Neuroanesthesia and Intensive Care

Remifentanil with morphine transitional analgesia shortens neurological recovery compared to fentanyl for supratentorial craniotomy

[L'analgésie transitionnelle avec du rémifentanil et de la morphine, comparés au fentanyl, diminue le temps de récupération neurologique suivant une craniotomie sus-tentorielle]

Adrian W. Gelb MB CHB,* Frederick Salevsky MD,† Frances Chung MBBS,‡ Ken Ringaert MD,§ Robert M.C. McTaggart-Cowan MD,¶ Ted Wong,* Pirjo H. Manninen‡

Purpose: To compare the recovery profiles, efficacy and safety of remifentanil and morphine for transitional analgesia with fentanyl in patients undergoing elective craniotomy for supratentorial mass lesions.

Methods: Ninety-one patients were enrolled in this prospective, randomized, multicentre study. Anesthesia was induced with thiopental and remifentanil (1.0 $\mu g \cdot kg^{-1}$ bolus and a 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion) or fentanyl (1 $\mu g \cdot kg^{-1}$ bolus and a 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion). The opioid infusion continued until the level of anesthesia was deemed appropriate for intubation. Anesthesia was maintained with N_2O/O_2, isoflurane 0.5 MAC and remifentanil 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or fentanyl 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At bone flap replacement, either morphine 0.08 $mg \cdot kg^{-1}$ (remifentanil group) or saline (fentanyl group) was given.

Results: Systolic blood pressure was greater in those receiving fentanyl during induction (145.6 ±17.5 mmHg *vs* 128.8 ±18.3 mmHg; $P = 0.006$) and intubation (126.9 ±17.1 *vs* 110.9 ±16.5 mmHg; $P < 0.001$). Median time to tracheal extubation was similar but less variable in the remifentanil group (remifentanil = 8 min: range = 2–44 min; fentanyl = 8 min: range = 1–732 min). The fentanyl patients required a longer time to achieve the first normal neurological score (fentanyl = 38.0 min; remifentanil = 26.0 min; $P = 0.035$). Both the anesthesiologists and the recovery room nurses rated remifentanil better with respect to level of consciousness. Analgesics were required earlier in patients receiving remifentanil; median time 0.5 *vs* 1.08 hr, $P < 0.001$.

Conclusions: Remifentanil is a suitable alternative to fentanyl in supratentorial craniotomy. Time to preoperative neurological recovery is faster and morphine provides some transitional analgesia without compromising the quality of recovery.

Objectif : *Comparer les profils de récupération, l'efficacité et l'innocuité de l'analgésie transitionnelle avec rémifentanil et morphine, ou avec fentanyl, chez des patients devant subir une craniotomie réglée pour des masses intracrâniennes sus-tentorielles.*

Méthode : *Quatre-vingt-onze patients ont participé à l'étude prospective, randomisée et multicentrique. L'anesthésie a été induite avec du thiopental et du rémifentanil (bolus de 1,0 $\mu g \cdot kg^{-1}$ et perfusion à 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) ou du fentanyl (bolus de 1 $\mu g \cdot kg^{-1}$ et perfusion à 1,0 $\mu g \cdot kg^{-1} \cdot min^{-1}$). La perfusion d'opioïde s'est poursuivie jusqu'à un niveau d'anesthésie jugé approprié pour l'intubation. L'anesthésie a été maintenue avec un mélange N_2O/O_2, 0,5 CAM d'isoflurane et 0,2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ de rémifentanil ou 0,04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ de fentanyl. Au moment de replacer le volet osseux, soit 0,08 $mg \cdot kg^{-1}$ de morphine (groupe rémifentanil), soit une solution saline (groupe fentanyl) a été administrée.*

Résultats : *La tension artérielle systolique a été plus élevée avec l'utilisation du fentanyl pendant l'induction (145,6 ± 17,5 mmHg vs 128,8 ± 18,3 mmHg ; $P = 0,006$) et l'intubation (126,9 ± 17,1 vs 110,9 ± 16,5 mmHg ; $P < 0,001$). La durée moyenne de l'extubation endotrachéale a été similaire, mais moins variable avec le rémifentanil (rémifentanil = 8 min : étendue = 2–44 min ; fentanyl = 8 min : étendue = 1–732 min). Le premier score neurologique normal a été plus tardif avec le fentanyl (fentanyl = 38,0 min ; rémifentanil = 26,0 min ;*

From the Departments of Anaesthesia, London Health Sciences Centre,* London, Ontario; Montreal Neurological Hospital,† Montreal, Quebec; The Toronto Western Hospital,‡ University Health Network, Toronto, Ontario; Health Sciences Centre,§ Winnipeg, Manitoba; and the Foothills Hospital,¶ Calgary, Alberta, Canada.

Address correspondence to: Dr. Adrian W. Gelb, Department of Anaesthesia, London Health Sciences Centre - University Campus, 339 Windermere Road, London, Ontario, N6A 5A5, Canada. Phone: 519-663-3022; Fax: 519-663-3161; E-mail: agelb@uwo.ca.

This study was funded by GlaxoWellcome Inc, Mississauga, Ontario, Canada.

Accepted for publication January 23, 2003.

Revision accepted July 21, 2003.

P = 0,035). Les anesthésiologistes et le personnel infirmier de la salle de réveil ont mieux coté le rémifentanil quant au niveau de conscience. Les analgésiques ont été demandés plus tôt par les patients recevant le rémifentanil ; temps moyen de 0,5 vs 1,08 h, P< 0,001.

Conclusion : *Le rémifentanil remplace le fentanyl de façon appropriée pendant une craniotomie sus-tentorielle. Le temps nécessaire à la récupération de la fonction neurologique préopératoire est plus court et la morphine fournit une analgésie transitionnelle sans compromettre la qualité de la récupération.*

REMIFENTANIL hydrochloride (Ultiva™, GlaxoWellcome Inc., Mississauga, ON, Canada) has a rapid onset of action and an ultra-short duration of action, which does not increase with prolonged administration. These properties make it useful in settings such as intracranial surgery when rapid drug titration and recovery from anesthesia would be advantageous. Remifentanil may thus provide benefits by enhancing timely and complete neurological assessments of patients shortly after the completion of surgery.

Remifentanil and fentanyl have been compared in prospective, randomized, double-blind, multicentre studies in patients undergoing supratentorial craniotomy for space-occupying lesions.[1–3] Hemodynamics, intracranial pressure and cerebral perfusion pressure were similar as were median time to extubation. Fentanyl patients required greater adjuvant anesthetic and naloxone use while analgesics were required earlier in patients receiving remifentanil. These trials have, in general, used a narcotic based anesthetic with inhalational agents used either for management of "breakthrough" hypertension or used entirely at the discretion of the anesthesiologist. It is the belief of the investigators that it is more common, especially in Canada, to routinely use a mixture of narcotic and anesthetic vapour.

Here we report the results of a randomized, prospective double-blinded, Canadian multicentre study in patients undergoing elective supratentorial craniotomy. The aims of the study were: 1) to compare the efficacy and recovery profiles of remifentanil and fentanyl when used in conjunction with nitrous oxide-oxygen and 0.5 MAC isoflurane and 2) to evaluate a postoperative analgesia strategy of administering *iv* morphine at the time of craniotomy closure in the remifentanil group.

Methods

Study design

The respective Institutional Review Boards of the five study centres approved the study protocol. Written informed consent was provided by all study participants or the appropriate next of kin.

This study was conducted in two parts. The initial part was an open-label phase in which the first two patients enrolled at each of the five study centres received remifentanil in order to allow the anesthesiologists to gain familiarity with the study procedures. After completion of the open-label phase, each subsequent patient was then randomized to receive one of the two anesthetic regimens in a double-blind fashion. Randomization was performed according to a code generated using SAS®, version 6.12 (SAS Inc., Cary, NC, USA). Patients eligible for randomization were assigned the lowest available treatment number in chronological order at each centre. Each treatment number was assigned to only one subject. Opioid infusion syringes were prepared by the hospital pharmacy at each centre according to randomization schedules. Different syringes were prepared for each stage of the procedure (induction, maintenance, and emergence) and the participating anesthesiologists were blinded to the contents of the syringes.

Patient selection

Patients 18 to 65 yr, ASA status I, II or III, and who were scheduled for elective surgical removal of a supratentorial mass lesion were eligible for inclusion in the study. Patients were excluded if they had any of the following neurological conditions: cerebral aneurysms, intracranial arteriovenous malformations (except cavernomas), posterior fossa tumours, symptoms of uncontrolled increased intracranial pressure (ICP), risk of impending cerebral herniation. Also excluded were patients requiring procedures performed in the sitting or prone position and patients with clinically relevant preoperative systemic conditions such as poorly controlled ischemic heart disease, congestive heart failure or uncontrolled hypertension; patients weighing more than 100% above ideal body weight; and patients with known hypersensitivity to opioids; a history of psychiatric illness that may impair the patient's ability to provide informed consent. For women of childbearing potential, a pregnancy test was performed at the hospital within 24 hr before surgery. Patients who were pregnant or breastfeeding were also excluded. A computerized tomography or magnetic resonance imaging scan was obtained within six weeks before surgery and all were interpreted by a single experienced neuroradiologist.

Chronic medications were allowed on the day of surgery. However, no premedicants (except for 1–2 mg midazolam) were allowed.

Anesthetic protocol

The anesthetic protocol was very similar to that used by Guy *et al.*[2] Anesthesia was induced with 3 to 5 $mg \cdot kg^{-1}$ *iv* thiopental supplemented with either remifentanil (1.0 $\mu g \cdot kg^{-1}$ bolus followed by 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion) or fentanyl (1 $\mu g \cdot kg^{-1}$ bolus followed by 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion). The study drug infusion continued until the attending deemed by clinical judgement that an adequate level of anesthesia for intubation was achieved or a maximum of ten minutes had elapsed. The appropriate amount of thiopental and level of anesthesia were not predefined and were left to the clinical judgement of the attending anesthesiologist. Hemodynamic and respiratory measurements were recorded beginning just before thiopental was administered, and until intubation.

Intubation was achieved with 0.6 to 1.0 $mg \cdot kg^{-1}$ succinylcholine after pancuronium, 0.01 to 0.02 $mg \cdot kg^{-1}$. A response to intubation was treated with an increase in study drug infusion rate. Each infusion rate increase was separated by a minimum of two minutes. After intubation, mechanical ventilation began with 50% N_2O/O_2 (1:1). Ventilation was adjusted to maintain $PaCO_2$ 30 to 35 mmHg. Supplementary thiopental, 50 to 150 mg, was given as needed for treatment of responses to intubation and placement of the head pins.

Five minutes after intubation, the study drug infusion was decreased to 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (remifentanil group) or 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (fentanyl group). For the remainder of the surgery anesthesia was maintained with 50% N_2O/O_2 (1:1), 0.5% end-tidal isoflurane and the study drug infusion. Incremental doses of pancuronium were given as needed to maintain adequate muscle relaxation. Blood pressure and heart rate (HR) were recorded every 15 min intraoperatively. Intraoperative responses were treated with study opioid boluses and rate increases as deemed necessary by the anesthesiologist. Each bolus consisted of 1 $\mu g \cdot kg^{-1}$ remifentanil or 2 $\mu g \cdot kg^{-1}$ fentanyl administered over 30 sec. Rate increase was set at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (remifentanil group) or 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (fentanyl group). Boluses were separated by at least one minute and infusion rate increases by at least two minutes. A maximum of four boluses and two infusion rate increases were allowed. Beyond this, isoflurane in 0.2% increments would be given as needed. Hypotension and/or bradycardia were treated with fluid boluses, 0.2% decrements of isoflurane, and reductions in study drug infusion. Ephedrine, phenylephrine, atropine, labetalol, hydralazine or esmolol could be administered at any time, as deemed necessary by the anesthesiologist, for unacceptable hemodynamic events.

At the time of bone flap replacement, 0.08 $mg \cdot kg^{-1}$ *iv* morphine for the remifentanil group or saline for the fentanyl group was given. The drug infusions were changed so that the fentanyl group received saline and the remifentanil group, remifentanil. Isoflurane was discontinued at the start of skin closure. Labetalol, esmolol and/or hydralazine could be given for treatment of emergent hypertension during application of the head dressing.

At the end of surgery (defined as the time of completion of head dressing, with head pins removed), residual neuromuscular blockade was reversed as needed with 0.04 to 0.07 $mg \cdot kg^{-1}$ neostigmine and either 0.015 $mg \cdot kg^{-1}$ atropine or 0.01 $mg \cdot kg^{-1}$ glycopyrrolate, as needed. When reversal was adequate, N_2O and study drug infusion (remifentanil or saline) were discontinued.

Postoperatively, patients with moderate or severe postoperative pain were given Codeine 30 to 60 mg *im* or Demerol 50 to 150 mg *im* four hourly, as needed.

Outcome measures

The primary efficacy measure was the time from the end of surgery to extubation. Other efficacy measures included responses to surgical stimuli, vital signs, need for rescue medications and recovery times for verbal response and ability to follow commands. Hemodynamic responses were defined as a systolic blood pressure (SBP) increase of > 15 mmHg from baseline or HR > 90 $beats \cdot min^{-1}$. Somatic response was defined as movement, eye opening, or grimacing. Autonomic response was defined as tearing or sweating.

The level of brain relaxation was rated by the neurosurgeon at the time of dural opening using a four-point scale: 1 = excellent, no swelling; 2 = minimal swelling, but acceptable; 3 = serious swelling, no treatment required; 4 = severe brain swelling requiring intervention.

Pain was assessed every 20 min for the first two hours after surgery, then every 60 min until eight hours after surgery. Patients were asked to describe their level of pain as none (score = 0), mild (= 1), moderate (= 2), or severe (= 3). The time from the end of surgery to the first use of analgesics was recorded.

Nausea assessments, based on patient's response to the question "Are you feeling nauseated?" were done at patient's arrival at the recovery room, 15 min after, and upon arrival in the ward. The occurrence of nausea and vomiting, time to vomiting, duration and severity of nausea/vomiting were recorded as well.

The quality of emergence at the time the patient was brought into the postanesthesia care unit (PACU) was assessed independently by the recovery room

nurse and the anesthesiologist, using the same questionnaire which assessed patient comfort, hemodynamic profile, level of consciousness and overall quality of emergence (defined as better, similar, or worse than that usually observed for this procedure).[2] The investigator using the Aldrete scoring system assessed anesthetic recovery. Neurological recovery was assessed by the patient's level of consciousness, orientation, ability to follow verbal commands, motor function and presence of agitation.[2]

The incidence of adverse events was recorded throughout the study. Hypotension (defined as SBP < 80 mmHg·min^{-1}) requiring treatment with vasopressor or anticholinergic agents was reported as an adverse event, as well as bradycardia (defined as HR < 40 beats·min^{-1}).

Statistical analysis

An *a priori* power analysis was performed. A minimum of 45 patients per treatment group was anticipated to provide 80% power of detecting a reduction in the time to extubation by a factor of 1.75 for patients on remifentanil, at a two-tailed significance level of 0.05. Assessment of treatment efficacy was based on an intent-to-treat (ITT) population. The non-randomized, open-label pilot patients were excluded from the ITT population. The primary efficacy measure, the time to extubation from end of surgery, was analyzed using the Wilcoxon test. For all analyses of proportions, the Chi square statistic without continuity correction, stratified by centre, was used or the Fisher's exact test without adjustment for centre used, if cell frequencies were low. Parametric values are reported as means ± SD. SBP and HR during different phases of anesthesia were calculated as means and analyzed using analysis of covariance with the baseline value as the covariate. Brain relaxation scores and ratings of quality of emergence from anesthesia were compared between treatments using the Wilcoxon test. Rank correlations between recovery room nurse and anesthetist ratings were performed. Statistical analyses were performed using SAS® Software (version 6.12 for Windows NT, 4.0). All statistical tests were two-tailed, with statistical significance defined as $P < 0.05$.

Results

One hundred and one patients were enrolled in the study, ten in the open-label phase and 91 in the randomized, double-blind study (44 remifentanil and 47 fentanyl). One patient receiving remifentanil was withdrawn from the study at the start of surgery due to a change of surgical procedure. Data for this patient were included in the analysis through to the point of intubation. No important differences were noted in patient demographics and tumour characteristics between the two study groups (Table I).

TABLE I Patient demographics

	Remifentanil	*Fentanyl*
Age*	42 ± 11	45 ± 13
M/F	24/20	20/27
Weight*	76 ± 16	75 ± 15
Tumour diameter*	4 ± 2	4 ± 2
Location F/T/P	14/8/19	24/10/13
Mass Effect M/M/S	21/12/1	15/13/4
Surgery (hr)*	5.5 ± 2.5	5.8 ± 2.8

F/T/P = frontal, temporal, parietal. M/M/S = mild, moderate, severe. * = mean ± SD.

TABLE II Quality of emergence - % better

Anesthesiologist	*Remifentanil (n = 44)*	*Fentanyl (n = 45)*
Level of consciousness	71*	27
Patient comfort	46	42
Hemodynamic profile	49	42
PACU nurse		
Level of consciousness	44*	22
Patient comfort	29	28
Hemodynamic profile	27	22

*$P < 0.05$ compared to fentanyl. PACU = postanesthesia care unit.

The median duration of study drug infusion was 5.1 hr for remifentanil and 5.6 hr for fentanyl patients. Isoflurane was used in all the remifentanil patients and all but one fentanyl patient. The mean total dose of remifentanil was 77.1 ± 39 μg·kg^{-1} (range 8–240 μg·kg^{-1}). The mean total dose of fentanyl was 29.8 ± 10 μg·kg^{-1} (range 12–51 μg·kg^{-1}). The amount of opioid infused prior to intubation was remifentanil 3.6 ± 1.5 μg·kg^{-1} and fentanyl 4 ± 2.3 μg·kg^{-1}.

SBP was similar at baseline (Figure 1). One patient in the remifentanil group, and none in the fentanyl group, developed drug-related hypotension requiring treatment during the induction period. SBP was lower in patients in the remifentanil group at most measurement points (Figure 1). HR was similar at baseline and during the procedure except lower in the remifentanil group during intubation (remifentanil, 70 ± 10 beats·min^{-1}; fentanyl, 77 ± 11 beats·min^{-1}; $P < 0.001$) and head dressing (remifentanil, 67 ± 14 beats·min^{-1}; fentanyl, 74 ± 15 beats·min^{-1}; $P = 0.023$). Significantly more patients in the fentanyl group, 55%, had increases in blood pressure or HR at intubation ($P < 0.001$;

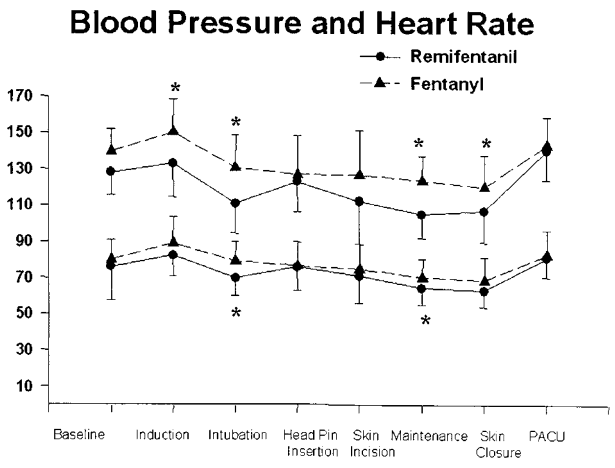

FIGURE 1 Systolic blood pressure and heart rate during the study. *$P < 0.05$ between groups.

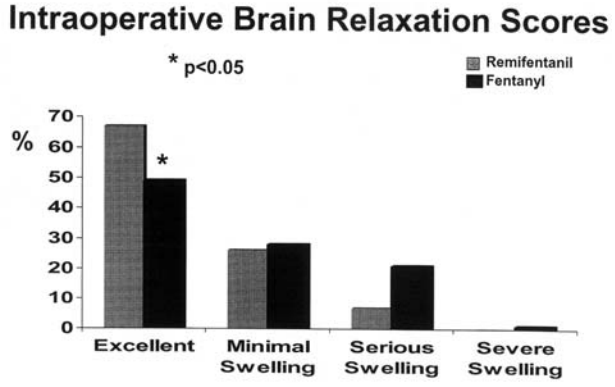

FIGURE 2 The level of brain relaxation as rated by the neurosurgeon at the time of dural opening using a four-point scale: excellent, no swelling; minimal swelling, but acceptable; serious swelling, no treatment required; severe brain swelling requiring intervention. More remifentanil compared to fentanyl patients were rated as "excellent" ($P < 0.05$).

Figure 2). Conversely, 45% of remifentanil patients as compared with 21% fentanyl ($P < 0.016$) had hypotensive or bradycardia responses during maintenance with hypotension being the primary event and in 24% of the remifentanil patients a vasopressor was used. No significant differences in SBP or HR were observed between groups during the recovery period.

Significantly more patients in the remifentanil group achieved an excellent score for brain relaxation than in the fentanyl group ($P = 0.033$; Figure 3). End-tidal CO_2 was similar between the groups at this time, remifentanil 28 ± 4 mmHg and fentanyl 27± 3 mmHg.

Median time to tracheal extubation was similar (remifentanil = 8 min; range = 2–44 min; fentanyl = 8 min: range = 1–732 min). The median times to emergence and to achieve an Aldrete score > 9 were similar between groups, 21 ± 30 and 34 ± 50 min for remifentanil and fentanyl respectively. The patients in the fentanyl group required a longer time (38 min) to achieve their preoperative neurological score than patients in the remifentanil group (26 min; $P = 0.035$). More remifentanil patients achieved neurological recovery within 30 min of the end of surgery than fentanyl patients (57% *vs* 36%, $P = 0.045$). Similar statistically significant differences between the groups were also found in the times to patient's responses to verbal questions ($P < 0.05$). Three fentanyl patients (6%) received naloxone as compared with none (0%) in the remifentanil-treated group, but the difference was not statistically significant.

Ratings by anesthesiologists on the quality of emergence (including patient comfort, hemodynamic profile, level of consciousness and overall quality) were similar between the groups, except for significantly higher ratings for the remifentanil group with respect to level of consciousness ($P < 0.001$; Table II). Seventy-one percent of the remifentanil-treated patients were given the rating of "better than usual" compared with only 27% of fentanyl-treated patients. Recovery room nurses also gave remifentanil-treated patients higher ratings for level of consciousness ($P = 0.005$).

There was no difference in the percentage of patients in each group who needed analgesia; remifentanil 77%, fentanyl 68% but patients in the remifentanil group had higher initial pain scores than the fentanyl group, 24% with severe pain *vs* 11% ($P = 0.011$). The median time to first analgesic use occurred earlier in the patients in the remifentanil group, 0.5 hr compared to 1.08 hr for fentanyl ($P < 0.001$).

There was no significant difference in the number of patients experiencing postoperative nausea and vomiting (remifentanil = 89% and 73%; fentanyl = 81% and 57%; $P = 0.319$, $P = 0.127$, respectively). However, more remifentanil-treated patients had emesis present during the follow-up period than fentanyl-treated patients (remifentanil = 69%; fentanyl = 46%; $P = 0.024$).

Discussion

It is advantageous to the patient undergoing supratentorial craniotomy to emerge and recover from anesthesia quickly as this allows prompt neurological assessment and determination of the need for urgent intervention. Fentanyl has been the standard narcotic for this type of surgery. The results of the current study demonstrate that the ultra-short acting opioid, remifentanil, is an effective and safe alternative to fentanyl, even when morphine is given at the end of the procedure to provide transitional analgesia.

Remifentanil and fentanyl were similar in overall efficacy in this study. The primary efficacy variable, time to extubation, was very similar in the two treatment groups. This finding is supported by a similar study conducted by Guy *et al.*,[2] although the time to extubation was about double in the present study compared to their study (8 *vs* 4 min). Other studies of this type of surgery have also demonstrated a shorter time to extubation than we found whether remifentanil was used or other anesthetic combinations such as propofol/fentanyl and isoflurane/nitrous oxide.[3–5] These differences possibly reflect differences in anesthetic protocols between the studies. The present study and the study by Guy *et al.*[2] had similar protocols and used similar total doses of opioids but differed in the required use of isoflurane in the current study. Guy *et al.* used a total of remifentanil 73 $\mu g \cdot kg^{-1}$ and fentanyl 34 $\mu g \cdot kg^{-1}$ while the use in our report was remifentanil 77 $\mu g \cdot kg^{-1}$ and fentanyl 30 $\mu g \cdot kg^{-1}$.

Both HR and blood pressure were lower in the remifentanil group than the fentanyl group at intubation with significantly more patients in the fentanyl group, 55%, having light anesthesia responses (Figure 2). Indeed, these variables tended to be lower throughout the procedure in the remifentanil group with 45% of remifentanil patients as compared with 21% of fentanyl patients ($P < 0.016$) having hypotension and/or bradycardia during maintenance, with hypotension being the more common event. These finding are consistent with other similar studies.[2,3] Possible explanations include a greater depth of anesthesia in the remifentanil group either because the doses of drug chosen were not exactly equipotent or because they differ in their potentiation of isoflurane or because fentanyl has less of a propensity to cause hypotension.[2,6–8]

The neurosurgeon's subjective assessment of "brain relaxation" or operating condition at the time of dural opening significantly favoured remifentanil with 67% *vs* 49% scoring the brain condition as "excellent" ($P < 0.03$). This has not been noted in any previous study although in the study by Guy *et al.*, which had a much smaller sample size, a similar trend is apparent.[2] Neither remifentanil nor opioids in general, have been shown to reduce ICP or cerebral blood volume. Previous human and animal studies of the effects of remifentanil on ICP have found it to produce no effect.[9,10] It is conceivable that the blood pressure surge at induction in the fentanyl group left the brain engorged or that remifentanil has some unique ability to improve operating conditions. If autoregulation were intact one would predict that the lower blood pressure in the remifentanil group would result in compensatory cerebral vasodilation and potentially an increase in ICP. Conversely if autoregulation were lost, the drop of blood pressure in a pressure passive vasculature would decrease intracranial blood volume. However, there is no evidence that remifentanil abolishes autoregulation.[9]

In terms of emergence characteristics, this study showed an advantage for remifentanil, with several events occurring significantly earlier in the remifentanil patients. The fentanyl group required a longer time (38 min) to achieve their first normal neurological score than the remifentanil patients (26 min; $P = 0.035$). More remifentanil patients achieved full neurological recovery within 30 min of the end of surgery than fentanyl patients (57% *vs* 36%, $P = 0.045$). Statistically significant differences between the groups were also found in the times to patient's responses to verbal commands. Three fentanyl patients and no remifentanil patients received naloxone. These results are similar to others and they indicate that the benefits in terms of emergence characteristics of the shorter duration of action of remifentanil are not altered by the use of morphine for transitional analgesia.[2]

The overall quality of emergence in the two groups was rated as similar by the anesthesiologists and the recovery room nurses, as were patient comfort and hemodynamic profile. However, both groups gave the remifentanil patients significantly higher ratings with respect to level of consciousness ($P < 0.001$; Table II). Compared to their usual experience with this type of patient, 71% of the remifentanil-treated patients were given the rating of "better" by the anesthesiologists; compared with only 27% of fentanyl-treated patients. Guy *et al.* found only a trend to a difference in the anesthesiologists' rating of quality of emergence ($P = 0.08$) and a statistical difference in the neurosurgeons' assessment when assessments were made before discharge from the recovery area.[2] Their study however had a much smaller sample size and our assessments were made at the time that patients were brought into the PACU rather than later in their stay. Balakrishnan *et al.*, using a protocol where drug choice or dose

were less rigidly controlled also found a statistically significant difference in favour of remifentanil.[3]

Previous studies with remifentanil identified pain and the need for early analgesia in the PACU as problems in the use of such a short acting drug.[2,11] An important aim of the present study was the evaluation of the use of morphine 0.8 $mg \cdot kg^{-1}$ *iv* at dural closure for transitional analgesia. This proved effective in that early recovery of superior quality was still found in the remifentanil group without early pain requiring urgent treatment. Although many neurosurgeons seem to avoid morphine, this study demonstrates that, when carefully used in an appropriate patient care setting, it is an acceptable drug. However, the remifentanil patients still required supplemental analgesia earlier than the fentanyl group, median time 30 *vs* 65 min. The earliest opioid administration was at 25 min in the fentanyl group and 12 min in the remifentanil group.

We conclude that remifentanil is a viable alternative to fentanyl in supratentorial craniotomy. The time from the end of surgery to extubation was very similar for both groups of patients. For most other intra- and postoperative variables, remifentanil and fentanyl-treated patients were also similar. However, remifentanil was superior in terms of surgeons' assessment of operating conditions, time to achieve preoperative neurological examination and quality of emergence. These latter benefits were present after morphine 0.08 $mg \cdot kg^{-1}$ provided adequate transitional analgesia.

References

1 *Ostapkovich ND, Baker KZ, Fogarty-Mack P, Sisti MB, Young WL.* Cerebral blood flow and CO_2 reactivity is similar during remifentanil/N_2O and fentanyl/N_2O anesthesia. Anesthesiology 1998; 89: 358–63.

2 *Guy J, Hindman BJ, Baker KZ, et al.* Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions. Anesthesiology 1997; 86: 514–24.

3 *Balakrishnan G, Raudzens, P, Samra SK, et al.* A comparison of remifentanil and fentanyl in patients undergoing surgery for intracranial mass lesions. Anesth Analg 2000 91: 163–9.

4 *From RP, Warner DS, Todd MM, Sokoll MD.* Anesthesia for craniotomy: a double-blind comparison of alfentanil, fentanyl, and sufentanil. Anesthesiology 1990; 73: 896–904.

5 *Todd MM, Warner DS, Sokoll MD, et al.* A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Anesthesiology 1993; 78: 1005–20.

6 *Lang E, Kapila A, ShlugmanD, Hoke JF, Sebel PS, Glass PS.* Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology 1996; 85: 721–8.

7 *Hogue CW Jr, Bowdle TA, O'Leary C, et al.* A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery Anesth Analg 1996; 83: 279–85.

8 *Twersky RS, Jamerson B, Warner DS, Fleisher LA, Hogue S.* Hemodynamics and emergence profile of remifentanil versus fentanyl prospectively compared in a large population of surgical patients. J Clin Anesth 2001; 13: 407–16.

9 *Warner DS, Hindman BJ, Todd MM, et al.* Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. Anesth Analg 1996; 83: 348–53.

10 *Hoffman WE, Cunningham F, James MK, Baughman VL, Albrecht RF.* Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide. Anesthesiology 1993; 79: 107–13.

11 *Burkle H, Dunbar S, Van Aken H.* Remifentanil: a novel, short-acting, μ-opioid. Anesth Analg 1996; 83: 646–51.