Recovery of Cognitive Function After Remifentanil-Propofol Anesthesia: A Comparison with Desflurane and Sevoflurane Anesthesia

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We compared the recovery characteristics of remifentanil, desflurane, and sevoflurane when used for anesthesia in elective operative procedures. Sixty ASA physical status I and II patients, aged 18–65 yr, were randomly assigned to receive remifentanil-propofol, desflurane-N_2O, or sevoflurane-N_2O anesthesia. Before the induction of anesthesia, the patients of the desflurane and sevoflurane groups received fentanyl 2 μg/kg. In all groups, anesthesia was induced with propofol and maintained either with remifentanil 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$, desflurane, or sevoflurane 0.85 MAC with 65% nitrous oxide in oxygen. Anesthetics were titrated to achieve an adequate level of surgical anesthesia and to maintain mean arterial pressure within 20% of baseline values. Early recovery times and a modified Aldrete Recovery Score > 9 were recorded. Trieger Dot Test and Digit Substitution Test (DSST) were performed the day before surgery and in the postanesthesia care unit to evaluate intermediate recovery. The remifentanil-propofol group had a significantly faster emergence than desflurane or sevoflurane, with no difference between both inhaled anesthetics. Thirty min after anesthesia administration, patients in the remifentanil-propofol and in the desflurane groups gave significantly more correct responses in the DSST compared with sevoflurane (remifentanil 87%, desflurane 83%, sevoflurane 56%), the impairment in the sevoflurane patients corresponding to the effects of a blood alcohol level of approximately 0.1% and, thus, being of clinical importance. Ninety minutes after anesthesia administration, no significant difference could be demonstrated among the groups in the DSST scores. Emergence and return of cognitive function was significantly faster after remifentanil-propofol compared with desflurane and sevoflurane up to 60 min after anesthesia administration. **Implications:** We compared awakening and intermediate recovery times after remifentanil-propofol anesthesia to desflurane-N_2O and sevoflurane-N_2O anesthesia. Emergence and return of cognitive function was significantly faster after remifentanil-propofol compared with desflurane and sevoflurane up to 60 min after anesthesia administration.

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The pharmacokinetics of remifentanil allow easy titration to changing intraoperative conditions and swift and predictable emergence from anesthesia. A total IV anesthesia (TIVA) regimen with remifentanil and propofol is a useful anesthetic technique, effectively controlling responses to tracheal intubation and intense surgical stimulation, while allowing for rapid emergence from anesthesia without prolonged respiratory depression (1).

The low blood/gas and tissue/blood partition coefficients of desflurane and sevoflurane provide a rapid uptake during the induction of anesthesia, rapid changes in depth of anesthesia, and rapid elimination, resulting in a rapid emergence and recovery relative to other volatile anesthetics (2–6). Yet direct comparisons of these volatile anesthetics with remifentanil-based TIVA are lacking. Therefore, the aim of this study was to compare the clinical properties of these three new anesthetics with regard to recovery from anesthesia and postoperative cognitive function.

Methods

Sixty healthy male and female ASA physical status I and II patients, aged 18–65 yr, scheduled for elective operative procedures, were enrolled in the study after approval by the ethics committee and patients' written, informed consent. The assignment of patients to TIVA or inhaled anesthesia groups was randomized and single blinded:

- Group 1 = TIVA with remifentanil/propofol,

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- Group 2 = balanced anesthesia with desflurane/fentanyl/N_2O, or
- Group 3 = balanced anesthesia with sevoflurane/fentanyl/N_2O.

Exclusion criteria for potential subjects were (a) a history of a significant cardiac, pulmonary, hepatic or renal disease, (b) chronic drug or alcohol abuse, (c) morbid obesity, (d) disabling neuropsychiatric disorders, (e) hypersensitivity to anesthetics or familial history of malignant hyperthermia, (f) women who were pregnant or breast-feeding, and (g) patients who refuse to give consent.

On the day before surgery, hemodynamic variables (systolic, mean, and diastolic arterial blood pressure) and psychomotor state (Trieger Dot Test [TDT], Digit Symbol Substitution Test [DSST]) were assessed. In the TDT, patients were asked to connect dots within 1 min; missed dots and the distance line-dot (mm) were noted. In the DSST, patients were given 1 min to replace digits with appropriate symbols located in a legend at the top of the page. In the evening, all patients received diazepam 5–10 mg orally.

Forty five minutes before the induction of anesthesia, all patients were given midazolam 7.5 mg orally for premedication. Usual monitors were used. The inspired oxygen concentration and end-tidal concentrations of N_2O, desflurane, and sevoflurane were recorded at 5-min intervals on discontinuation of the inhaled anesthetic. Desflurane was administered by using a vaporizer (Devapor; Dräger, Lübeck, Germany) and sevoflurane by using a Dräger vaporizer 19.3.

A modified lactated Ringer's solution, was started at a rate of 3 $mL \cdot kg^{-}1 \cdot h^{-1}$, and a second line was inserted for the administration of propofol and remifentanil. Blood pressure, heart rate, O_2 saturation, and end-tidal CO_2 concentration were measured and recorded before the induction of anesthesia, every minute during induction, and every 5 min thereafter. The end-tidal CO_2 concentration was maintained at 35 mm Hg with controlled ventilation. After the induction of anesthesia, all patients received paracetamol 1000 mg supplement for reducing postoperative pain. All patients breathed 100% oxygen for 3 min before the induction of anesthesia.

In patients randomized to receive remifentanil-propofol, infusion was started at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until patients felt dazed. Thereafter, anesthesia was induced by propofol in a dose adequate for loss of eye-lash reflex, followed by rocuronium 0.6 mg/kg for tracheal intubation. After intubation, remifentanil infusion was reduced to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and a propofol infusion was started at a rate of 3 $mg \cdot kg^{-1} \cdot h^{-1}$ and maintained throughout surgery. During the maintenance of anesthesia, patients were ventilated with a fresh gas flow of 2 L/min of oxygen 35% in air by using a semiclosed circle system. No inhaled anesthetics were given.

Patients assigned to Groups 2 and 3 received anesthesia according to the following protocol: Before the induction of anesthesia, all patients received fentanyl 2 μgkg IV, then breathed 100% oxygen for 3 min. Anesthesia was induced with propofol 2 mgkg IV. After loss of consciousness, patients received either desflurane at an end-tidal concentration of 5% or sevoflurane 1.7% and rocuronium 0.6 mg/kg to facilitate endotracheal intubation. Maintenance of anesthesia was provided with the respective volatile anesthetic (0.85 minimum alveolar anesthetic concentration [MAC]) with N_2O 65% in O_2; the inspired concentration was adjusted to maintain mean arterial pressure (MAP) within 20% of baseline values. The value of MAC was corrected for age in each subject of both groups.

Anesthetics (remifentanil, propofol, desflurane, and sevoflurane) were decreased only in response to hypotension that was not responsive to replacement of intraoperative fluid losses or bradycardia. When clinically indicated (MAP below 20% of preinduction baseline value), a vasopressor (cafedrine/theodrenaline) 0.3–2.0 mL was administered to increase MAP to acceptable levels. Bradycardia was defined as heart rate < 50 bpm and treated with atropine 0.5 mg IV. Anesthetics (remifentanil, propofol, desflurane, and sevoflurane) were increased to control the hemodynamic responses to surgical stimulation, assigned by MAP $>$ 20% of the preinduction baseline values and/or heart rate $>$ 90 bpm or clinical signs of light anesthesia (patient movement, eye opening, swallowing, grimacing, lacrimation, or sweating). In the volatile anesthetic groups, additional bolus doses of fentanyl 1 μg/kg were given. In the TIVA group, the remifentanil infusion rate was increased by increments of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Only in case this alone was judged insufficient to readjust an adequate level of anesthesia, the infusion rate of propofol could be increased by increments of 1 $mg \cdot kg^{-1} \cdot h^{-1}$. At the end of surgery, all anesthetics (remifentanil, propofol, desflurane, sevoflurane, N_2O) were turned off simultaneously without previous tapering, and ventilation was controlled with 6 L/min of oxygen until the return of spontaneous ventilation. The trachea was extubated when adequate spontanous ventilation (tidal volume $>$ 4 mL/kg), and patient response to verbal commands were established. Emergence times (min) from discontinuation of anesthesia to eye opening, hand pressing, spontaneous breathing, tracheal extubation, recalling name and date of birth, and a modified Aldrete recovery score (7) $\geq$9 were measured. Any intra- and postanesthesia adverse events or experiences were assessed and recorded.

DSST and TDT were repeated in the postanesthesia care unit at 30, 60, and 90 min after discontinuation of

anesthesia by the same observer who was blinded to the anesthetia the patients had received. Pain intensity was estimated by a numerical rating scale, with scores ranging from 0 to 10. Shivering was treated with meperidine IV, postoperative pain with the long acting opioid piritramid IV. In the evening during the postanesthesia visit, all patients were asked to evaluate their satisfaction with the anesthesia by a numerical rating scale, based on school marks with items between 1 (best) and 6 (worst). None of the patients had previous experience with one of the anesthetic procedures used in the study.

Before the beginning of the study, an *a priori* power analysis suggested a sample size of 17 patients for each group to provide 80% power at $\alpha = 0.05$. Data were presented as means (SD) unless otherwise stated. Statistical analyses were performed using Kruskall-Wallis test, analysis of variance, Student-Newman-Keuls test, Wilcoxon test (*t*-test or matched pairs signed ranks test), or the χ^2 analysis, as appropriate. *P* values < 0.05 were considered statistically significant.

Results

There were no significant differences in demographic data, induction dose of propofol, duration of operation, or anesthesia among groups and fentanyl requirements in the desflurane and sevoflurane group. The rate of recovery was determined from a similar depth of anesthesia as measured by the end-tidal concentration of desflurane and sevoflurane and the maintenance dose of remifentanil and propofol (Table 1).

Remifentanil patients showed significantly faster emergence and awakening in the early recovery phase than patients receiving desflurane or sevoflurane, while no difference could be demonstrated between desflurane and sevoflurane, except minimally but significantly faster eye opening after desflurane (Table 2).

Remifentanil patients showed a tendency of fewer error responses on the TDT than patients after desflurane and sevoflurane anesthesia administration (Figure 1). At 30 min after termination of anesthesia, significantly more patients in the remifentanil and in the desflurane groups gave correct responses on the DSST than in the sevoflurane group, whereas at 60 min, this was only the case for remifentanil patients. 90 min after anesthesia administration, no difference could be demonstrated on this test among the three groups (Figure 2).

No difference could be demonstrated among groups with regard to postoperative pain intensity, need for analgesics, nausea/vomiting, or satisfaction with anesthesia, while significantly more patients developed chest wall rigidity during the induction of anesthesia with remifentanil (Table 3).

Discussion

Early recovery from anesthesia was significantly faster after remifentanil administration compared with desflurane and sevoflurane administration, whereas no difference, except for eye opening, was demonstrated between desflurane and sevoflurane. With few exceptions (8), most studies have shown early recovery to be faster after desflurane or sevoflurane administration in adults or children when compared with isoflurane or halothane (3,4,6,9,10) and have shown desflurane to be better than sevoflurane in this respect in ambulatory adult or pediatric patients (5,8,11) and in unpremedicated volunteers (12), even though the benefit of this effect leading to earlier discharge from the postanesthesia recovery room is not established. The absence of any difference between desflurane and sevoflurane regarding the speed of early recovery most probably is caused by the pharmacokinetics of both drugs, because it has been shown by Bailey (13) that, after anesthesia administration of intermediate duration (90 minutes), the 80% decrement times (time needed for 80% decrease in anesthetic concentration) of desflurane and sevoflurane are approximately 5 minutes, regardless of the duration of anesthesia. The major differences in the rate at which desflurane and sevoflurane are eliminated occur in the final 20% and 10% of the elimination process. After 90 minutes of anesthesia administration the 90% decrement time for sevoflurane increases significantly, while it remains <10 min for desflurane. Because MAC-awake values for desflurane have been determined to be $0.36 \times$ MAC and $0.35 \times$ MAC for sevoflurane (14,15), subMAC-awake values of both anesthetics had been achieved five minutes after termination of anesthesia administration in our patients.

However, faster awakening in the remifentanil group most probably was caused by a more rapid elimination of the drug compared with that of desflurane and sevoflurane. In addition, because fentanyl was administered to all patients in the desflurane and sevoflurane groups, this may have prolonged emergence from anesthesia as a result of a residual effect on MAC-awake of both anesthetics. Results from previous studies (16,17) indicate that early recovery from remifentanil based anesthesia even might be accelerated by combining remifentanil with an inhaled anesthetic in small (hypnotic) concentrations instead of propofol because of faster and more predictable elimination of the inhaled anesthetic when compared with propofol.

A major concern of measuring recovery in our study is equivalent depths of anesthesia as the starting point in the different groups. Because an electroencephalogram or other monitoring device of anesthetic depth was not available to ensure that patients began their recovery from comparable levels of anesthesia, the anesthesia provider was forced to rely on standard

Table 1. Demographic Data, Surgery, and Anesthesia

	Remifentanil (n = 20)	Desflurane (n = 20)	Sevoflurane (n = 20)
Sex (m/f)	13/7	14/6	13/7
Age (yr)	34 ± 13 (20–60)	37 ± 10 (20–55)	42 ± 13 (24–62)
Height (cm)	174 ± 9	175 ± 10	171 ± 8
Weight (kg)	69 ± 14	78 ± 17	79 ± 15
Surgery			
Duration of surgery (min)	62 ± 37	54 ± 28	74 ± 40
Osteosynthesis/arthroscopy/metal removal/soft tissue surgery (n)	4/6/6/4	5/8/2/5	10/4/3/3
Anesthesia			
Duration of anesthesia (min)	109 ± 41	108 ± 30	129 ± 40
Induction of anesthesia			
Propofol (mg)	143 ± 34	160 ± 39	156 ± 22
Fentanyl (μg)	—	0.16 ± 0.03	0.16 ± 0.03
Adjunctive fentanyl bolus (number of patients)	—	6	7
Maintenance of TIVA			
Propofol ($mg \cdot kg^{-1} \cdot h^{-1}$)	3.17 ± 0.5	—	—
Remifentanil ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.34 ± 0.1	—	—
Maintenance of inhalation anesthesia end-tidal (vol%)	—	3.8 ± 2.8	1.2 ± 1.0
MAC	—	0.63	0.6
Changes in dosage and concentration per patient *(n)*	3.3 ± 2.5	3.7 ± 2.8	3.7 ± 2.0
Total consumption of volatile anesthetic (g)		40.7 ± 19.2	23.4 ± 14

Values are mean ± SD (range).
TIVA = total IV anesthesia, MAC = minimum alveolar anesthetic concentration.
$P < 0.05$ between groups. No significant difference in tested variables.

clinical indicators to titrate the maintenance anesthetics as described in Methods. However, all anesthesia was provided by the same experienced anesthesiologist, and the doses of the anesthetics applied were comparable to those used in other studies to achieve a state of surgical anesthesia as judged clinically or by electroencephalogram monitoring or ist modifications (1,8–9,16,18–20)

The TDT and the DSST have been widely used for the assessment of the intermediate and late recovery of cognitive function in the postanesthesia recovery room (2,5,12,21), because they are simple and easy to perform. It appears, from these studies, that the DSST is the most sensitive of the tests for residual cortical depression by anesthetics, in particular, impairment of information processing performance and the ability to concentrate. In our study, patients in all groups demonstrated a significant delay in recovery of cognitive function during the first hour after anesthesia administration compared with preanesthesia values, with no difference among groups in the TDT. However, significantly more patients of the remifentanil and desflurane groups passed the DSST successfully 30 minutes after termination of anesthesia than of the sevoflurane group, whereas 60 minutes later, remifentanil patients performed better than desflurane and sevoflurane patients with no difference between desflurane and sevoflurane at this point. The almost 50% impairment in the DSST performance 30 minutes after sevoflurane anesthesia is of great clinical importance, because based on results of a previous study using alcohol as a standard to evaluate DSST performance (22), these changes of cognitive function are approximately the same amount as those produced by a blood alcohol level of approximately 0.1% (0.8 g/kg alcohol orally). In contrast, changes in the remifentanil (13%) and in the desflurane (17%) groups were much less pronounced; however, the clinical importance of this residual effect and its correspondence to a specific alcohol blood level has not been evaluated.

Thus, our study provides evidence that remifentanil offers a clinically important advantage with respect to an earlier return of cognitive function compared with desflurane and sevoflurane. Because propofol becomes the drug whose pharmacokinetics limit the rate of recovery when combined with remifentanil, intermediate recovery from remifentanil-based anesthesia might be accelerated with small concentrations of one of the new inhaled anesthetics used for hypnosis during surgery instead of propofol, in particular for long operative procedures. A similar effect should be achieved for total IV anesthesia by reducing the propofol and increasing the remifentanil concentration.

Also, in our study, desflurane patients performed better than sevoflurane patients 30 minutes after the termination of anesthesia. It has been demonstrated in previous studies that cognitive function is more rapidly restored after desflurane or sevoflurane anesthesia administration compared with isoflurane or propofol plus N_2O (2,4), even though criteria for home readiness and

Table 2. Emergence and Clinical Recovery

Recovery variable (min)	Remifentanil (n = 20)	Desflurane (n = 20)	Sevoflurane (n = 20)
Eye opening	3.7 ± 2.6‖¶	6.2 ± 2.6#	7.8 ± 2.9
Squeeze fingers	4.6 ± 2.5‖¶	6.5 ± 2.3	7.8 ± 2.5
Spontaneous breathing	5.5 ± 2.2	6.7 ± 4.3	6.9 ± 3.1
Extubation	6.0 ± 2.3	7.7 ± 4.0	8.5 ± 3.6
State name	6.3 ± 2.4†‖	8.5 ± 4.0	9.3 ± 3.6
State birth date	6.6 ± 2.4*§	8.8 ± 4.0	9.6 ± 3.7
Postanesthesia recovery score ≥9	7.2 ± 2.7*§	9.3 ± 4.1	10.6 ± 4.9

Values are mean ± SD or range.
* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ remifentanil versus desflurane.
§ $P < 0.05$, ‖ $P < 0.001$ remifentanil versus sevoflurane.
# $P < 0.05$ desflurane versus sevoflurane.

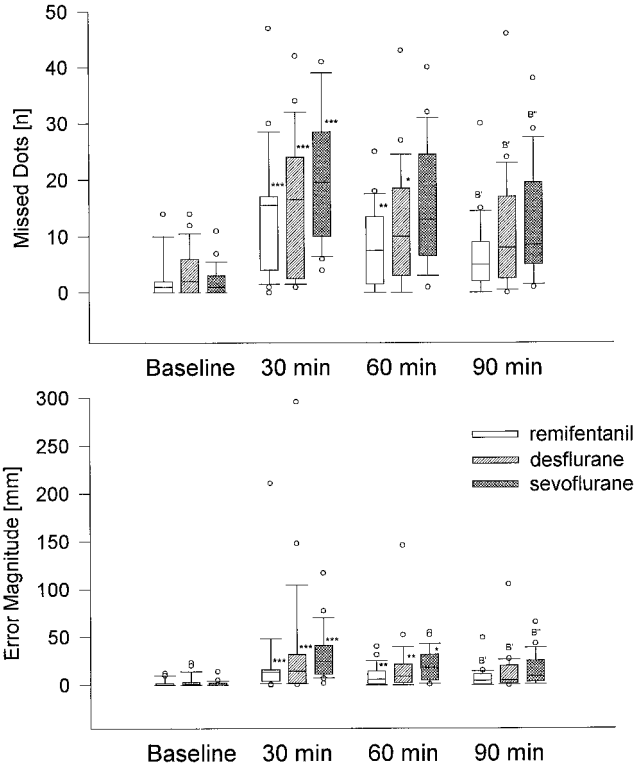

Figure 1. Trieger Dot Test. Number of missed dots and magnitude of error (distance dot-line [mm]) measured the day before surgery (Baseline) and 30, 60, and 90 min after discontinuation of anesthesia. n = 20 for each group. The nonparametric data are expressed as boxplots. $P < 0.05$ between groups is not significant. *$P < 0.05$, ***$P < 0.01$, ***$P < 0.001$ value versus previous value. B′$P < 0.01$, B′′$P < 0$ 0.001 value at 90 min versus Baseline value (Kruskal-Wallis test, one way analysis of variance on ranks, Wilcoxon's signed ranks test, Student-Newman-Keuls test).

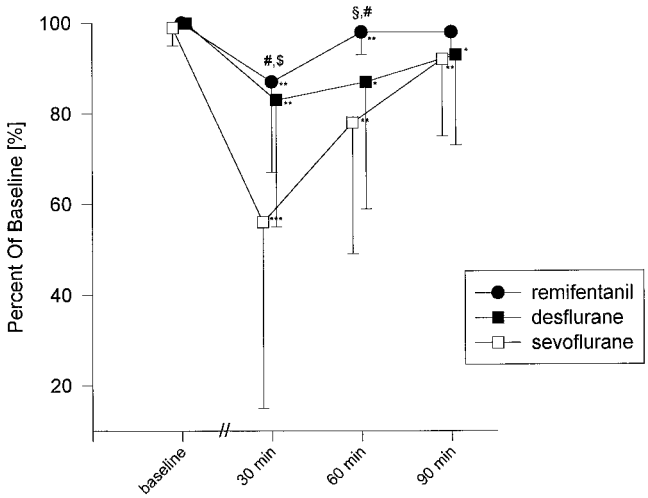

Figure 2. Digit Symbol Substitution Test. Results in the digit symbol substitution test expressed as percent of Baseline, measured the day before surgery (Baseline) and 30, 60, and 90 min after discontinuation of anesthesia. n = 20 for each group. Values are expressed as means ± SD. §$P < 0.05$ remifentanil versus desflurane. #$P < 0.05$ remifentanil versus sevoflurane. $$P < 0.05$ desflurane versus sevoflurane. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ value versus previous value. (Kruskal-Wallis test, one way analysis of variance on ranks, Student-Newman-Keuls test).

discharge times were not different in all of these studies. Direct comparisons of intermediate and late recovery characteristics of desflurane with sevoflurane have yielded conflicting results. As has been demonstrated before, most authors found early recovery to be faster after desflurane than after sevoflurane administration (5,8,11), while results from tests of intermediate recovery are inconsistent, with desflurane being superior to sevoflurane (5,12), equal to (8), or even marginally worse than sevoflurane (19). Again, no difference in discharge times between desflurane and sevoflurane could be demonstrated in clinical studies. While differences in intermediate recovery between remifentanil and inhaled anesthetics probably are caused by remifentanil's faster elimination from the brain, its weaker hypnotic potency, and the reduced dose of propofol in our study, the significantly faster intermediate recovery seen in volunteers after desflurane compared with sevoflurane anesthesia cannot be explained completely by differences in ventilation or alveolar or tissue elimination (12) of these anesthetics. However, the less pronounced differences in intermediate recovery between desflurane and sevoflurane in the clinical setting probably are results of the effects of co-medication and differences in study design. Perhaps the more favorable effects of desflurane compared with sevoflurane with regard to recovery will be more apparent after long surgical procedures.

Emergence from remifentanil-based anesthesia is usually swift and predictable (1), but may result in early postoperative pain because of the quick offset of its analgesic action. Therefore, prophylactic administration of analgesics and/or transition from remifentanil to some other long-acting analgesic is necessary for operations that result in significant postoperative pain. Thus, to prevent this undesirable effect of remifentanil, all patients in our study received paracetamol 1 g immediately

Table 3. Postoperative Pain, Analgesic Demands, Adverse Effects and Satisfaction with Anesthesia

	Remifentanil ($n = 20$)	Desflurane ($n = 20$)	Sevoflurane ($n = 20$)
Patients requiring additional analgesic in the PACU *(n)*	18	18	19
Time elapsed for first analgesic demand (min)	15.4 ± 6.6	16.5 ± 7.8	15.9 ± 7.6
Meperidine (mg)	40.0 ± 17.0	38.3 ± 16.7	41.0 ± 15.1
Piritramid (mg)	8.5 ± 8.1	5.4 ± 6.0	5.9 ± 7.7
NRS (0–10) for analgesia			
15 min	4.8 ± 3.4	4.9 ± 2.3	4.1 ± 3.5
30 min	4.5 ± 2.6	4.0 ± 1.8	4.0 ± 2.7
60 min	3.3 ± 2.0	3.2 ± 1.6	3.6 ± 2.0
90 min	2.3 ± 1.4	3.1 ± 1.7	3.4 ± 1.8
Rigidity of chestwall *(n)*	7*	—	3
Shivering *(n)*	11	6	7
Nausea/vomiting *(n)*	1/1	6/3	7/2
Satisfaction with anesthesia (1–6)	1.3	1.95	1.7
Future preference *(n)*	20	19	17

Values are expressed as means ± SD.
Satisfaction with anesthesia (1 = best to 6 = worst).
PACU = postanesthesia care unit, NRS = numerical rating scale, Future preference = number of patients who would choose the same anesthetic again.
* $P < 0.05$ remifentanil versus desflurane.

after the induction of anesthesia, then a long acting opioid in the recovery room. There were no differences in numerical pain scores and postoperative analgesic demand among the groups, indicating that for this type of elective surgery, remifentanil does not necessarily lead to intense pain shortly after recovery when accompanied by prophylactic analgesics.

Finally, how do the results benefit the anesthesiologist in the clinical setting? Even though the times to awakening and to achieving a recovery score of 10 were only a few minutes shorter for remifentanil compared with desflurane and sevoflurane, remifentanil patients were much less "sedated," more alert, and could be transferred from the operating room to the postanesthesia recovery room earlier, thus improving the efficiency in a busy operating area. However, of much greater importance are the differences in intermediate recovery or cognitive function between remifentanil and sevoflurane. While patients in the remifentanil group reached 87% correct answers in the DSST after 30 minutes and 98% after 60 min, for sevoflurane patients, this ability 30 minutes after anesthesia was impaired to a degree which roughly corresponds to an alcohol blood level of 0.1%. Even after 60 minutes, the rate of correct answers was only 78% for these patients, indicating a clinically important residual impairment. Complete awakening and orientation immediately after the termination of surgery is highly desirable when early neurological evaluation has to be performed, for instance after carotid artery surgery. Data from this study and preliminary results of our group suggest (23) that this goal can be most likely achieved by a remifentanil-based anesthesia. In addition, it appears, that remifentanil is of greater benefit in facilitating fast-tracking of patients from the recovery room or even bypassing the postanesthesia recovery after selected operations than sevoflurane.

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