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CLINICAL INVESTIGATIONS

Anaesthesia for carotid endarterectomy: comparison of hypnotic- and opioid-based techniques†

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Background. Although the synergistic interaction between hypnotics and opioids for total i.v. anaesthesia has been repeatedly demonstrated, questions about different dose combinations of hypnotics and opioids remain. The optimal combination would be based on maximal synergy, using the lowest dose of both drugs and having the lowest incidence of side-effects.

Methods. The major goal of this prospective randomized study was to compare two different dose combinations of propofol and remifentanil (both administered by target controlled infusion (TCI)) in respect of haemodynamics during surgery and recovery, and the need for cardiovascular treatment in the recovery room. A secondary goal was to compare pain scores (VAS) and morphine consumption in the recovery room. Anaesthesia was induced in both groups using TCI propofol, adjusted to obtain a bispectral index score (BIS) value between 40 and 60. TCI for remifentanil commenced at an initial effect-site concentration of 0.5 ng ml^{-1}, and was adjusted according to haemodynamics. Patients were divided into one of two groups during anaesthesia: (i) Group H, hypnotic anaesthesia (n=23), propofol effect-site concentration maintained at 2.4 μg ml^{-1}; and (ii) Group O, opioid anaesthesia (n=23), propofol effect-site concentration maintained at 1.2 μg ml^{-1}. In both groups, remifentanil effect-site concentration was adjusted according to haemodynamics and changes in BIS value.

Results. In Group O, more episodes of intraoperative hypotension (P<0.02) and hypertension (P<0.01), and fewer episodes of tachycardia were observed. More patients in Group O required nicardipine administration for postoperative hypertension (8 patients in Group H *vs* 15 patients in Group O, P<0.04). During recovery, morphine titration was necessary in ~50% of patients. No significant difference between groups was observed concerning pain scores or requirement for morphine titration.

Conclusions. Maintenance of anaesthesia predominantly with propofol and a low dose of remifentanil, both administered using TCI, is associated with greater stability in perioperative haemodynamics than anaesthesia predominantly with remifentanil alone. Postoperative pain was identical in both groups of patients who underwent relatively short duration, and relatively painless surgery.

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The anaesthetic state involves different components: loss of consciousness, amnesia, and loss of response to noxious stimulation. The synergistic interaction between hypnotics and opioids for total i.v. anaesthesia has been repeatedly demonstrated,[1–9] even if the modality of such interaction is still not well understood. In published studies, different dose

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combinations of hypnotics and opioids were used.[1–9] The optimal combination could be based on maximal synergy; that is using the lowest dose of both drugs and having the lowest incidence of side-effects.

In our population of patients undergoing carotid surgery, the incidence of haemodynamic side-effects during anaesthesia and surgery was high; hypotension occurs frequently, and hypertension and tachycardia are common events during recovery. Unfortunately, coronary artery disease is frequent in patients undergoing vascular surgery, in particular carotid artery surgery. In such patients, these haemodynamic events may be a trigger for coronary or neurological ischaemic adverse events, with potentially catastrophic consequences. Our hypothesis is that the incidence and the severity of hypotension during anaesthesia are closely related to the dose of anaesthetic agents used and could be influenced by different dose combinations of hypnotics and opioids.

The major goal of this prospective randomized study was to compare two different dose combinations of propofol and remifentanil (both administered by target controlled infusion (TCI)) for haemodynamic control during surgery and recovery, and to study the need for cardiovascular treatment in the recovery room. A secondary goal was to compare the degree of pain using a visual analogue scale (VAS) and morphine consumption in the recovery room in patients receiving different dose combinations of hypnotics and opioids.

Methods

After approval of the study by the Ethics Committee for Human Research of our institution, 46 patients scheduled for carotid surgery were enrolled in this prospective randomized study and gave informed consent. Our exclusion criteria were: urgent surgery; contraindication to using any of the drugs studied; severe heart failure (stage III–IV of the New York Heart Association); severe renal insufficiency (creatinine plasma concentration >200 μmol litre^{-1}); and inclusion in another study during the 3 months before surgery.

Anaesthesia

Patients were premedicated with midazolam 5 mg given orally 1 h before surgery. They received their cardiovascular medication on the morning of the operation, except angiotensin converting enzyme inhibitors and angiotensin II antagonists, which were discontinued the day before surgery.[10 11]

Standard intraoperative monitoring included ECG with continuous ST-segment analysis (lead D2, CS5, and V4; Marquette Monitor, Milwaukee, WI, USA), pulse oximetry, and invasive blood pressure measurement with a radial artery cannula inserted prior to induction of anaesthesia, under local anesthesia (EMLA cream). Baseline systolic blood pressure (SBP) and heart rate (HR) were defined as the average of three repeated measures on the day before surgery.

Depth of anaesthesia was monitored using BIS installed before induction. After a 10 ml kg^{-1} crystalloid bolus infused over 10–15 min, and denitrogenation with oxygen 100%, anaesthesia was induced in both groups using TCI propofol (at an initial central nervous system effect-site target concentration set at 3 μg ml^{-1}, with an induction lasting 3.5 min, the infusion pump being programmed using age and body weight), adjusted to obtain a BIS value between 40 and 50. Two minutes after the propofol infusion started, TCI of remifentanil commenced at an initial effect-site concentration of 0.5 ng ml^{-1} (using a three-compartment pharmacokinetic model for remifentanil to control a syringe infusion pump and the algorithm described by Minto[12]), increased by steps of 0.5 ng ml^{-1} according to haemodynamics, until the trachea was intubated.

All patients received atracurium 0.5 mg kg^{-1} and the lungs were ventilated with nitrous oxide 50% in oxygen, the tidal volume being adjusted to maintain P_{CO_2} ~4.7 kPa.

The patients were randomly allocated by computer (using a list compiled before the start of the study) to one of two groups for anaesthesia: (i) Group H, hypnotic anaesthesia (n=23), propofol effect-site concentration maintained at 2.4 μg ml^{-1}; and (ii) Group O, opioid anaesthesia (n=23), propofol effect-site concentration maintained at 1.2 μg ml^{-1}. In both groups, remifentanil effect-site concentration was adjusted by the anaesthetist in steps of 0.5 ng ml^{-1} according to haemodynamic changes and alterations in the BIS value during surgical stimulation.

Approximately 30 min before the end of surgery, patients in both groups received propacetamol 2 g and morphine 0.1 mg kg^{-1} i.v. Propofol and remifentanil infusions were stopped at skin closure. All patients were extubated in the operating room.

Haemodynamic management

Haemodynamic variables were recorded continuously from 10 min before the start of induction of anaesthesia until discharge from the recovery room. Haemodynamic intraoperative events were defined as: (i) hypotension—SBP <80 mm Hg lasting >30 s; (ii) hypertension—SBP >160 mm Hg lasting >30 s; (iii) tachycardia—HR >90 beats min^{-1} lasting >30 s; and (iv) bradycardia—HR <40 beats min^{-1} lasting >30 s.

Intraoperatively, the anaesthetist was required to maintain SBP and HR within 30% of baseline values using fluid administration and vasoconstrictive drugs (boluses of ephedrine 3 mg or phenylephrine 50 μg in cases of tachycardia, both repeated as necessary), or terlipressin (1 mg repeated once if necessary, this agent being indicated in case of refractory hypotension in patients chronically treated with angiotensin converting enzyme inhibitors and angiotensin II antagonists[13]).

Postoperative care

After surgery, patients were transferred to the recovery room. Haemodynamic events such as hypertension (>30% of control value) were treated with a i.v. bolus of nicardipine 1 mg, or titrated i.v. esmolol or propanolol when associated with an increased HR (>80 beats min^{-1}), or clonidine. Postoperative myocardial ischaemia defined as ST-segment depression >1 mm at 60 ms after the J-point was treated with diltiazem, or with nitrates in cases of poor left ventricular function as evidenced by echocardiography. Postoperative analgesia included morphine titration as needed (when VAS score >30). Pain, morphine titration requirements, and the number and duration of haemodynamic events were recorded, and total doses of vasoactive agents were noted in both groups of patients. The haemodynamic study ended at discharge from the recovery room.

Postoperative cardiac complications were defined as: congestive heart failure; pulmonary oedema; supraventricular arrhythmia; ventricular arrhythmia; new Q-wave or ST-T depression >48 h on twice-daily 12-lead ECG, whether or not associated with circulatory failure and the need for catecholamines, or a decrease in global or regional function on echocardiography, or an increase of cardiac troponin I (cTnI); or cardiac death. cTnI was measured at recovery and 1, 2, and 3 days after surgery, using an immunoenzymofluorometric assay on a Stratus autoanalyser (Dade-Behring, Paris La Défense, France). Normal values are <0.2 ng ml^{-1}.

Statistics

Statistical analysis was performed using a software package (NCSS 6.0, Kaysville, UT, USA). Prospective power analysis was based on haemodynamic variables. This showed that a sample size of 23 patients per group would have 90% power at the 5% significance level, to detect a difference in haemodynamic variables of 30%.

After the data had been checked for normality using the Kolmogorov–Smirnov test, clinical characteristics of the patients, haemodynamic events, medication requirements and use of vasoactive agents were analysed using unpaired *t*- or χ^2-tests when appropriate. $P<0.05$ was considered statistically significant.

Results

Patient characteristics were similar between the two groups in terms of age, sex, body weight, ASA physical status, and associated morbidity (Table 1). Mean (SD) duration of anaesthesia (Group H 132 (35) min *vs* Group O 141 (48) min), and surgery (Group H 83 (27) min *vs* Group O 99 (38) min) were similar in both groups, and no patient required postoperative ventilation in our study.

Propofol requirements are summarized in Table 2. Mean (SD) doses of remifentanil were 522 (235) μg (anaesthesia 3.9 (1) μg min^{-1}) in Group H, and 990 (415) μg (anaesthesia 7 (2) μg min^{-1}) in Group O. Total remifentanil requirements and remifentanil requirement per minute of anaesthesia were significantly different between the two groups.

Intraoperative haemodynamic events are summarized in Table 3. In Group O, fewer episodes of intraoperative tachycardia were observed ($P<0.05$), and more patients developed episodes of intraoperative hypotension ($P<0.05$), and hypertension ($P<0.01$). In both groups, the incidence of tachycardia was low (four patients in Group H *vs* no patient in Group O). The need for vasoactive drugs was not significantly different between groups.

Episodes of hypertension were similar in both groups and mainly occurred during intubation of the trachea, during skin incision, and during carotid cross-clamping. Episodes of hypotension were mainly observed during induction of anaesthesia.

During recovery, morphine titration was necessary in nearly 50% of patients. No significant difference between

Table 1 Clinical characteristics of the patients. Chronic renal disease is defined as creatinine plasma concentration between 120 and 200 mmol $litre^{-1}$. ACEI, angiotensin converting enzyme inhibitors; AIIA, angiotensin II antagonists. Data are presented as mean (SD or range). No statistically significant difference between groups

	Group H	Group O
Sex ratio (M/F)	15/8	18/5
Age (yr)	70 (54–85)	70 (52–87)
Body weight	68 (13)	72 (11)
Hypertension	17	21
Coronary disease (angina, history of myocardial infarction, previous coronary revascularization)	5	10
Chronic pulmonary disease	12	14
Chronic renal disease	2	0
Diabetes mellitus	5	4
ASA physical status II or III	23	23
Neurological status		
No symptom	12	16
Transient ischaemic attack	4	3
Previous stroke	7	4
Cardiovascular treatment		
Calcium channel blockers	7	7
β-blockers	7	8
ACEI or AIIA	10	9
Other vasoactive drugs	4	6

Table 2 Intraoperative characteristics. Data are presented as mean (SD). n.s.=not significant

	Group H	Group O	*P*-value
Duration of surgery (min)	83 (27)	99 (38)	n.s.
Duration of anaesthesia (min)	132 (35)	141 (48)	n.s.
Dose of propofol			
Total (mg)	1000 (405)	760 (235)	<0.05
Anaesthesia (mg min^{-1})	7.9 (3.6)	5.7 (1.9)	<0.01

Table 3 Haemodynamic events. Data are mean (SD). n.s.=not significant

	Group H	Group O	*P*-value
Number of intraoperative episodes			
Hypotension	20	26	n.s.
Hypertension	10	22	n.s.
Tachycardia	4	0	<0.05
Bradycardia	4	3	n.s.
Number of patients with at least one intraoperative episode			
Hypotension	11	18	<0.05
Hypertension	8	17	<0.01
Tachycardia	4	0	<0.05
Bradycardia	4	3	n.s.
Number of patients receiving vasoactive agents during surgery			
Ephedrine			
Patients	17	19	n.s.
Dose (mg)	10 (9)	14 (12)	n.s.
Phenylephrine			
Patients	11	15	n.s.
Dose (μg)	110 (160)	120 (150)	n.s.
Terlipressin			
Patients	1	1	n.s.
Dose (mg)	1	1	n.s.
Number of patients receiving nicardipine or a β-blocker during recovery			
Nicardipine			
Patients	8	15	<0.05
Dose (mg)	0.5 (0.7)	2.4 (3.2)	<0.01
β-blocker	11	10	n.s.

Table 4 Postoperative pain scores and morphine requirements. Data are presented as mean (SD). There were no statistically significant differences

	Group H	Group O
VAS		
Maximal value	33 (18)	35 (27)
Patients with at least 1 VAS >30 (*n*)	8	10
Morphine requirements		
Morphine (mg)	4.8 (4.5)	4.6 (5.1)
Patients requiring morphine (*n*)	14	12

groups was observed concerning pain scores or the need for morphine titration (Table 4). In contrast, more patients in Group O needed nicardipine for postoperative hypertension (8 patients in Group H *vs* 15 patients in Group O; $P<0.05$). No significant difference in β-blocker administration was noted between the two groups (Table 3).

During the study period, none of the patients developed myocardial ischaemia, neurological or surgical postoperative complications.

Discussion

Regardless of the type of surgery, remifentanil has been shown to improve intraoperative haemodynamic stability compared with other opioids. In a large-scale study of 2438 patients, Twersky and colleagues[14] confirmed better haemodynamic control using remifentanil compared with fentanyl. Remifentanil-treated patients had lower systolic and diastolic blood pressures (by 10–15 mm Hg) and lower HR (by 10–15 beats min^{-1}) intraoperatively compared with fentanyl-treated patients. These differences disappeared on wakening. These observations confirm the results of many other studies on more restricted populations. Mackey and colleagues[15] showed that on laryngoscopy, a situation during which high-risk patients undergo brief but very high levels of reflex-generating stimulation, fewer episodes of tachycardia and hypertension occurred using remifentanil compared with fentanyl. Prakash and colleagues[16] also found attenuated haemodynamic responses to rigid bronchoscopy using remifentanil compared with fentanyl. Nevertheless, one study reported deleterious effects of remifentanil used as an intraoperative analgesic.[17] This prospective study included 40 patients with ischaemic heart disease randomly assigned to one of two groups: patients in Group I received sevoflurane and remifentanil for induction of anaesthesia; and patients in Group II received etomidate and fentanyl for induction. The study had to be rapidly terminated because of a high incidence of bradycardia and asystolic episodes in the remifentanil group. Unfortunately, patients in the sevoflurane–remifentanil group were more frequently treated with regular β-adrenergic-blockers and had a lower pre-induction HR. Moreover, remifentanil for induction was used at the dose of 0.5 $\mu g\ kg^{-1}\ min^{-1}$ over 90 s after exposure to an inspired concentration of sevoflurane 5%.

Two articles focused on carotid artery surgery. In a prospective, randomized study including 56 endarterectomy patients undergoing general anaesthesia with remifentanil *vs* sufentanil for analgesia, Mouren and colleagues[18] concluded that remifentanil is more effective in blunting the increase in blood pressure and HR associated with intubation without worsening the hypotensive effect of induction or the blood pressure response to recovery, and that remifentanil was associated with a decrease in intraoperative drug requirements. Doyle and colleagues[19] showed that haemodynamic variables were similar during balanced anaesthesia for carotid endarterectomy using remifentanil or fentanyl, but in this study, the fentanyl-treated group had delayed recovery after a continuous perioperative fentanyl infusion.

Haemodynamic stability, recovery, and discharge may be improved by using TCI.[20] Changing the infusion rate allows a defined effect-site target to be achieved by integration of the duration of infusion, the pharmacokinetic properties of remifentanil and the patient's characteristics. This permits a reduction in fluctuations in drug concentration and effects. This is particularly important as the adverse effects of remifentanil mainly occur in cases of overdose.

Many problems remain to be solved when using TCI of remifentanil. The most important is the choice of pharmacokinetic model. According to whether the plasma or effect-site is targeted, emergence is predictable knowing the concentration needed for loss of consciousness and the drugs' pharmacokinetics. The three-compartment pharmacokinetic model of Minto is most commonly used, but a bi-

exponential decay curve[21] and other three-compartment models[22–24] have been described; none of them take into account remifentanil pharmacodynamic variability linked to the duration of infusion,[25] or the synergistic hypnotic–opioid interaction occurring during balanced anaesthesia. The best described interaction concerns propofol–remifentanil synergistic interaction.[8–11 13–24]

The interaction between propofol and opioids has been extensively studied. Using alfentanil, Iselin-Chaves and colleagues[9] clearly demonstrated that, under propofol anaesthesia, BIS was only affected by the presence of an opioid during a painful stimulus. Guignard and colleagues[25] evaluated the effect of remifentanil on the BIS changes and haemodynamic response to laryngoscopy and tracheal intubation. In their study, BIS values were not affected by remifentanil administration before laryngoscopy. They concluded that the addition of remifentanil to propofol affects BIS only when a painful stimulus is applied, and that BIS changes are only as sensitive as the haemodynamic response after a painful stimulus to detect deficits in the analgesic component of anaesthesia. BIS monitoring is also useful to evaluate the depth of anaesthesia in patients in whom HR or arterial pressure responses to noxious stimuli are impaired because of drug medication and/or cardiovascular disease. In contrast, Han[1] and Kazama[2] with fentanyl, Hentgen[3] with sufentanil, Vuyk with alfentanil,[4 5] and Hoymork,[6] Strachan,[7] and Röpcke[8] with remifentanil, found a significant correlation between the dose of opioid and the depth of anaesthesia, some of them using BIS. In the sufentanil studies, the dose regimen were similar to those used in our study. These data support the argument for adjusting remifentanil dose according to the BIS, as in our study.

In our study we found that hypnotic-based anaesthesia in carotid artery surgery is associated with better perioperative haemodynamic stability compared with opioid-based anaesthesia. Patients in our study were almost 70 yr old and frequently had hypertension and coronary artery disease, as expected in patients undergoing carotid surgery. Our results confirm that hypotension occurs frequently during carotid surgery, and that hypertension and/or tachycardia are common events during the recovery period. The relatively high rate of intraoperative haemodynamic events in our patients is because of the strict detection and control of such events to ensure aggressive anaesthetic management. This allows us to maintain adequate cerebral perfusion and continually adjust cardiovascular variables to reduce the risk of potentially adverse neurological or cardiovascular sequelae.

A secondary end-point of our study was to compare pain scores (VAS scores) and morphine consumption in the recovery room based on the hypothesis demonstrated in other studies that higher doses of intraoperative remifentanil cause acute opioid tolerance and hyperalgesia.[26 27]

In respect of postoperative pain, rapid development of acute opioid tolerance is well established, particularly where large doses of ultra short-acting drugs such as remifentanil are used.[26 27] In healthy volunteers undergoing general anaesthesia using remifentanil, Gustorff and colleagues[28] found no evidence of this phenomenon. However, postoperative pain in carotid artery surgery is not influenced by the opioid used perioperatively, the VAS remaining comparable with remifentanil or fentanyl.[19] In our study, the lack of difference between the two groups in respect of the intensity of postoperative pain and postoperative morphine consumption does not confirm this secondary hyperalgesia phenomenon, but carotid endarterectomy falls within the spectrum of relatively painless, short-duration surgery. Two other hypotheses could explain our results. The central nervous system target for remifentanil used in our study is nearly half that in the Guignard study,[26] and could be less than the trigger value causing secondary hyperalgesia. The duration of infusion may also be insufficient to induce clinically relevant postoperative hyperalgesia, this tolerance being noticeable with remifentanil only when the infusion exceeds 2 h, according to Vinik's study.[27]

In conclusion, we have found that maintenance of anaesthesia predominantly with propofol and a low dose of remifentanil, both administered using TCI, is associated with better stability in perioperative haemodynamics compared with anaesthesia with higher doses of remifentanil. The exception is the change in HR, which is probably blunted by higher dose of remifentanil. As all agents were given by infusion, the more stable blood pressure can be related only using a smaller dose of remifentanil.

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