Assessment of Depth of Anesthesia and Postoperative Respiratory Recovery after Remifentanil- versus Alfentanil-based Total Intravenous Anesthesia in Patients Undergoing Ear–Nose–Throat Surgery

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Background: The authors investigated whether total intravenous anesthesia (TIVA) with precalculated equipotent infusion schemes for remifentanil and alfentanil would ensure appropriate analgesia and that remifentanil would result in better recovery characteristics.

Methods: Forty consenting patients (classified as American Society of Anesthesiologists physical status I–III) scheduled for microlaryngoscopy were randomized to receive, in a double-blind manner, either remifentanil (loading dose 1 \( \mu \)g/kg; maintenance infusion, 0.25 \( \mu \)g \( \cdot \) kg \(^{-1} \) \( \cdot \) min \(^{-1} \)) or alfentanil (loading dose, 50 \( \mu \)g/kg; maintenance infusion, 1 \( \mu \)g \( \cdot \) kg \(^{-1} \) \( \cdot \) min \(^{-1} \)) as the anesthetic component of TIVA. They were combined with propofol (loading dose, 2 mg/kg; maintenance infusion, 100 \( \mu \)g \( \cdot \) kg \(^{-1} \) \( \cdot \) min \(^{-1} \)). To ensure an equal state of anesthesia, the opioids were titrated to maintain heart rate and mean arterial pressure within 20% of baseline, and propofol was titrated to keep the bispectral index (BIS) less than 60. Neuromuscular blockade was achieved with succinylcholine. Drug dosages and the times from cessation of anesthesia to extubation, verbal response, recovery of ventilation, and neuropsychological test-performance, orientation, and discharge readiness were recorded.

Results: Demographics, duration of surgery, and anesthesia were similar between the two groups. Both groups received similar propofol doses. There were no difference in BIS values preoperatively (mean, 96), intraoperatively (mean, 55), and postoperatively (mean, 96). Recovery of BIS and times for verbal response did not differ. At 20, 30, and 40 min after terminating the opioid infusion, the peripheral oxygen saturation and respiratory rate were significantly higher in the remifentanil group compared with the alfentanil group.

Conclusions: When both the hypnotic and analgesic components of a TIVA-based anesthetic are administered in equipotent doses, remifentanil provides a more rapid respiratory recovery, even after brief surgical procedures, compared with alfentanil.

WITH the introduction of new potent anesthetics (sevoflurane, desflurane, propofol) and analgesics (remifentanil) into contemporary clinical anesthesia practice, it is important to validate the advantages of regimens using these compounds to provide optimal anesthesia.1–5 Preclinical and clinical studies indicated that remifentanil, a new esterase-metabolized \( \mu \) opioid, provides analgesia and a rapid decrease in drug concentration because of its unique pharmacokinetics. It was therefore proposed that the use of remifentanil allows for a more rapid recovery compared with other opioids. Total intravenous anesthesia (TIVA) has gained a new interest with the clinical availability of remifentanil.4 However, the coadministration of a potent analgesic alters the plasma concentration of the coadministered hypnotic required to provide loss of consciousness (LOC) and prevention of movement to skin incision.5–7 Thus, the use of different opioids for TIVA implies complex pharmacology.6 To establish any differences in recovery profile between opioids, it is critical that the same degree of hypnosis is achieved when making comparisons. In addition, when using opioids in high concentrations, clinical signs of awareness might be masked. Thus, monitoring of the state of consciousness appears to be necessary.9 Conventional clinical signs in enabling anesthetists to recognize periods of conscious awareness may be less reliable with the administration of remifentanil to maximal analgesic concentrations.9 The bispectral index (BIS), a derived value of the electroencephalogram, has become a reliable measure for LOC and loss of recall for volatile and intravenous agents.10–13 The present study was designed to test the hypothesis that TIVA with precalculated equipotent infusion schemes for remifentanil and alfentanil would ensure appropriate analgesia, and an equal state of LOC and remifentanil administration would result in better recovery characteristics.

Methods

After institutional review board approval from Wilhelm-Universität Münster and informed consent were obtained, 42 patients classified as American Society of Anesthesiologists physical status I–III who were scheduled for microlaryngoscopy were enrolled in the study. Exclusion criteria were age younger than 18 yr or older than 70 yr, use of analgesics or sedatives within the previous 24 h before the study, a known pseudocholinesterase deficiency, and failure at the time of the preoperative interview to complete a series of neuropsychological function tests as described below. Patients

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were also excluded if they were more than twice ideal body weight, significantly hypertensive (diastolic blood pressure $>100\text{ mmHg}$) or hypotensive (systolic blood pressure $<100\text{ mmHg}$), or presented any previous signs of bradycardiac heart disorders.

Patients were prospectively studied and assigned in a randomized, double-blind manner to one of two treatment groups: (1) intravenous remifentanil (loading dose, $1.0\text{ g/kg}$ over 120 s; maintenance, $0.25\text{ g/kg} \cdot \text{min}^{-1}$); or (2) intravenous alfentanil (loading dose, $50\text{ g/kg}$ over 120 s; maintenance, $1\text{ g/kg} \cdot \text{min}^{-1}$). These infusion schemes were determined through pharmacokinetic simulations to achieve equipotent opioid concentrations based on a potency ratio of 1 ng/ml (plasma) remifentanil equivalent to 40 ng/ml (whole blood) alfentanil. The dilution of remifentanil was 3 mg/50 ml and for alfentanil 12 mg/50 ml, which provided equal infusion rates for maintenance in both groups. No premedication was given. Standard monitoring included continuous heart rate via electrocardiogram, noninvasive blood pressure obtained every 1–5 min, and continuous pulse oximetry. An electroencephalogram signal was obtained using electrodes applied in a bifrontal montage (Fp1–A1 and Fp2–A2 in the International 10–20 System of electrode placement). Impedance was less than 5 kΩ. The BIS value was displayed using an Aspect electrophenogram monitor (Model A-1050; Aspect Medical Systems, Natick, MA). An interviewer who was not aware of the study drug (supplied as coded bolus and infusion syringes) recorded all perioperatively obtained measurements at 1-min intervals during induction of anesthesia and subsequently at 2–5-min intervals during the maintenance period. They also performed all tests in the postoperative anesthetic care unit (PACU). On arrival in the operating room, the baseline values for BIS, heart rate, blood pressure, and pulse oximetry were obtained, and an intravenous catheter was placed. Before induction of anesthesia, patients breathed 100% oxygen for 5 min and were given 5 ml/kg intravenous fluid (e.g., lactated Ringer’s solution). Before delivery of a loading bolus of remifentanil or alfentanil (over 120 s), 0.5 mg atropine was injected. The continuous infusion of remifentanil or alfentanil was started at a rate of $0.25\text{ g/kg} \cdot \text{min}^{-1}$ for remifentanil or $1\text{ g/kg} \cdot \text{min}^{-1}$ for alfentanil. Induction bolus of propofol (2 mg/kg) was injected simultaneously with the analgesic and continued at $100\text{ g/kg} \cdot \text{min}^{-1}$ throughout the procedure. Once LOC (no verbal response) was achieved, a succinylcholine infusion was started at a maintenance dose of $100\text{ g/kg} \cdot \text{min}^{-1}$.

Oxygen was delivered concomitantly via face mask until endotracheal intubation was performed using a special high-frequency jet ventilation tube. All patients were mechanically ventilated using a high-frequency jet ventilation technique. Inspiratory oxygen concentration was maintained to achieve adequate levels of oxygen saturation ($\text{SpO}_2 > 93$). Blood pressure, heart rate, $\text{SpO}_2$, and BIS were monitored and recorded at 1-min intervals during induction of anesthesia and subsequently at 5-min intervals throughout anesthesia.

Inadequate hypnosis was defined as BIS greater than 60 and was treated with a bolus dose of propofol 1 mg/kg. Inadequate analgesia was defined as responses to surgical stimuli by hypertension (systolic blood pressure $>20\%$ above preoperative baseline value for more than 5 min) or tachycardia (heart rate $>20\%$ above preoperative baseline values).

Responses were initially treated by administering one or two bolus doses of study drug (remifentanil group = $0.5\text{ g/kg}$; alfentanil group = $4\text{ g/kg}$). If this treatment was unsuccessful, the study drug infusion rate was doubled. Hypotension (mean arterial pressure $<60\text{ mmHg}$) was treated by fluid delivery (5 ml/kg intravenous lactated Ringer’s solution) or vasopressor if this treatment was ineffective. To assess intraoperative awareness, in addition to a standard interview obtained postoperatively to elicit any recall events during anesthesia, a number was repetitively told to each patient four times during anesthesia at 5, 10, 15, and 20 min by the observer. The patient was specifically questioned for recall of this number.

At the end of surgery, all infusions were terminated, and 100% oxygen was applied through the high-frequency jet ventilation tube until the return of spontaneous respiration. The trachea was then immediately extubated. The patient received oxygen delivered via an open face mask with a flow of 4 l/min for the next 5 min. Recovery times were determined in 1-min intervals from cessation of the TIVA delivery until the patient qualified for transfer to the PACU. In the PACU, criteria for discharge were evaluated every 2–5 min. There was no reaction.

### Table 1. Vigilance Scores after Camron

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No reaction</td>
</tr>
<tr>
<td>1</td>
<td>Unspecific body movements</td>
</tr>
<tr>
<td>2</td>
<td>Unspecific mimic motions</td>
</tr>
<tr>
<td>3</td>
<td>Eye opening</td>
</tr>
<tr>
<td>4</td>
<td>Directed eye movements</td>
</tr>
<tr>
<td>5</td>
<td>Hand shaking</td>
</tr>
<tr>
<td>6</td>
<td>Telling residency</td>
</tr>
<tr>
<td>7</td>
<td>Telling age and date of birth</td>
</tr>
<tr>
<td>8</td>
<td>Completion of interference task</td>
</tr>
<tr>
<td>9</td>
<td>Recognition of complex graphic pattern</td>
</tr>
<tr>
<td>10</td>
<td>Drawing of pattern</td>
</tr>
</tbody>
</table>

### Table 2. Demographics and Operation Times

<table>
<thead>
<tr>
<th>Group</th>
<th>Remifentanil</th>
<th>Alfentanil</th>
<th>U Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>17/3</td>
<td>15/5</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>$174 \pm 8$</td>
<td>$170 \pm 7$</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>$78 \pm 15$</td>
<td>$75 \pm 11$</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>$52 \pm 12$</td>
<td>$57 \pm 8$</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>$19 \pm 9$</td>
<td>$24 \pm 13$</td>
<td>NS</td>
</tr>
<tr>
<td>Anesthesia (min)</td>
<td>$30 \pm 9$</td>
<td>$34 \pm 13$</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.
no oxygen supplied if not indicated (\(\text{SpO}_2 < 90\%\)). During
the recovery period, patients had to complete a vigilance test (Camron
test\textsuperscript{14}) to evaluate their psychometric and psychomotor function. This test consists of
10 different graded tasks displayed in table 1. Each task
follows one after the other, if they are completed adequately. The Camron test is summarized as a score of
vigilance, with 0 being unconscious and 8–10 absolutely
alert. To gain reproducible scores, each patient was
introduced to the test the day before surgery with simi-lar, but not the same, tasks. Patients failing to complete
the test or with baseline values less than 8 were ex-
cluded from the study. In addition, Aldrete scores were
recorded concomitantly, and BIS were monitored until
actual discharge from the PACU.

Recovery included the time from the end of surgery
until achievement of adequate respiratory function and
time until adequate completion of psychomotor and
psychometric tests defined as a Camron score greater
than 8 and an Aldrete score greater than 9. Secondary
end points of this study were the comparison of BIS
indices and hemodynamic responses to stimuli for the
two distinct TIVA schemes. Using pharmacokinetic sim-
ulations (http://pkpd.icon.palo-alto.med.va.gov/), we
determined the predicted plasma concentrations for
remifentanil and alfentanil based on previously pub-
lished pharmacokinetic parameters for each study pa-
tient after completion of the study.

Statistical analysis included the Kolmogorov-Smirnov
test for all data. Analysis of variance followed by post hoc
analysis (Scheffé test) and Mann–Whitney U test were
used as appropriate. A Wilcoxon test was performed for
respiratory rate and pulse oximetry. All tests were per-
formed with commercially available statistic software
(SPSS Inc., Chicago, IL). In all tests, a \(P\) value less than
0.05 was considered to be significant. Before the study,
we performed a power analysis with previously obtained
data at our institution to assess the sample size required
to detect a difference of 30\% time to achieve an Aldrete
score of 8 or greater. This suggested a sample size of 15
patients for each group (power of 0.81 \(\alpha \alpha 0.05\)).

### Results

A total of 42 patients were enrolled in the study. One
patient was withdrawn because of a severe asthmatic
episode after cessation of the study drug (alfentanil) that

![Calculated plasma levels for Remifentanil and Alfentanil](https://example.com/calculated-plasma-levels.png)

Fig. 1. Data displaying the individual plasma concentrations for remifentanil (top) and alfentanil (bottom), using pharmacokinetic simulations.
required pharmacologic intervention, and another patient was withdrawn because of inability to complete the psychometric and psychomotor tests at the presurgical interview. Thus, data of 40 patients were analyzed. The two treatment groups were comparable with respect to the demographic data, American Society of Anesthesiologists physical status, and duration of surgery and anesthesia (table 2).

Both groups required a similar total dose of intravenous propofol (table 3; \( P < 0.05 \)). There was also no statistical significant difference with respect to the total dose of intravenous succinylcholine.

Simulations revealed remifentanil concentrations were more variable compared with alfentanil (fig. 1). However, there was a faster decay in drug plasma concentration with cessation of infusion for remifentanil versus alfentanil (fig. 1).

Mean arterial pressure decreased by 37 mmHg \( \pm 11 \) (\( \pm \) SD) in the remifentanil group after induction compared with 45 \( \pm 5 \) mmHg in the alfentanil group (\( P < 0.05 \)). By 10 min after induction there was a greater increase in mean arterial pressure in the alfentanil group compared with the remifentanil group (\( P < 0.05 \); fig. 2, bottom). However, both groups revealed hemodynamics within an acceptable clinical range.

Mean heart rate changed by 8 \( \pm 12 \) beats/min for remifentanil and by 14 \( \pm 14 \) beats/min for alfentanil (fig. 1). Heart rates differed between remifentanil- and alfentanil-treated patients within the first 3 min after start of induction and from 10–20 min after the infusion had been stopped (fig. 2, top).

Time until extubation was not different for both groups (remifentanil, 9 \( \pm 2 \) min; alfentanil, 11 \( \pm 5 \) min; \( P > 0.05 \)). Respiratory rates and \( \text{SpO}_2 \) values revealed a significantly faster recovery for remifentanil-treated patients compared with the alfentanil group. Within the first 40 min after termination of the opioid infusion, remifentanil-treated patients had returned to preoperative respiratory rates, whereas alfentanil-treated patients had lower respiratory rates and \( \text{SpO}_2 \) (fig. 3).

The preoperative BIS index baseline values were similar in both groups (mean, 96 \( \pm 2 \) SD). This index
decreased within the first 3 min after induction to values of 52 ± 6 (remifentanil) or 54 ± 12 (alfentanil) and remained at similar values throughout the maintenance period (fig. 4 and table 3). There was no significant difference between groups at any distinct time. After termination of TIVA delivery, both groups revealed a similar increase in the recovery of their BIS indices (recovery within 13 min for remifentanil and within 12 min for alfentanil; \( P > 0.05 \); fig. 4).

Vomiting was observed only in one patient in each group, pruritus was experienced by three alfentanil patients and one remifentanil patient, and shivering was experienced by one remifentanil patient.

Discussion

The present study investigated the recovery profile of a TIVA technique with equipotent infusion schemes for the two short-acting \( \mu \)-opioids, remifentanil and alfentanil, while maintaining intraoperatively a similar degree of hypnosis in both groups. TIVA with remifentanil resulted in a superior recovery profile compared with an alfentanil-based TIVA, as shown by a more rapid recovery of ventilatory function and higher Aldrete scores at 10 and 30 min. This more rapid recovery is likely to be caused by the unique esterase metabolism of remifentanil that results in a very rapid decay in its blood concentration (fig. 1).

The theoretical advantage of remifentanil is that it can be administered at maximal analgesic efficacy during a surgical procedure but still enable a rapid recovery and return of adequate spontaneous ventilation. Microvascular surgery is a surgical procedure requiring intense analgesia and rapid recovery and thus should be an ideal procedure in which to use the properties of remifentanil. Alfentanil also has a rapid onset and can provide intense analgesia but, based on its context-sensitive decrement times, would be predicted to provide slower recovery of respiratory function, especially when given for a procedure requiring more than a single bolus dose. In addition, alfentanil displays considerable variability in its pharmacokinetics because of its hepatic metabolism. Numerous studies to date have compared remifentanil to alfentanil, but none has attempted to administer them at equipotent concentrations and then evaluate recovery for both drugs. Although the brief duration of the procedure used in our experimental design might not be the optimal condition to elucidate differences of both opioids in terms of the speed of recovery, the observed differences already suggest even more distinct discrepancies for prolonged procedures.

Recent research focusing on the pharmacologic interaction between anesthetics and opioids has revealed complex pharmacokinetic and pharmacodynamic interactions. Increasing opioid concentration decreases the concentration of propofol required to prevent movement at skin incision in a nonlinear interaction. Recovery after a combination of propofol and opioid is dependent on the propofol reaching its wake-up concentration and
the opioid decreasing to a concentration below which adequate ventilation occurs. Thus, when evaluating recovery from a TIVA technique, it is important to insure that both the opioid and the hypnotic is administered to equivalent effect in both groups. These complexities may have limited the ability to perform such comparative studies.

Bispectral analysis is a quantitative technique that measures the consistency of the phase and power relations of the electroencephalogram signals derived, and it returns a single number, the BIS. The BIS has been shown to predict LOC and loss of recall for volatile and intravenous anesthetics. An index value less than 60 correlated with LOC and loss of recall in 95% of patients. For both analgesics, remifentanil and alfentanil, recent reports indicate that reliable LOC is not achievable when they are administered alone. Thus, a hypnotic drug is required when using these opioids to ensure adequate anesthesia. The contribution of the hypnotic to the anesthetic state can be determined using the BIS. Using precalculated dosing schemes, based on pharmacokinetic parameters from previous studies, we calculated that the propofol rate administered will result in plasma concentrations of propofol of \( 2.2 - 2.9 \text{ mg/ml} \) over a 30-min infusion period. This concentration of propofol is associated with LOC when combined with the analgesic concentrations of the opioid used in this study. By ensuring that propofol achieved equal BIS values in both groups, the difference in recovery from anesthesia was dependent on the concomitant opioid.

The second factor in providing appropriate comparisons between opioids is to insure they are administered at equipotent concentrations. Several investigators have tried to establish the relative potency of remifentanil to alfentanil. As we were observing their action in a balanced anesthetic technique, we based our relative potency on their ability to reduce the minimum alveolar concentration of isoflurane. Based on this estimate, remifentanil (blood concentration) is 40 times more potent than alfentanil (plasma concentration). This was also recently confirmed in another comparative study with remifentanil and alfentanil using ventilatory depression as the measure of opioid effect, and thus equipotent infusion schemes were used in our study.

In a recently reported comparison of remifentanil and alfentanil in coadministration with isoflurane in outpatient surgery, alfentanil displayed a more favorable profile compared with remifentanil with regard to recovery.
of verbal responsiveness, adequate respiration, and tracheal extubation. However, the applied dosing scheme of alfentanil 25 \( \mu g/kg \) as bolus dose and 0.5 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) as infusion would be below our calculated lower range of an alfentanil plasma concentration that was equipotent with their remifentanil dosing scheme. This was supported by the higher incidence of supplemental analgic injections in the alfentanil group in this study.

In conclusion, we present a study in which we compared the intraoperative and recovery profile after the equipotent administration of remifentanil to alfentanil during brief car–nose–throat procedures. We found that the intraoperative course was similar, but respiratory recovery was more rapid with remifentanil. These findings would imply that for brief procedures with intense nocuous stimulation, remifentanil may be the opioid of choice, especially if rapid respiratory recovery is mandatory.

The authors thank Aspect Medical Systems, Space Lab, Germany, for providing the bispectral index monitor and disposable electrodes; and Döring Technology, Germany, for providing the infusion pump system.

References