# Continuous opioid infusions for neurosurgical procedures: a double-blind comparison of alfentanil and fentanyl

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*The ability of continuous infusions of opioids to control hypertension at the end of neurosurgical procedures without compromising prompt emergence was studied in patients undergoing craniotomy for supratentorial tumours. Four infusion regimens were compared in a randomized double-blind fashion; three of alfentanil and one of fentanyl. Low-dose alfentanil was administered to nine patients (35.1 $\mu g \cdot kg^{-1}$ then a continuous infusion of 16.2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$); mid-dose alfentanil to eight patients (70.2 $\mu g \cdot kg^{-1}$ then 32.4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$); high-dose alfentanil to eight patients (105.3 $\mu g \cdot kg^{-1}$ then 48.6 $\mu g \cdot kg^{-1} \cdot hr^{-1}$). Eight additional patients were given fentanyl (8.3 $\mu g \cdot kg^{-1}$ then 1.6 $\mu g \cdot kg^{-1} \cdot hr^{-1}$). Using published values for the pharmacokinetic variables of alfentanil and fentanyl, modelling predicted stable concentrations of 60, 120, 180 ng $\cdot ml^{-1}$ for the alfentanil infusion regimens respectively and 2 ng $\cdot ml^{-1}$ with the fentanyl regimen. Maintenance anaesthesia comprised the opioid infusion, 50% $N_2O$ in $O_2$ and isoflurane titrated to control mean arterial pressure (MAP) within 20% of ward MAP. Isoflurane was discontinued after closure of the dura. Nitrous oxide was discontinued at the same time as reversal of neuromuscular blockade. The opioid infusion was discontinued with closure of the galea. A greater time-averaged isoflurane concentration was required to control MAP within the prescribed limits in the low alfentanil group (ANOVA; $P < 0.05$). The $PaCO_2$ at two, five and 30 min after extubation were not different among groups. The times from discontinuing $N_2O$ to eye opening and tracheal extubation were not different. The time to follow commands was longer in the low alfentanil group ($P < 0.05$). Vasodilator therapy (to control MAP < 120% of ward MAP) with either labetalol or diazoxide was required less often in the high alfentanil group (3/8 patients; 38%) versus 100% in the low alfentanil groups ($P < 0.05$). Prompt emergence with the higher doses of opioids suggests that the volatile agent sparing effect of opioids can be used to advantage in these procedures.*

*Les effets de la perfusion continue d'opiacés sans compromettre le réveil rapide sur le contrôle de l'hypertension après les procédures neurochirurgicales furent étudiés chez des patients subissant une craniotomie pour des tumeurs cérébrales. Quatre régimes de perfusion furent comparés d'une façon randomisée à double insu, trois d'alfentanil et une de fentanyl. Des doses faibles d'alfentanil furent administrées chez neuf patients (35,1 $\mu g \cdot kg^{-1}$ suivies d'une perfusion continue de 16,2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$); des doses moyennes d'alfentanil pour huit patients (70,2 $\mu g \cdot kg^{-1}$ suivi 32,4 $\mu g \cdot kg^{-1} \cdot hre^{-1}$); des doses élevées d'alfentanil pour huit patients (105,3 $\mu g \cdot kg^{-1}$ suivi 48,6 $\mu g \cdot kg^{-1} \cdot hre^{-1}$. On a donné du fentanyl chez huit patients additionnels (8,3 $\mu g \cdot kg^{-1}$ suivi de 1,6 $\mu g \cdot kg^{-1} \cdot hre^{-1}$). Utilisant les valeurs publiées sur les variables pharmacocinétiques de l'alfentanil et du fentanyl, des concentrations stables furent prédites pour 60, 120, 180 ng $\cdot ml^{-1}$ pour les perfusions d'alfentanil respectivement et pour 2 ng $\cdot ml^{-1}$ pour le régime au fentanyl. Le maintien de l'anesthésie a compris la perfusion d'opiacés, 50% $N_2O$ et oxygène avec l'isoflurane titré afin de contrôler la pression artérielle moyenne (MAP) à l'intérieur de 20% des valeurs obtenues sur les étages. L'isoflurane fut cessé après fermeture de la dure-mère. Le protoxide d'azote fut cessé en même temps qu'on a antagonisé le blocage neuromusculaire. La perfusion d'opiacé fut discontinué à la fermeture de l'aponévrose. Une plus grande concentration d'isoflurane fut requise afin de contrôler le MAP à l'intérieur des limites prescrites par le groupe à dose faible d'alfentanil (ANOVA: P <*

**Key words**
ANAESTHETICS, INTRAVENOUS: fentanyl, alfentanil;
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*0,05). La $PaCO_2$ à deux, cinq et trente minutes après extubation n'était pas différente entre les groupes. Les temps à partiir de la cessation de protoxyde d'azote jusqu'à l'ouverture des yeux et l'extubation n'étaient pas différents entre les groupes. Les temps de réponse aux ordres étaient plus longs dans le groupe à dose faible d'alfentanil ($P < 0,05$). La thérapie aux vasodilatateurs (afin de contrôler une MAP < 120% des valeurs sur l'étage) avec soit du labétalaol ou diazoxide était moins fréquemment requise dans le groupe alfentanil à haute dose (3/8 des patients ; 38%) versus 100% dans le groupe à basse dose d'alfentanil ($P < 0,05$). Le réveil rapide avec les hautes doses d'opiacés suggèrent que l'effet d'économie des opiacés par l'agent volatil peut être utilisé avec avantage dans ces procédures.*

The incidence of hypertension during emergence from anaesthesia following neurosurgical procedures exceeds 90% in some studies.[1] Hypertension occurs so frequently, in part, because the anaesthetist strives for a very light plane of anaesthesia at the end of the operative procedure to permit early neurological assessment of the patient. Hypertension following neurosurgical procedures is usually treated aggressively because impaired cerebrovascular autoregulation raises concerns for postoperative intracranial bleeding or cerebral oedema.

Fentanyl infusions are frequently used for other surgical procedures to attenuate haemodynamic responses to noxious stimuli without producing cardiovascular depression.[2] Such infusion regimens may decrease the requirements for volatile agents.[3,4] High-dose fentanyl infusions are inappropriate for neurosurgical procedures because prompt emergence without respiratory depression is desired. In the absence of $N_2O$ or volatile anaesthetics plasma fentanyl concentrations less than 1–2 $ng \cdot ml^{-1}$ (i.e., the threshold concentration) must be achieved before patients can maintain an adequate minute ventilation.[5,6] Following neurosurgical procedures low end–tidal concentrations of volatile agents are usually present so that the threshold fentanyl concentration for adequate minute ventilation may be even less than 1–2 $ng \cdot ml^{-1}$.

Alfentanil is a synthetic opioid with a shorter elimination half-life ($t_{\frac{1}{2}}\beta$) than fentanyl (approximately 90 min versus 222 min).[6,7] Also, alfentanil equilibrates more rapidly between the blood and its sites of action than does fentanyl as evidenced by its more rapid EEG effects.[8] Threshold concentrations for alfentanil are 100–200 $ng \cdot ml^{-1}$. Such an opioid, in appropriate doses, may provide a smoother intraoperative course for neurosurgical procedures, with less emergence hypertension, less risk for opioid overdose and a more prompt recovery if relative overdose occurs.

We hypothesized that opioid infusions would facilitate anaesthetic emergence following neurosurgical procedures by attenuating emergence hypertension, decreasing the requirement for volatile agent while permitting prompt emergence with adequate minute ventilation. Low-, mid- and high-dose alfentanil infusion regimens (chosen to provide expected plasma concentrations of 60, 120 and 180 $ng \cdot ml^{-1}$ respectively) were compared with our standard fentanyl infusion regimen.

## Methods

This study was approved by the Faculty Committee on the Use of Human Subjects in Research at the University of Manitoba. A randomized, double-blind protocol was followed. Patients undergoing craniotomy for resection of supratentorial tumours were studied. All subjects gave written informed consent. Patients excluded were those <18 or>75 yr, >100 kg, with ASA physical status >III, uncontrolled hypertension, an expressive or receptive dysphasia, a Glasgow Coma Scale of <15, or with a dependence on opioids. The evening before surgery the patients were weighed and had their heart rate (HR) and blood pressure (×3 by cuff sphygmomanometry) determined. The averages of these were defined as the ward values for HR and MAP. Ninety minutes before surgery the patients received their normal *po* medications and 150 mg ranitidine. No other preanaesthetic medication was given. Following arrival in the operating room, patients had a large-bore intravenous and radial artery cannulae placed under local anaesthesia. The ECG and neuromuscular blockade (pollicis brevis muscle twitch response to train-of-four stimulation) were also monitored.

Four groups of patients were studied. The loading dose and maintenance infusion rates were based on the method of Wagner.[9] Dosages for each group were as follows: (1) fentanyl group (fentanyl; calculated stable plasma concentration of 2 $ng \cdot ml^{-1}$) 8.3 $\mu g \cdot kg^{-1}$ loading dose then 1.6 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ continuous infusion; (2) low-dose alfentanil group (low alfentanil; calculated stable plasma concentration of 60 $ng \cdot ml^{-1}$) 35.1 $\mu g \cdot kg^{-1}$ loading dose then 16.2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ continuous infusion; (3) mid-dose alfentanil group (mid alfentanil; calculated stable plasma concentration of 120 $ng \cdot ml^{-1}$) 70.2 $\mu g \cdot kg^{-1}$ loading dose then 32.4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ continuous infusion; and (4) high-dose alfentanil group (high alfentanil; calculated stable plasma concentration of 180 $ng \cdot ml^{-1}$) 105.3 $\mu g \cdot kg^{-1}$ loading then 48.6 $\mu g \cdot kg^{-1} \cdot hr^{-1}$).

Anaesthesia was induced with thiopentone 4 $mg \cdot kg^{-1}$ and vecuronium 0.15 $mg \cdot kg^{-1}$. With loss of lid reflex, the loading dose of opioid was administered *iv* over two minutes. Ventilation with oxygen was assisted, then controlled manually, before tracheal intubation. If MAP decreased by >20% from the ward value, ephedrine (2.5–5 mg) was administered as required. Immediately

after tracheal intubation the continuous infusion of opioid was initiated. Maintenance anaesthesia comprised $N_2O$ 50% in $O_2$. If MAP increased >20% above ward MAP, isoflurane was titrated to control MAP. Vecuronium was administered by continuous infusion to ablate the second twitch of the train-of-four. End-tidal $CO_2$ and isoflurane concentrations were recorded throughout the operation using calibrated monitors. Isoflurane was discontinued with closure of the dura irrespective of the MAP. If and when MAP increased to >20% above ward MAP following cessation of isoflurane, hypertension was treated by the following sequence: labetalol in 0.15 $mg \cdot kg^{-1}$ boluses to 200 mg if HR > 50 bpm; then diazoxide in 0.5–1.0 $mg \cdot kg^{-1}$ boluses to 300 mg (initial therapy if the HR was <50 bpm or if β-receptor antagonism was contraindicated). If hypertension persisted, an infusion of sodium nitroprusside (SNP) was administered. The opioid infusion was continued until the start of skin closure. Immediately before discontinuing the opioid infusion a 10 ml sample of blood was withdrawn to determine plasma opioid concentration (in selected cases). Following application of the scalp bandage the $N_2O$ was discontinued. Emergence times were referred to the time of discontinuing $N_2O$ at which time neuromuscular blockade was reversed with atropine 0.015 $mg \cdot kg^{-1}$ and edrophonium 0.75 $mg \cdot kg^{-1}$. Extubation occurred when minute ventilation was adequate (end-tidal $CO_2$ < 45 mmHg) and when the patient opened his eyes. Arterial blood gas (ABG) analyses were obtained at two, five and 30 min after extubation. The time until the patient could follow commands ("squeeze my fingers") was determined. Opioid effects were reversed with naloxone (0.04 mg increments) if assisted ventilation was required to maintain end-tidal $CO_2$ < 45 mmHg ten minutes following reversal of neuromuscular block, with evidence of sustained tetanus at 50 Hz. At the end of the procedure the patient was transferred to the recovery room. The study was terminated after vital signs were determined in the recovery room and an ABG sample was obtained 30 min after tracheal extubation. Subsequent patient care followed the usual protocols.

Data were continuously collected on a four-channel strip chart recorder. Data from the following time periods were analyzed: (1) control (immediately before induction); (2) one minute after induction; (3) one minute after intubation; (4) placement of skull tongs; (5) dural closure (isoflurane off); (6) removal of skull tongs; (7) reversal of neuromuscular block ($N_2O$ off); (8) two minutes after extubation; (9) five minutes after extubation; (10) in the recovery room. Data collected at each time period were HR, MAP, end-tidal $CO_2$, end-tidal isoflurane concentration, and requirement for antihypertensive therapy. The peak end-tidal isoflurane concentration for each five-minute interval was determined retrospectively from the strip chart recordings from the time initiated to extubation. The mean end-tidal isoflurane was then calculated and represented the time-averaged isoflurane concentration.

TABLE I Patient demographic data

| *Variable* | *Fentanyl* $n = 8$ | *Low-dose alfentanil* $n = 9$ | *Mid-dose alfentanil* $n = 8$ | *High-dose alfentanil* $n = 8$ |
|---|---|---|---|---|
| Age (yr) | 57 ± 12 | 53 ± 14 | 57 ± 16 | 61 ± 06 |
| Weight (kg) | 73 ± 11 | 75 ± 06 | 82 ± 09 | 83 ± 15 |
| MAP (mmHg) | 97 ± 06 | 94 ± 06 | 100 ±08 | 98 ± 07 |
| Heart Rate (bpm) | 76 ± 10 | 72 ± 08 | 71 ± 08 | 77 ± 06 |
| Anaesthesia Duration (min) | 220 ± 68 | 214 ± 76 | 194 ± 84 | 238 ± 113 |

Mean ± SD.
bpm = beats per minute; Anaesthesia duration = time from induction to emergency; no significant difference among groups for any variable.

After the randomization code was broken, serum alfentanil concentrations were determined in three patients, in duplicate, by gas-liquid chromatography.[10] The coefficient of variation of the assay was 9% over the concentration range from 2–2000 $ng \cdot ml^{-1}$.

Time-related changes were analyzed by repeated measures ANOVA. When the F-statistic was significant, within and between group comparisons were made using the least squares means test. A $P$-value <0.05 following Bonferroni's correction was considered statistically significant. The times to eye opening, tracheal extubation and following commands, mean end-tidal isoflurane concentration were determined by ANOVA. The requirement for vasopressor administration after induction, vasodilator therapy during emergence and anti-emetics postoperatively were compared among groups by Fisher's exact test using 2 × 2 contingency tables. $P < 0.05$ was considered significant.

The randomization code for the opioid given to each patient was broken after data analysis was completed.

## Results

Thirty-eight patients were enrolled in the study. Five patients initially enrolled were subsequently removed from data analysis for the following reasons: the opioid infusion infiltrated subcutaneously in one patient (high alfentanil), two patients had an intraventricular haemorrhage and delayed emergence (high and low alfentanil), two patients had protracted surgery with major blood loss (fentanyl and low alfentanil).

Of the 33 patients who completed the study eight each were in the fentanyl, mid and high alfentanil groups, and nine patients were in the low alfentanil group. The

TABLE II Heart rate (HR) for the opioid groups

| *Variable* | *n* | *Control* | *Post-ind* | *Post-intub* | *Tongs on* | *Tongs off* | *Reversal* | *2' Post-extub* | *PARR* |
|---|---|---|---|---|---|---|---|---|---|
| Fentanyl | 8 | 80 ± 19 | 73 ± 17 | 75 ± 19 | 66 ± 09 | 69 ± 15 ($n = 7$) | 73 ± 22 ($n = 7$) | 82 ± 19 | 71 ± 15 ($n = 7$) |
| High-dose alfentanil | 8 | 80 ± 19 | 70 ± 15 | 76 ± 14 | 72 ± 14 ($n = 7$) | 71 ± 10 | 79 ± 16 | 87 ± 14 ($n = 7$) | 73 ± 13 |
| Mid-dose alfentanil | 8 | 68 ± 18 | 66 ± 13 | 77 ± 14 | 67 ± 20 ($n = 7$) | 69 ± 12 | 65 ± 13 | 74 ± 11 | 74 ± 13 ($n = 7$) |
| Low-dose alfentanil | 9 | 75 ± 14 | 67 ± 09 | 69 ± 14 | 81 ± 16 | 78 ± 10 ($n = 7$) | 73 ± 11 | 81 ± 13 | 91 ± 14 ($n = 8$) |

Mean ± SD.
No significant difference among groups for any time period.
Control = Pre-induction; Post-ind = 1 minute after induction; Post-intub = 1 min after intubation; Tongs-on = 1 min after skull tongs on; Tongs off = 1 min after skull tongs off; Reversal = $N_2O$ off and reversal ofneuro muscular blockade; 2' Post-extub = 2 min after extubation; PARR = postanaesthetic recovery room.

TABLE III Mean arterial pressure (MAP) for the opioid groups

| *Variable* | *n* | *Control* | *Post-ind* | *Post-intub* | *Tongs on* | *Tongs off* | *Reversal* | *2' Post-extub* | *PARR* |
|---|---|---|---|---|---|---|---|---|---|
| Fentanyl | 8 | 104 ± 09 | 86 ± 14 | 97 ± 27 | 105 ± 19 | 99 ± 09 ($n = 7$) | 97 ± 05 | 96 ± 12 ($n = 7$) | 89 ± 06 |
| High-dose alfentanil | 8 | 99 ± 12 | 80 ± 17 | 87 ± 18 | 93 ± 15 ($n = 7$) | 98 ± 08 | 102 ± 20 | 105 ± 17 ($n = 7$) | 102 ± 12 |
| Mid-dose alfentanil | 8 | 104 ± 18 | 86 ± 17 | 87 ± 19 | 101 ± 11 | 111 ± 14 | 104 ± 08 | 113 ± 22 | 112 ± 20 ($n = 7$) |
| Low-dose alfentanil | 9 | 105 ± 13 | 90 ± 20 | 93 ± 25 | 108 ± 20 | 104 ± 12 ($n = 7$) | 98 ± 12 | 106 ± 16 | 103 ± 14 ($n = 8$) |

Mean ± SD.
No significant difference among groups for any time period.
Control = Pre-induction; Post-ind = 1 min post induction; Post-intub = 1 min post intubation; Tongs-on = 1 min post skull tongs on; Tongs off = 1 min post skull tongs off; Reversal = $N_2O$ off and reversal of neuro muscular blockade; 2' Post-extub = 2 minute post extubation; PARR = postanaesthetic recovery room.

demographic data for the four groups are shown in Table I. There were no differences in mean age, weight, baseline HR and MAP or duration of the surgical procedure. No obvious difference was seen among groups in the requirement for preoperative antihypertensive therapy.

The HR and MAP changes over time for each of the four groups are shown in Tables II and III respectively. No significant difference in HR or MAP was seen at any time period among groups.

After induction there was no difference among groups in vasopressor requirement (administered when MAP decreased to 80% of ward MAP). Ephedrine was administered to 1/8 patients in the fentanyl group, 2/9 in the low alfentanil group, 2/8 patients in the mid alfentanil group and 3/8 patients in the high alfentanil group.

The time-averaged end-tidal concentrations of isoflurane for each group are shown in Figure 1. A treatment effect was seen ($P < 0.05$). The end-tidal concentration in the low alfentanil group was significantly higher than for the other three groups.

The requirement for vasodilator therapy (either labetalol or diazoxide) following cessation of volatile agent until end of stay in the neurosurgical suite is shown in Figure 2. No patient required treatment with SNP to control emergence hypertension. Fewer interventions to treat hypertension (3/8; 38%) were seen in the high alfentanil group than in the low alfentanil group ($P < 0.05$ Fisher's exact test). A trend was seen for the high alfentanil group versus the mid alfentanil group ($P < 0.06$, Fisher's exact test). No difference was seen when comparing the other groups. The vasodilator doses administered to each patient are shown in Table IV.

No treatment effects were seen for the time to eye opening or for tracheal extubation, but a treatment effect was seen with time to follow commands ($P < 0.05$;

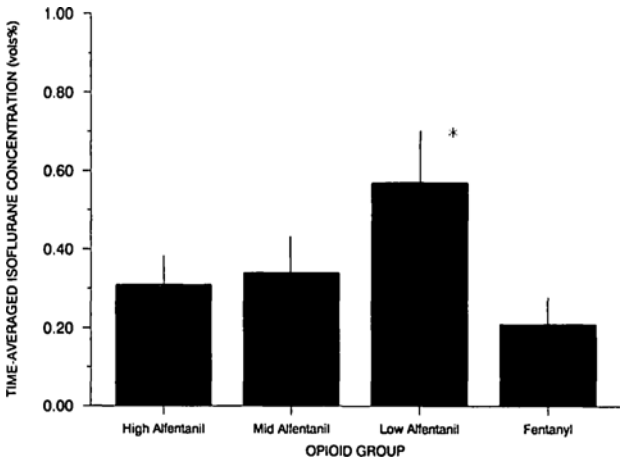


FIGURE 1 Time-averaged end-tidal isoflurane concentration for the four groups. Significantly higher concentrations of end-tidal isoflurane were seen for the low alfentanil group. Data is mean ± SEM; * $P < 0.05$ for treatment effect by repeated measures ANOVA.

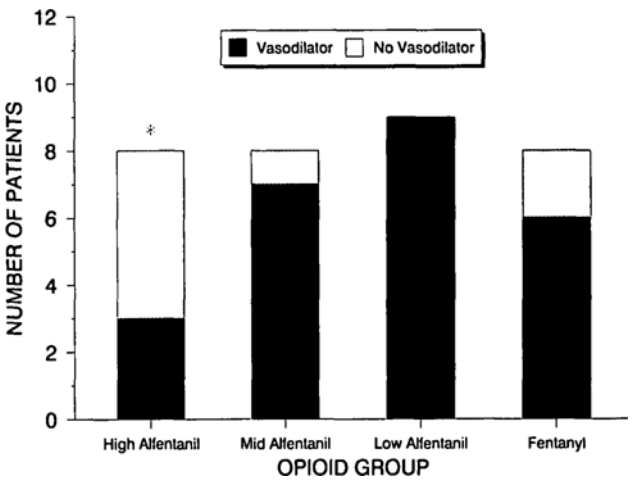


FIGURE 2 The number of patients in each opioid group requiring vasodilator therapy (labetalol or diazoxide) for control of MAP during emergence from anaesthesia at the end of the neurosurgical procedure; *$P < 0.05$ high alfentanil versus the low alfentanil group and $P < 0.06$ versus the mid alfentanil group by Fisher's exact test.

Figure 3). Patients in the low alfentanil group took significantly longer to follow commands than did patients in the high alfentanil or fentanyl groups ($P < 0.05$).

After extubation there was no treatment effect of $PaCO_2$ seen over the three time periods examined (Figure 4). Only one patient (mid alfentanil) was given naloxone (0.04 mg) because of inadequate minute ventilation (respiratory rate five breaths per minute) ten minutes after reversal of neuromuscular blockade.

Anti-emetics were administered after surgery in the recovery room to 2/8 patients in the fentanyl group, 2/9 patients in the low alfentanil group and in 0/8 patients in the mid and high alfentanil groups (NS among groups).

Plasma alfentanil concentrations immediately before turning off the infusion were examined in two patients in the high-dose alfentanil group who required vasodilator therapy for control of blood pressure and in one patient who had a $PaCO_2$ of 62 mmHg two minutes after extubation but who followed commands within two minutes of discontinuing $N_2O$. The two patients requiring vasodilator therapy had low plasma alfentanil concentrations (61 ± 3 and 128 ± 3ng·ml$^{-1}$). The patient who developed hypercarbia had an end-infusion plasma concentration of 215 ± 6 ng·ml$^{-1}$. This patient had the shortest duration of anaesthesia (time from induction to emergence) of any patient studied (116 min).

## Discussion

After neurosurgical procedures the anaesthetist and surgeon desire prompt emergence, stable haemodynamic

TABLE IV Vasodilator administration for each patient

| *Fentanyl* | | *Low-dose alfentanil* | | *Mid-dose alfentanil* | | *High-dose alfentanil* | |
|---|---|---|---|---|---|---|---|
| *Labetalol (mg)* | *Diazoxide (mg)* | *Labetalol (mg)* | *Diazoxide (mg)* | *Labetalol (mg)* | *Diazoxide (mg)* | *Labetalol (mg)* | *Diazoxide (mg)* |
| 15 | 0 | 10 | 0 | 30 | 0 | 10 | 0 |
| 10 | 0 | 100 | 240 | 30 | 0 | 5 | 0 |
| 100 | 45 | 30 | 105 | 50 | 0 | 125 | 135 |
| 0 | 0 | 50 | 300 | 0 | 180 | 0 | 0 |
| 0 | 0 | 30 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 10 | 0 | 50 | 0 | 0 | 0 |
| 0 | 60 | 20 | 0 | 0 | 120 | 0 | 0 |
| 60 | 0 | 100 | 0 | 60 | 0 | 0 | 0 |
| N/A | N/A | 95 | 240 | N/A | N/A | N/A | N/A |

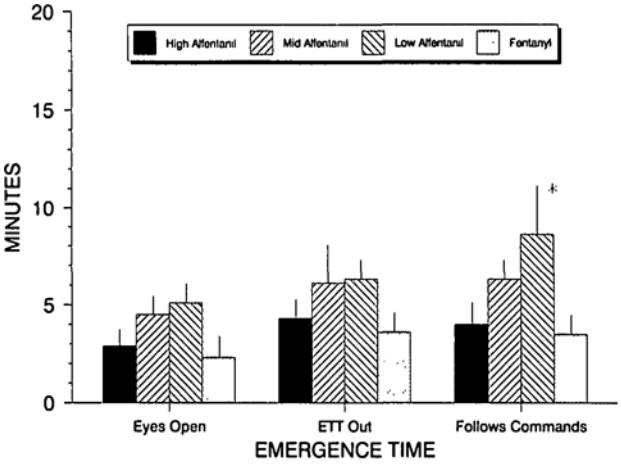


FIGURE 3 Time in minutes for emergence from anaesthesia (zero time at $N_2O$ off) for the four groups. Data is mean ± SEM; $*P <$ 0.05 for low alfentanil versus high alfentanil and fentanyl groups.

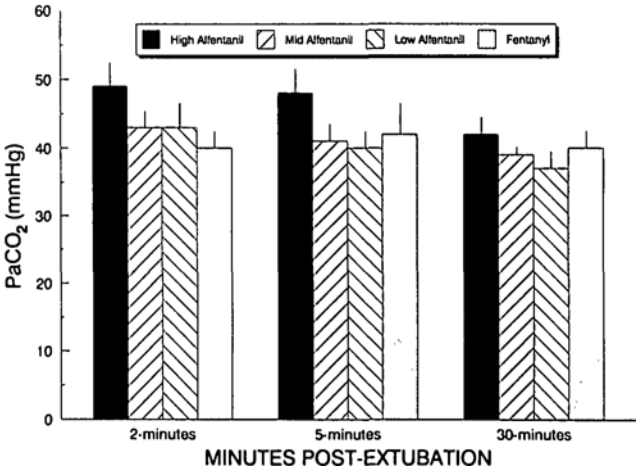


FIGURE 4 $PaCO_2$ for the four groups at two, five and 30 min post-extubation. Data are mean ± SEM; $P < 0.05$ for high alfentanil group versus other three groups by least squares mean test with Bonferroni's correction.

status, normal or low $PaCO_2$ and no coughing before the trachea is extubated. Satisfying all of these requests simultaneously is difficult. If a prompt emergence is desired, hyperdynamic circulatory responses due to light anaesthesia are usually controlled with vasoactive agents. Recently Muzzi *et al.* have studied the use of β-receptor antagonists for control of emergence hypertension.[1] We investigated the possiblility of controlling the unwanted hyperdynamic circulatory responses at the end of the neurosurgical procedure with a continuous opioid infusion. Historically, neurosurgeons have opposed the use of opioids intraoperatively because of the risk of respiratory depression at the end of the operative procedure.[11,12] However, high-dose opioids (fentanyl 100 $\mu g \cdot kg^{-1}$ and sufentanil 20 $\mu g \cdot kg^{-1}$) have been administered to neurosurgical patients.[13] In this study, bolus administration of naloxone was necessary to permit extubation of patients approximately 30 min after the completion of surgery and continuous infusions of naloxone were required for 16–17 hr. Ausems *et al.* have demonstrated that the $CP_{50}$ for alfentanil (i.e., that plasma concentration associated with a 50% probability of requiring naloxone administration for adequate ventilation) was 223 $ng \cdot ml^{-1}$.[14] In another study by Dubois *et al.*[15] alfentanil was administered in 150 or 200 $\mu g \cdot kg^{-1}$ boluses and then infused continuously at 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ respectively. In that study the alfentanil infusions were discontinued about one hour before the end of surgery. The mean time from the end of surgery to tracheal extubation was 11.5 min. In our study we continued the opioid infusion until the start of skin closure (i.e., at the end of the surgical procedure). We have demonstrated that fentanyl and alfentanil can be safely infused until the end of neurosurgical procedures and still permit prompt emergence without hypercarbia after extubation.

No treatment (group-time) interactions were seen for HR and MAP over the course of the experiments which indicates that for each group we were able to control the haemodynamic variables. However, the manner in which haemodynamic control was obtained differed among groups. A greater time-averaged end–tidal concentration of isoflurane was necessary to maintain MAP at ward values ±20% for the low alfentanil group than for the other three groups. This suggests that when higher relative doses of either fentanyl or alfentanil were administered, a volatile agent sparing effect was seen.

We demonstrated a very high incidence of emergence hypertension in three of four groups (defined as >120% of ward MAP) following neurosurgical procedures (75–100% of patients). Others have demonstrated similar findings.[1] Fewer patients (3/8, i.e., 38%) receiving the high-dose alfentanil infusion regimen required vasodilators for control of hypertension. Pharmacokinetic modelling predicts that this group of patients should have a stable plasma alfentanil concentration of approximately 180 $ng \cdot ml^{-1}$. Of those patients in this group requiring vasodilator therapy, two had low plasma concentrations. The patient who required both labetalol and diazoxide had a plasma concentration of only 61 ± 3 $ng \cdot ml^{-1}$. The patient who required 10 mg of labetalol had a plasma concentration of 128 $ng \cdot ml^{-1}$. The other patient who required vasodilator therapy in this group received only 5 mg of labetalol for control of blood pressure. We did not increase the opioid infusion rate or administer bolus doses of opioid to treat hyperdynamic responses intraop-

eratively. Thus, in the high alfentanil group additional alfentanil could likely have been safely administered to those patients who required vasodilator therapy. For this group as a whole, however, mean $PaCO_2$ at two and five minutes post-extubation were increased (49 ± 3 and 48 ± 3 mmHg respectively) and probably represent the upper limit that most anaesthetists would accept following neurosurgical procedures. Thirty minutes after extubation $PaCO_2$ had decreased to 42 ± 2 mmHg. The highest alfentanil plasma concentration was seen in one patient in the high alfentanil group who was alert but had a $PaCO_2$ of 62 mmHg at two min and 50 mmHg at 30 min after extubation respectively. The finding of relatively high mean $PaCO_2$ at extubation in this group suggests that higher alfentanil doses to control hyperdynamic responses would be inappropriate with fixed infusion regimens for such a patient population. Possibly variable infusion regimens with bolus administration to control hyperdynamic responses may yield better haemodynamic control.

Emergence times were rapid irrespective of the opioid regimen used (Figure 3). No difference in the times to eye opening or tracheal extubation were seen. The time until patients could follow commands correctly was greatest in the low alfentanil group. This group also had a greater time-averaged end-tidal isoflurane concentration. This suggests that delayed emergence in the low alfentanil group was due to the need for higher mean end-tidal concentrations of isoflurane during the operative procedure.

In conclusion, opioids can be infused for supratentorial neurosurgical procedures and result in prompt emergence with acceptable extubation $PaCO_2$ values if doses that produce concentrations within the "threshold" range for adequate minute ventilation are used. A slower emergence was seen in those patients with higher end-tidal concentrations of isoflurane at the end of the procedure. This suggests that the volatile agent sparing effect of opioids can be used to advantage in neuroanaesthesia. In this study the most stable emergence following neurosurgical procedures was seen with the high-dose alfentanil infusion regimen (105 $\mu g \cdot kg^{-1}$ bolus and 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In this group emergence hypertension occurred in significantly fewer patients (38%) versus 100% in those patients receiving the lowest dose of alfentanil.

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