A Comparison of Effects of Alfentanil, Fentanyl, and Remifentanil on Hemodynamic and Respiratory Parameters During Stereotactic Brain Biopsy

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Abstract: The aim of this study was to compare the effects of 3 different sedative-analgesic regimens in patients with intracranial mass lesions undergoing stereotactic brain biopsy. A 135 outpatients with American Society of Anesthesiologists I to II were divided into 3 groups: group A (n = 45) received a loading dose of IV alfentanil 7.5 μg/kg followed by infusion rate of 0.25 μg/kg/min; group F (n = 45) received a bolus dose of 1 μg/kg IV fentanyl and repeated as needed; and group R (n = 45) received infusion of 0.05 μg/kg/min remifentanil. Target level of sedation was 3 to 4 of the Ramsay Sedation Scale. Systolic and diastolic blood pressure, heart rate, respiratory rate, peripheric oxygen saturation (SpO_2), and end-tidal carbon dioxide were recorded at different stages of the procedures. The patients in group F had significantly lower mean heart rate than those in groups A and R, but this was not in the limits of the bradycardia. The patients in group A had significantly lower mean SpO_2 than those in the other groups, but mean SpO_2 values did not drop below 94%. There were no significant differences in end-tidal carbon dioxide and respiratory rate values among the groups. Our results suggest that all 3 regimens have relatively similar hemodynamic and respiratory responses. The use of bolus fentanyl technique caused less hemodynamic stability. The continuous infusion technique of remifentanil or alfentanil provided better control on hemodynamic parameters.

Key Words: fentanyl, alfentanil, remifentanil, stereotactic brain biopsy, hemodynamic parameters, respiratory parameters

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Stereotactic brain biopsy with computer-assisted imaging techniques is used increasingly in the diagnosis of mass lesions of the brain. The technique provides a method of obtaining tissue for pathologic diagnosis under local anesthesia without craniotomy. The discomfort associated with drilling a hole through the calvarium and advancing the biopsy needle requires sedation and analgesia.[1] Opioid-benzodiazepine combinations are in general used to achieve different components of anesthesia and sedation, a benzodiazepine for hypnosis and an opioid for blockage of responses to noxious stimulation. Additionally, these 2 groups of agents interact favorably with regard to the hypnotic component of anesthesia.[2–5] However, excessive use of these drugs can produce life-threatening complications.[6,7] The fear of producing carbon dioxide (CO_2) retention and a secondary increase of intracranial pressure sometimes preclude the use of sedation or premedication for the spontaneously breathing patient in the presence of an intracranial space occupying lesion.[8]

The ideal sedation technique for patients undergoing stereotactic brain biopsy should provide adequate analgesia and depth of sedation without significant cardio-respiratory alterations, and rapid recall. The present study was designed to compare the effects of 3 different sedative-analgesics (fentanyl, alfentanil, and remifentanil) with the most usual doses at clinical practise on hemodynamic and respiratory parameters in patients with intracranial mass lesions undergoing stereotactic brain biopsy.

METHODS

A 135 unpremedicated, outpatients with American Society of Anesthesiologists physical status I to II, undergoing stereotactic brain biopsy were studied according to Local Ethics Committee-approved protocol. The procedure was explained to all patients in detail and evaluated their capacity of understanding, their fears, and motivation and appropriate consent was obtained. Exclusion criteria included age less than 18 years, history of drug or alcohol abuse, or an allergic reaction to one of the study medications, presence of ventricular drain, taking psychotropic drugs (benzodiazepines and barbiturates), and obesity (body mass index $> 35\,kg/m^2$). Intubated patients and those who had a prior craniotomy were also excluded.

After a scalp nerve block was performed to all patients with 20 mL of a mixture of prilocaine 2% and bupivacaine 0.5% in equal amounts, the stereotactic frame was installed and the patient was brought to the radiology suite for a computed tomography. The interval between the performance of the scalp nerve block and the

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beginning of the stereotactic biopsy was approximately 1 hour.

The stereotactic frame has no mobile face element. Thus, in the case of airway control loss, the screwdrivers are necessary to remove the frame and all airway equipments like nasal or oral airways, laryngeal mask airway, endotracheal tube, and McCoy laryngoscope were ready before sedation.

After the placement of standard anesthesia monitors [electrocardiogram, noninvasive blood pressure, peripheral oxygen saturation (SpO_2), and end tidal CO_2 ($ETCO_2$) (Drager-CATO)], application of supplemental O_2, 3 L/min by nasal prongs, 0.03 mg/kg IV midazolam for sedation, and metoclopramide 10 mg IV for antiemetic effect were administered to all patients. Patients were randomized to receive alfentanil, fentanyl, or remifentanil sedative regimens. Group A (n = 45) received a loading dose of IV alfentanil 7.5 μg/kg followed by infusion rate of 0.25 μg/kg/min. Group F (n = 45) received a bolus dose of 1 μg/kg IV fentanyl and repeated as needed. Group R (n = 45) received infusion of 0.05 μg/kg/min remifentanil. The infusion rates were varied to maintain an adequate and constant sedative state (Ramsay Sedation Scale score 3 or 4).[9] Sedation score, systolic and diastolic blood pressures (SBP, DBP), heart rate (HR), respiratory rate (RR), SpO_2, $ETCO_2$ were recorded on arrival at the operating room (baseline) and 2 minutes after the bolus or loading dose, or commencement of drug infusion, after infiltration of skin with local anesthesia, at skin incision, at bone flap removal, at dural incision, during biopsy, at dural closure, at bone flap closure, at skin closure, and after cessation of study drugs at the end of the surgery. All the surgeries were started after 10 minutes of the bolus or loading dose, or commencement of drug infusion, and 5 minutes of skin infiltration with prilocain. To provide the patient with the best comfort, we did not insert a foley catheter. All patients received 0.9% normal saline 5 mL/kg/h IV throughout the procedure. Precordial doppler was used to detect venous air embolism in patients with semisitting position.

Intraoperative side effects including patient movements, pain and discomfort, headache, nausea, vomiting, convulsions, bradypne (RR < 8 breaths/min) or apnea (respiratory arrest for > 15 s), bradycardia (HR < 45 beats/min), hypotension (systolic blood pressures decrease more than 20% from baseline and/or < 80 mm Hg), and hypertension (systolic blood pressures increase more than 20% from baseline and/or > 150 mm Hg) were also recorded. If hypertension occurred, a remifentanil 0.05 μg/kg bolus or alfentanil 15 μg/kg bolus, or fentanyl 1 μg/kg bolus was administered. If hypotension occurred, drug infusions were discontinued temporarily. When the patient failed to respond to either additional alfentanil or remifentanil, or fentanyl or discontinuing the infusions within 3 minutes, a rescue medication with nitroglycerin (80 μg IV) or ephedrine (0.1 mg/kg IV) was administered, respectively. During bradypnea or oxygen desaturation ($SpO_2 \leq 94\%$ of more than 10 s), the infusion rate of drugs was decreased or discontinued and the patients were requested to breathe deeply. The infusion rate was restarted at a lower infusion rate when the SpO_2 increased above 95% with RR > 8 breaths/min. At the end of the procedure, the infusions were discontinued and all the patients were transported to the postanesthesia care unit.

Descriptive statistics were given as mean ± SE for continuous variables. Parametric paired sample *t* test and nonparametric Wilcoxon test were used to compare the obtained values at different times within groups according to baseline. For comparing of percent changes between groups, Kruskall Wallis test was performed. Any *P* values less than 0.05 were considered significant ($P < 0.05$). All analyses were performed using SPSS for windows computer software 13.0 program.

RESULTS

All 3 groups were comparable regarding demographics data and duration of sedation (Table 1). All groups were similar in terms of preoperative data (Table 2).

Although some significant alterations were observed in SBP from baseline values in all groups, generally no significant differences were noted among groups, except only in DBP in groups F and R at skin incision (Fig. 1). During the procedure, the patients in group F had significantly lower mean HR than those in groups A and R. Significantly lower mean HR was detected in groups F and A than baseline, but this was not in the limits of bradycardia (Fig. 2). The patients in group A had significantly lower mean SpO_2 than those in the other groups, but mean SpO_2 values did not drop below 94% (Fig. 3). A significant decrease in $ETCO_2$ was observed at DC when compared with baseline values in group R ($P < 0.05$). However, there were no significant differences in $ETCO_2$ and RR values among the groups. Intraoperative side effects were summarized in Table 3.

Two patients in group F and 1 patient in group A experienced pain and discomfort. One patient in group F had nausea, but none of the patients vomited. Two patients in group R and 1 patient in group F had convulsions and received IV diazepam (5 mg). One patient developed apnea in group R after an additional bolus administration of 0.05 μg/kg IV remifentanil for relief of pain at the beginning of the procedure. Laryngeal mask

TABLE 1. Patients' Demographic Data and Duration of Sedation (Mean ± SE)

	Group A (n = 45)	Group F (n = 45)	Group R (n = 44)
Demographic data			
Age (y)	54.1 ± 2.0	50.0 ± 2.1	59.2 ± 2.0
Weight (kg)	67.7 ± 1.7	67.0 ± 2.0	68.1 ± 1.7
Sex (male/female)	22/23	21/24	21/24
ASA (I/II)	28/17	30/15	29/16
Duration of sedation (min)	42.7 ± 3.8	37.4 ± 4.6	42.3 ± 3.6

A indicates alfentanil; F, fentanyl; R, remifentanil.

TABLE 2. Preoperative Signs and Symptoms of the Patients With Tumor Localizations

	Group A (n = 45)	Group F (n = 45)	Group R (n = 44)
Consciousness (n)	44	45	43
Desorientation (n)	1	—	1
Tumor localization (n)			
Frontal	9	13	9
Temporal	13	11	11
Parietal	12	10	13
Thalamic	7	9	8
Multifocal	4	2	3
Tumor size (cm)			
$< 3 \times 3$	26	28	27
$\geq 3 \times 3$	19	17	17
Peritumoral edema (n)	13	12	9
Midline shift (n)	7	5	4
Hydrocephalus (n)	1	2	1
Headache (n)	17	13	10
Nausea (n)	6	3	2
Vomiting (n)	3	-	-
Papilledema (n)	5	6	3

A indicates alfentanil; F, fentanyl; R, remifentanil.

was inserted immediately and ventilated for a short period. The results of this case were excluded from analysis. Another 1 patient in the same group developed

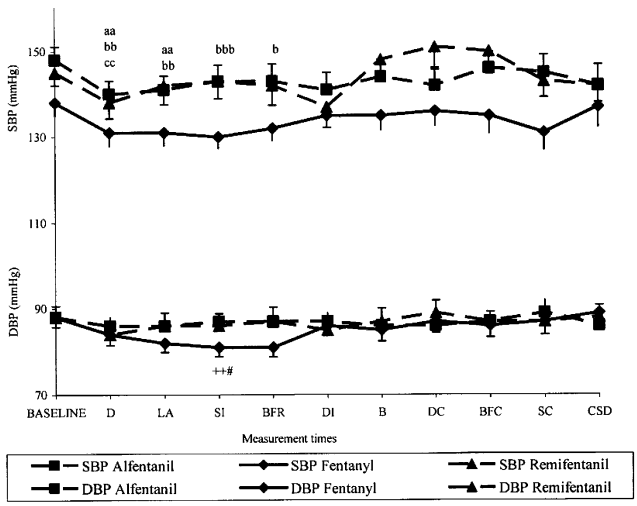

FIGURE 1. Systolic and diastolic blood pressure (SBP, DBP) changes for alfentanil, fentanyl, and remifentanil groups during the surgery (mean ± SE). D, Two minutes after the bolus or loading dose, or commencement of drug infusion; LA, after infiltration of skin with local anesthesia; SI, at skin incision; BFR, at bone flap removal; DI, at dural incision; B, during biopsy; DC, at dural closure; BFC, at bone flap closure; SC, at skin closure; CSD, after cessation of study drugs at the end of the surgery.

a: Group A comparison with baseline, aa: p<0.01
b: Group F comparison with baseline, b: p<0.05 bb: p<0.01 bbb: p<0.001
c: Group R comparison with baseline, cc: p<0.01
+: Group F and A compared with each other, ++: p<0.01
#: Group A and R compared with each other, #: p<0.05.

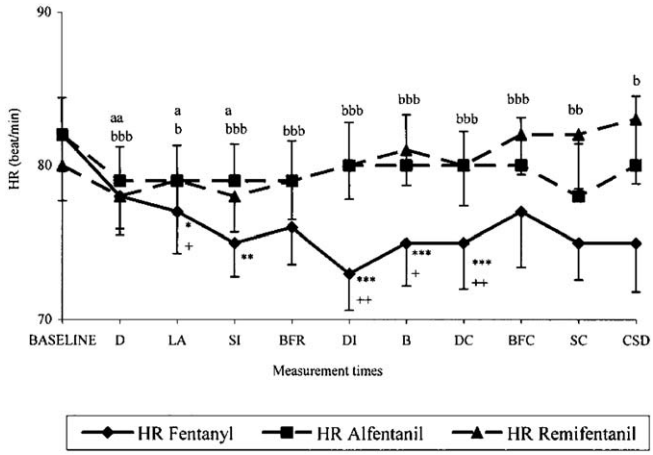

FIGURE 2. Heart rate (HR) alterations for alfentanil, fentanyl, and remifentanil groups during the surgery (mean ± SE). D, Two minutes after the bolus or loading dose, or commencement of drug infusion; LA, after infiltration of skin with local anesthesia; SI, at skin incision; BFR, at bone flap removal; DI, at dural incision; B, during biopsy; DC, at dural closure; BFC, at bone flap closure; SC, at skin closure; CSD, after cessation of study drugs at the end of the surgery.

a: Group A comparison with baseline, a: p<0.05 aa: p<0.01
b: Group F comparison with baseline, b: p<0.05 bbb: p<0.001
+: Group F and A compared with each other, +: p<0.05 ++: p<0.01
*: Group F and R compared with each other, *: p<0.05 **: p<0.01 ***: p<0.001.

bradypnea before skin incision, but he recovered immediately after taking a deep breath. Hypoxemic episodes were observed with a total of 5 times in 2 patients in group A and 2 times in 1 patient in group F, and totally 7 times in 3 patients in group R. Three patients had bradycardia in group F and 1 patient in group A. Hypotension was recorded in 2, 3, and 1 patients in groups A, F, and R with a sum of 3, 4, and 3 times, respectively. Two patients had hypertension with a total of 3 times in group A, 3 patients totally 5 times in group F, and 2 patients totally 2 times in group R.

DISCUSSION

This study indicates that moderate fentanyl sedation results in lower HR than the use of alfentanil and remifentanil sedation, and moderate alfentanil sedation results in lower SpO_2 groups than the use of fentanyl and remifentanil sedation in patients with brain tumor undergoing stereotactic brain biopsy.

The use of sedation during local anesthesia can enhance patient comfort and thereby improve operative conditions. During stereotactic brain biopsy, local anesthesia and monitored sedation is an accepted technique. Analgesia-based sedation techniques, which focus on patient comfort rather than on patient sedation by

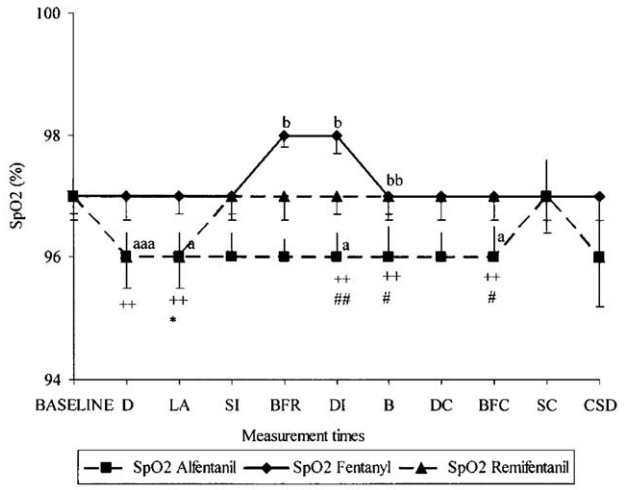

FIGURE 3. Peripheric oxygen saturation (SpO_2) alterations for alfentanil, fentanyl, and remifentanil groups during the surgery (mean ± SE). D, Two minutes after the bolus or loading dose, or commencement of drug infusion; LA, after infiltration of skin with local anesthesia; SI, at skin incision; BFR, at bone flap removal; DI, at dural incision; B, during biopsy; DC, at dural closure; BFC, at bone flap closure; SC, at skin closure; CSD, after cessation of study drugs at the end of the surgery.

a: Group A comparison with baseline, a: $p<0.05$ aaa: $p<0.001$
b: Group F comparison with baseline, b: $p<0.05$
+: Group F and A compared with each other, +: $p<0.05$ ++: $p<0.01$
#: Group A and R compared with each other, #: $p<0.05$ ##: $p<0.01$.
*: Group F and R compared with each other, *: $p<0.05$ **: $p<0.01$.

delivering analgesic needs of the patient and adding a sedative only if necessary, are becoming more important during short painful surgical procedures such as stereotactic biopsy. Opioid receptor agonists, including the synthetic opioids fentanyl and alfentanil, are frequently used as anesthetic adjuncts during the perioperative management of neurosurgical patients.[10,11] Remifentanil is accepted as a reasonable alternative in neuroanesthesia.[11,12]

Sedative-hypnotics and opioid analgesics are frequently used in combination to provide patient comfort, sedation, anxiolysis, and supplemental analgesia during outpatient surgical procedures performed under local anesthesia as part of a monitored anesthesia care technique. The degree of noxious stimulation varies during surgical procedure, requiring frequent adjustments in the depth of sedation and analgesia. During stereotactic brain biopsy, there are periods of intense stimulation (eg, head pinning and scalp incision) alternating with periods of minimal stimulation (eg, brain biopsy). Systemic analgesia is desirable during the initial infiltration of the local anesthetic solution, and to prevent the discomfort associated with bone flap removal and dural incision.

The doses chosen in this study were not strictly equipotent, but they were considered comparable and were meant to reflect those used or suggested for use in clinical practise. The doses of alfentanil that was selected by the manufacturer's prescribing information were at the lower end of the suggested dose range, but were considered appropriate for the anticipated duration of surgery. The doses of remifentanil were derived from dose finding studies. In a study in which remifentanil was the sole analgesic in 31 pediatric cases during painful medical procedures, the infusion dose required for those patients was 0.5 ± 0.3 μg/kg/min.[13] Remifentanil is reported as 15 times more potent than alfentanil, based on the median effective dose to achieve loss of response to a verbal command.[14] The starting maintenance infusion rate was reported in some studies to be 0.1 μg/kg/min, which was then titrated according to the clinical end points of comfort, relief of anxiety and pain, and attenuation of hemodynamic responses to surgical stimuli without excess sedation, respiratory depression, or apnea.[15,16]

Opioids characteristically cause dose-dependent depression of the ventilatory response to hypercarbia and blunting of the ventilatory response to hypoxia.[7,17] Respiratory depression in neurosurgical patients is an important issue because elevated partial arterial carbon dioxide pressure and decreased partial arterial oxygen pressure values produce an increase in cerebral blood volume, thereby worsening brain swelling. Patients having spontaneous respiration cannot be passively hyperventilated, and because urinary catheters were not routinely employed, administration of diuretics was avoided to decrease cerebral volume. Although there were no significant differences among groups in RR and $ETCO_2$ values, significant decreases in SpO_2 in group A were observed in our study. Dose-dependent and delayed respiratory depression with the preservation of adequate RR has also been reported with alfentanil infusion techniques.[18–20] It was shown that alfentanil caused no adverse hemodynamic effects, but respiratory depression in association with analgesia.[21]

TABLE 3. Number of Patients With Adverse Events During the Procedure (n)

	Group A (n = 45)	Group F (n = 45)	Group R (n = 44)
Complaints of pain and discomfort	1	2	—
Headache	—	—	—
Nausea	—	1	—
Vomiting	—	—	—
Convulsions	—	1	2
Bradypnea (RR < 8 breath/min)	—	—	1
Apnea (respiratory arrest for > 15 s)	—	—	1
Desaturation (SpO_2 < 94%)	2	1	3
Bradycardia (HR < 45 beats/min)	1	3	—
Hypotension (SBP < 20% of baseline)	2	3	1
Hypertension (SBP > 20% of baseline)	2	3	2

A indicates alfentanil; F, fentanyl; R, remifentanil SBP, Systolic blood pressure; HR, heart rate; RR, respiratory rate; SpO_2, peripheric oxygen saturation.

In a study that investigated the effects of combining midazolam and fentanyl on the slope of the ventilatory response to hypercarbia, the incidence of apnea was significantly increased when fentanyl was added to midazolam.[9]

Respiratory depression is an expected adverse effects of remifentanil administration. It is more frequently observed with infusion rates $> 0.2\,\mu g/kg/min$. However, in the study of Gold et al,[16] respiratory profiles of remifentanil administration were found stable despite frequent alterations of the infusion rate. The pharmacokinetics of remifentanil are independent of the total dose, as well as the rate and duration of infusion. In addition, there is no accumulation of remifentanil even in patients with severe renal or hepatic dysfunction.[22] The danger of bolus administration of remifentanil was also been outlined in studies in which remifentanil was used to provide postoperative analgesia in spontaneously breathing patients.[23] Respiratory depression was reported to be linked to the blood concentration of remifentanil.[24] A theoretic advantage of using remifentanil is the rapid return of ventilatory drive once the infusion is discontinued.[13] However, similar incidences of respiratory depression with remifentanil and alfentanil in volunteers were reported.[22]

There are reports that a remifentanil-based anesthetic technique provided stable and similar hemodynamics when compared with a fentanyl-based anesthetic in patients undergoing surgery for intracranial mass lesions.[11,14] Use of continuous infusions of short-acting anesthetic and analgesic drugs has been found to be associated with fewer side effects and shorter recovery times than intermittent bolus techniques.[25,26] Also, continuous infusion of sedative-hypnotic drugs provides a stable level of sedation.[27,28] In a large-scale study of 2438 patients, Twersky and colleagues[29] confirmed better hemodynamic control using remifentanil than using fentanyl. Alfentanil infusions have been shown to provide hemodynamic stability.[30,31]

The present study demonstrates that it is possible to maintain a stable level of sedation by using midazolam and variable-rates of alfentanil or remifentanil infusions or bolus fentanyl administration. Although some statistically significant differences were noted in hemodynamic and respiratory parameters among the groups, no life-threatening event was encountered. As these differences were accepted as clinically insignificant, our results suggest that all 3 regimens have relatively similar hemodynamic and respiratory responses. The use of bolus fentanyl technique caused less hemodynamic stability. The continuous infusion technique of remifentanil or alfentanil provided better control on hemodynamic parameters. Thus, the 3 IV sedative-analgesic regimens, including alfentanil, fentanyl, and remifentanil that we evaluated, seemed to be highly effective and safe.

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