference in recovery seen when remifentanil is used. The impact of the amount of the inhaled anaesthetic on awakening from anaesthesia is known from animal and human studies: Eger and Johnson[11] investigated rats that were anaesthetized for 2 h with different volatile anaesthetics and at different multiples of their MAC values. Awakening was typically most rapid with the lowest concentration of the inhaled anaesthetic; this also applies to the results of our study: At the end of surgery, the mean end-tidal desflurane concentration was 3.5 vol% in the fentanyl group, but only 1.9 vol% in the remifentanil group. Similar results were obtained by Smiley and co-workers[12] in patients undergoing elective surgery with desflurane or isoflurane anaesthesia with 0.65× or 1.25×MAC: recovery was faster with the lower anaesthetic concentration.

In addition to the difference in desflurane concentration, the opioid itself will influence the time course of awakening. Glass and colleagues[13] argued that only small amounts of fentanyl or remifentanil are necessary to reduce the MAC, and this also applies to the alveolar concentration of the volatile anaesthetic, at which patients will awake from anaesthesia. Thus, the duration of pharmacodynamic interaction will depend on the duration of the opioid effect; this will clearly be longer with fentanyl than with remifentanil.

A similar anaesthetic technique was proposed by Gerhardt and Grichnik[3] who reported the use of remifentanil in a 60 yr old patient undergoing combined CEA and coronary artery bypass grafting. Their dosage regimen was nearly identical to ours: a remifentanil infusion was titrated to clinical needs and 1/3 MAC (i.e. 0.4 vol%) of isoflurane was added (we used 1/3 MAC of desflurane, i.e. 2 vol%). The authors concluded that remifentanil may retain the haemodynamic stability of an opioid-based anaesthetic technique while allowing for early extubation and neurological examination.

A potential shortcoming of the present study is the question of equivalent levels of anaesthesia in the two groups. The dosage regimens used in this study are comparable to that of other remifentanil-based anaesthesia studies and have been empirically effective. All anaesthetics were delivered by the same experienced anaesthesiologist, who relied on standard clinical signs as described in 'Patients and methods'. Apart from a better reduction in the haemodynamic response to intubation with remifentanil, the haemodynamic characteristics were very similar in the two groups (Table 2). This suggests the equivalence of anaesthesia in the two treatment groups, especially at the end of surgery when the assessment of recovery characteristics was started.

In conclusion, rapid postoperative awakening, quicker recovery and earlier neurological examination suggest that remifentanil–desflurane is a suitable alternative to fentanyl–desflurane as a general anaesthetic for patients undergoing carotid artery surgery.

Acknowledgements

The authors wish to thank T. Georg, Dipl.-Math. (statistician, Institute of Medical Biometrics, Epidemiology and Informatics) and T. Ziegenfuss, MD (Department of Anaesthesiology and Intensive Care Medicine, University of Saarland) for their valuable help in conducting this investigation. This study was supported by departmental funding.

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