

Remifentanil Compared with Alfentanil for Ambulatory Surgery Using Total Intravenous Anesthesia

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The purpose of this study was to test the hypothesis that using a 1:4 ratio of remifentanil to alfentanil, a remifentanil infusion would provide better suppression of intraoperative responses and comparable recovery profiles after ambulatory laparoscopic surgery than an alfentanil infusion, as part of total intravenous anesthesia. Two hundred ASA physical status I, II, or III adult patients participated in this multicenter, double-blind, parallel group study. Patients were randomly assigned 2:1 to either the remifentanil-propofol or alfentanil-propofol regimens. The anesthesia sequence was propofol (2 mg/kg intravenously [IV] followed by $150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and either remifentanil ($1 \mu\text{g}/\text{kg}$ IV followed by $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or alfentanil ($20 \mu\text{g}/\text{kg}$ IV followed by $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and vecuronium. After trocar insertion, infusion rates were decreased (propofol to $75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; remifentanil to $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; alfentanil to $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Alfentanil and propofol were discontinued at 10 and 5 min, respectively, before the anticipated end of surgery (last surgical suture); remifentanil was

discontinued at the end of surgery. Recovery times were calculated from the end of surgery. The median duration of surgery was similar between groups (39 min for remifentanil versus 34 min for alfentanil). A smaller proportion of remifentanil patients than alfentanil patients had any intraoperative responses (53% vs 71%, $P = 0.029$), had responses to trocar insertion (11% vs 32%, $P < 0.001$), or required dosage adjustments during maintenance (24% vs 41%, $P < 0.05$). Early awakening times were similar. Remifentanil patients qualified for Phase 1 discharge later and were given postoperative analgesics sooner than alfentanil patients ($P < 0.05$). Actual discharge times from the ambulatory center were similar between groups (174 min for remifentanil versus 204 min for alfentanil) ($P = 0.06$). In conclusion, remifentanil can be used for maintenance of anesthesia in a 1:4 ratio compared with alfentanil, for total IV anesthesia in ambulatory surgery. This dose of remifentanil provides more effective suppression of intraoperative responses and does not result in prolonged awakening.

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General anesthesia with intravenous drugs only, or total intravenous anesthesia (TIVA), is gaining increasing acceptance because of the

availability of short-acting hypnotics and opioids, and improved infusion systems (1). With TIVA, the analgesic and hypnotic components of anesthesia can be titrated separately to control the depth of anesthesia despite changing surgical stimulus. For ambulatory patients, short-acting drugs are needed for TIVA so as not to delay recovery. At the present, propofol is the hypnotic choice, and alfentanil is the most widely used opioid in ambulatory TIVA regimens. However, the dose of alfentanil that can be used is limited by its accumulation after prolonged infusion, with the risk of prolonged recovery. A shorter acting opioid would be advantageous for ambulatory surgery TIVA.

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Remifentanil hydrochloride (Ultiva™; Glaxo Wellcome Inc, Research Triangle Park, NC), formerly known as GI87084B, has a context-sensitive half-time (time for a 50% decrease in blood remifentanil concentrations after discontinuation of a prolonged infusion) of approximately three to six minutes, which is independent of the duration of infusion, and a terminal elimination half-life of approximately 10–20 min (2,3). Unlike other opioids, remifentanil is rapidly metabolized by hydrolysis of the methyl ester linkage on the parent piperidine molecule by nonspecific plasma and tissue esterases (4,5). Thus, remifentanil does not accumulate in the body and should allow for rapid and predictable emergence.

We chose the dose of remifentanil identified from previous studies which provided maximal suppression of response to intubation ($1 \mu\text{g}/\text{kg} + 0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and intraoperative stimuli ($0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) (6,7). Remifentanil is approximately five to ten times more potent than alfentanil when administered by continuous infusion¹ (data on file, Glaxo Wellcome Inc.). We chose not to use an equipotent dose of alfentanil because of the potential for prolonged recovery. Therefore, a clinically acceptable dose of alfentanil ($1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was chosen and discontinued in time to permit awakening. The purpose of this study was to test the hypothesis that in a 1:4, nonequipotent dose ratio, remifentanil infusion would provide better suppression of intraoperative responses and comparable recovery profiles after ambulatory laparoscopic surgery than an alfentanil infusion as part of TIVA.

Methods

This randomized, double-blind, parallel-group study enrolled ASA physical status I–III adults who were scheduled for laparoscopic surgery with expected surgery time greater than 30 min. Females were postmenopausal, surgically sterile, or had a negative urine or serum pregnancy test on the day of surgery. Patients with the following history were excluded: known hypersensitivity to opioids, opioid use within 12 h of surgery, and ethanol or drug abuse. The study was conducted at seven medical centers in the United States and Canada. The protocol was approved by the institutional review board at each center, and all patients provided written informed consent. Two to four patients at each center received open-label remifentanil during the pilot phase to familiarize investigators with study procedures. After the pilot phase, subjects were randomly assigned 2:1 to a remifentanil-propofol

regimen or to an alfentanil-propofol regimen. The unbalanced study design was chosen to maximize the number of patients exposed to remifentanil without sacrificing statistical power as determined by a *a priori* power analysis.

Randomization codes for each study site were generated by SAS version 6.08 (SAS Institute, Cary, NC) using a block size of 6 (4 remifentanil; 2 alfentanil). Patients eligible for randomization were assigned the lowest available treatment number in chronological order of presentation to the anesthesiologist. Each treatment number was assigned to only one patient.

Solutions of remifentanil hydrochloride were prepared by the hospital pharmacy at each center, and provided in syringes identified as bolus syringe, maintenance Syringe 1, and maintenance Syringe 2. Each syringe was labeled with the patient's number and initials, and neither the treatment assignment nor the contents of the syringe were known by the anesthesia staff or the patient. The maintenance concentration of remifentanil in the syringes was $125 \mu\text{g}/\text{mL}$ and alfentanil was $500 \mu\text{g}/\text{mL}$. Therefore, rate adjustments were made as the same number of milliliters per minute for both opioids.

Lactated Ringer's solution, 5–10 mL/kg, was infused prior to induction followed by a rate sufficient to replace fluid losses. A second line was inserted for administration of the propofol and other intraoperative medications. Two lines were used because the compatibility of remifentanil and propofol had not yet been confirmed; recent data have confirmed that remifentanil and propofol are compatible. Patients were given midazolam 1 mg prior to induction of anesthesia. In the operating room, a pulse oximeter, automated blood pressure cuff, and lead II electrocardiogram were placed. A priming dose of vecuronium ($0.01 \text{ mg}/\text{kg}$) was then given to patients to facilitate intubation. Anesthesia was induced with a bolus dose of propofol $2 \text{ mg}/\text{kg}$ followed by a continuous infusion of $150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Immediately after the propofol was begun, patients received the assigned treatment in the bolus syringe (either remifentanil $1 \mu\text{g}/\text{kg}$ or alfentanil $20 \mu\text{g}/\text{kg}$) followed by maintenance Syringe 1 (either remifentanil $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or alfentanil $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Loss of consciousness was assessed with lack of response to verbal command. Patients then received vecuronium (up to $0.1 \text{ mg}/\text{kg}$) to facilitate endotracheal intubation. After intubation, patients' lungs were ventilated with oxygen or oxygen/air mixtures. Five minutes after skin incision/insufflation/trocar insertion (hereafter, called trocar insertion, due to close proximity of events), infusion rates were decreased: remifentanil to $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, alfentanil to $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and propofol to $75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Incremental doses of vecuronium were given if needed to maintain adequate muscle

¹Glass PSA, Hardman HD, Kamiyama, Y, et al. Pharmacodynamic comparison of GI87084B (GI), a novel ultra-short acting opioid, and alfentanil (ALF) [abstract]. *Anesth Analg* 1992;74:S113.

relaxation. Blood pressure and heart rate were recorded every 10 min intraoperatively, and at 1, 3, and 5 min after changes in study opioid infusion rates. $PETCO_2$ was maintained between 36 and 40 mm Hg for the duration of the surgery.

Patients were observed for responses to intubation, trocar insertion, and light anesthesia throughout maintenance. Light anesthesia was characterized by hemodynamic (systolic blood pressure [SBP] >15 mm Hg above preoperative baseline for ≥ 1 min or heart rate [HR] >90 bpm for ≥ 1 min), somatic (movement, eye opening, or grimacing), or autonomic (tearing or sweating) changes. Light anesthesia responses were treated by administering a bolus of the study drug to be followed by 50% increments in infusion rate from the current rate (remifentanil, 0.5 $\mu\text{g}/\text{kg}$ and 0.125 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; alfentanil, 10 $\mu\text{g}/\text{kg}$ and 0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Each infusion rate increase was separated by a minimum of 2 min. Further responses were treated with rescue propofol (up to two 20-mg boluses). If two propofol boluses were unsuccessful, then an additional 20-mg bolus was given, and the propofol infusion rate was increased by 50 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Once the patient's response was considered adequately controlled, the propofol infusion was decreased to 75 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (original maintenance period infusion rate).

During maintenance, patients were also monitored for signs of deep anesthesia, defined as SBP < 80 mm Hg and/or HR < 40 bpm for >1 min. Hypotension was treated with fluids and 50% decrements in infusion rate (0.125 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for remifentanil and 0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for alfentanil). If a decrease in study opioid was unsuccessful, pressor or anticholinergic drugs were administered. For bradycardia, the study opioid infusion rate was decreased, and pressor or anticholinergic drugs were administered.

Ten minutes before the anticipated end of surgery (defined as the last surgical suture or the time legs were taken out of the stirrups), the opioid infusion syringe was changed for all patients to a second syringe provided by the pharmacy. The syringe contained remifentanil for the remifentanil group and normal saline for the alfentanil group. Alfentanil was discontinued to minimize the occurrence of delayed emergence. This procedure conforms to the Alfenta[®] (Janssen Pharmaceutica, Titusville, NJ) package insert. The propofol infusion was discontinued 5 min before the anticipated end of surgery, and patients received neostigmine 0.04–0.07 mg/kg and glycopyrrolate 0.01 mg/kg for neuromuscular block reversal. The study opioid infusion (remifentanil or normal saline) was discontinued at the end of surgery. Mechanical ventilation was discontinued at the end of surgery and patients were ventilated by hand every 30 s until spontaneous and adequate respiration was achieved (respiratory rate ≥ 8 breaths/min and/or $PETCO_2$ < 50 mm/Hg). If adequate respiration

did not occur within 10 min after the end of surgery, incremental doses of naloxone (0.04 mg) were given every 2 min until respiration became adequate. Patients were monitored in the ambulatory surgical facility for a minimum of 2 h after surgery. Patients with moderate or severe pain were given fentanyl in 12.5- μg increments, or other analgesics deemed appropriate by the clinician until pain was controlled (defined as none or mild).

Patients' responses to skin incision, insufflation, or trocar insertion were noted. Since these three events occurred in close proximity, a response to any one could not be separated, and all events were recorded as a response to trocar insertion. Recovery times were calculated from the end of surgery, which was defined as the discontinuation of Syringe 2 (remifentanil or normal saline). Recovery was evaluated by obtaining the times to spontaneous respiration, adequate respiration, response to verbal commands (open eyes; lift extremity; state name; and state date of birth), extubation, first analgesic used, able to sit unaided, and able to ambulate. The primary efficacy assessment was the time to adequate respiration. Qualification for discharge from the postanesthesia care unit (PACU) Phase 1 was defined as Aldrete score ≥ 9 with pain, nausea, and vomiting controlled (9). Qualification for discharge from PACU Phase 2 was defined as postanesthesia discharge score (PADS) ≥ 9 with the patient being able to ambulate unassisted (10). Times to qualify for and actual discharge from PACU Phase 1 and Phase 2 were recorded.

Psychomotor and cognitive function tests administered during the study included the Trieger Dot Test (11) and the Digit Symbol Substitution Test (DSST) (12). In addition, patients were verbally asked to rate their sedation on a numerical rating scale from 0 to 10 (0 = alert, 10 = very sleepy). The tests were administered to patients preoperatively (baseline), and at 30, 60, 90, and 120 min after the end of surgery. Nausea assessments were obtained by asking patients whether they were nauseated, and responses were graded on a four-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Nausea assessments were made upon arrival in PACU Phase 1, 15 min after arrival in Phase 1, upon arrival in Phase 2 recovery, and immediately before discharge home. Vomiting was recorded anytime it occurred. Reasons for delays between qualifying for PACU Phase 2 discharge and actual discharge from the ambulatory center were recorded. On the first postoperative day, patients were telephoned and asked about adverse events, medication use since discharge, and recall of events during surgery.

Statistical analyses were performed using SAS. All statistical results were presented using two-sided *P* values, and *P* values less than 0.05 were considered statistically significant. The proportion of patients with responses to intubation, trocar insertion, skin closure, and study opioid dose adjustments were compared between treatment

Table 1. Patient Demographics and Intraoperative Responses

	Remifentanil (<i>n</i> = 157)	Alfentanil (<i>n</i> = 66)
Male:female	0:157	1:65
Mean age, yr (range)	32 (18–51)	33 (19–47)
ASA physical status, <i>n</i> , I:II:III	106:50:1	45:21:0
Median anesthesia duration, min (range)	63 (9–273)	55 (31–177)
Median surgery duration, min (range)	39 (13–252)	34 (17–150)
Response to intubation, <i>n</i> (%) ^a	25 (19)	19 (29)
Response to trocar insertion, <i>n</i> (%) ^a	14 (11)*	21 (32)
Response to skin closure, <i>n</i> (%) ^a	25 (19)	13 (20)
Response to light anesthesia, <i>n</i> (%) ^a	71 (53)*	47 (71)
Study opioid dose adjustments ^a		
To correct light anesthesia response: bolus and/or rate increase, <i>n</i> (%)	26 (20)*	26 (39)
To correct deep anesthesia response: rate decreases, <i>n</i> (%)	22 (17)	14 (21)

^a Randomized patients included in efficacy analysis: *n* = 133 for remifentanil; *n* = 66 for alfentanil.

* *P* < 0.05 for remifentanil versus alfentanil.

groups using a logistic regression model adjusted for study sites (13). The proportion of patients with light anesthesia responses to surgical events, requiring propofol rescue after intubation, requiring analgesics, and with nausea and vomiting were compared between groups using a Cochran-Mantel-Haenszel test stratified by study site (14). Times to recovery assessments were compared between groups using Cox's semiparametric proportional hazards model adjusted for study sites (15). Sedation scores, the number of Trieger dots missed, and the number of correct responses for DSST scores were compared between groups using an analysis of variance model with effects for study sites and baseline.

The weighted mean propofol infusion rate was calculated as the area under the curve over time for each interval divided by the duration of the measurement, assuring a step-wise distribution. Mean weighted infusion rates were then summarized across all patients in a treatment group. Propofol bolus doses were not included in the calculation. The mean total fentanyl dose used in the PACU for each group was calculated by averaging the total doses of fentanyl used by each patient who required additional analgesic.

Results

Two hundred twenty-three patients (157 receiving remifentanil and 66 receiving alfentanil) were enrolled in the study and included in the safety analyses. Twenty-three patients participated in the open-label pilot portion of the study and were not included in the efficacy analyses; 200 patients were randomized and included in the efficacy analyses. The majority of patients (90%) underwent diagnostic laparoscopy; the remaining patients underwent bilateral tubal ligation, and one patient underwent a hernia repair. Demographic characteristics were similar between groups

(Table 1) and across study sites. One remifentanil patient was withdrawn from the study due to an adverse event (wheezing) after intubation.

There were no significant differences between groups with respect to median time to loss of consciousness or the mean doses of propofol used for induction. No differences were observed between groups in the weighted mean propofol infusion rates from 5 min after trocar insertion until the end of propofol infusion ($77.2 \pm 8.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $81.5 \pm 16.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for the remifentanil and alfentanil groups, respectively). No differences were observed between groups for blood pressure or HR.

Overall, a smaller proportion of remifentanil patients responded to trocar insertion than alfentanil patients (Table 1). An increase in SBP was the most common response for both intubation and trocar insertion; somatic responses and an increase in SBP were common responses for skin closure. A smaller proportion of remifentanil patients also had responses to light anesthesia. The most common response to light anesthesia for both groups was an increase in SBP.

Overall, a smaller proportion of remifentanil patients (24%) required a study opioid adjustment compared with alfentanil patients (41%), with a statistically significant difference observed between groups for adjustments (study opioid boluses or infusion rate increases) needed to treat light anesthesia responses (Table 1). The proportion of patients requiring a study opioid decrease was comparable between groups. The weighted mean infusion rates calculated from 5 min after skin incision until the end of anesthetic were $0.29 \pm 0.08 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for remifentanil and $1.34 \pm 0.59 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for alfentanil. The weighted mean remifentanil infusion rate calculated from the switch of syringes until the end of anesthetic was $0.27 \pm 0.06 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

Table 2. Median Recovery Times (Range) in Minutes, Calculated from the End of Surgery

Events	Remifentanil (n = 133)	Alfentanil (n = 66)
Spontaneous respiration	2 (-5 to 16)	1 (-6 to 18)
Adequate respiration	3 (-3 to 22)	3 (-1 to 20)
Extubation	4 (-4 to 24)	4 (-1 to 19)
Follow verbal commands	6 (-2 to 28)	7 (-1 to 23)
First Aldrete score ≥ 9	10 (1 to 124)	10 (-2 to 34)
First analgesic use	23 (5 to 197)*	39 (2 to 168)
Qualify for Phase 1 discharge	42 (5 to 200)	21 (5 to 113)*
Time to sit unaided	66 (4 to 210)	60 (2 to 239)
Actual Phase 1 discharge	69 (7 to 230)	59 (7 to 214)
Ambulation	87 (36 to 395)	102 (14 to 288)
Qualify for Phase 2 discharge	100 (37 to 291)	117 (14 to 293)
Actual Phase 2 discharge	174 (94 to 486)†	201 (94 to 472)

* $P < 0.05$ remifentanil versus alfentanil.† $P = 0.06$.

When assessed from the end of surgery, median early recovery times were not significantly different between groups (Table 2). Four remifentanil patients (3%) and five alfentanil patients (8%) were given naloxone to establish adequate ventilation. The time to first analgesic use was significantly shorter for remifentanil patients compared with alfentanil patients ($P < 0.05$), and the time to qualify for Phase 1 discharge was significantly longer. Overall, a larger proportion of remifentanil patients required analgesics (87%) compared with alfentanil patients (65%) ($p < 0.001$) while in the hospital. Among those patients who did receive fentanyl for postoperative pain, the mean dose of fentanyl administered was similar and clinically acceptable in both treatment groups: $76.7 \pm 55.5 \mu\text{g}$ with remifentanil and $75.0 \pm 65.3 \mu\text{g}$ with alfentanil. In the 24-h period after discharge from the ambulatory center, the incidence of analgesic use for pain was also similar between groups: 82% for remifentanil and 77% for alfentanil.

The mean sedation scores were similar between groups at baseline, and at the 30- and 120-min postoperative assessments. However, remifentanil patients had less sedation at the 60- ($P = 0.015$) and 90-min ($P = 0.012$) assessments compared with alfentanil patients. The number of Trieger dots missed were similar at baseline, and at 30-, 60-, and 120-min assessments, but at the 90-min assessment, remifentanil patients missed significantly fewer dots than alfentanil patients ($P = 0.015$). No differences in the number of correct responses for DSST scores were observed between groups.

At the 24-h follow-up telephone interview, the proportion of patients who remembered entering the operating room was similar between groups (81% for remifentanil; 86% for alfentanil). Two patients, one in each group, remembered early aspects of the operation. Both patients received inadequate doses of propofol until after skin incision due to infusion pump malfunctions.

No significant differences were noted between groups in the incidence of nausea or vomiting at any measurement point during recovery (Figure 1). The incidence of nausea for remifentanil patients did not exceed 30% at any time point during recovery, while the incidence of nausea was as high as 52% in alfentanil patients before discharge home. Overall, the incidence of nausea was 44% and 53% for remifentanil and alfentanil patients, respectively, and the incidence of vomiting was 21% and 29% for remifentanil and alfentanil patients, respectively.

Two remifentanil patients (1%) experienced muscle rigidity during the induction phase. The median duration of muscle rigidity was 3.5 min (range, 3-4 min), and both episodes were rated as mild in severity. Two alfentanil patients (3%) experienced a single episode of respiratory depression during the recovery phase. The median duration of respiratory depression was 5.5 min (range, 3-8 min), and both episodes were rated as moderate in severity. No cases of venous irritation were observed.

Discussion

In this study, we compared the use of a remifentanil-propofol regimen administered in the TIVA regimen with an alfentanil-propofol regimen in patients undergoing ambulatory laparoscopic procedures scheduled to last more than 30 minutes. With the larger relative dose used, remifentanil provided better intraoperative stability than alfentanil, as indicated by fewer hemodynamic responses to intubation and trocar insertion, and fewer dose adjustments during maintenance. Our results suggest that remifentanil may be the desired opioid for ambulatory TIVA, especially in patients where hemodynamic control is important.

Due to the pharmacokinetic differences between the two opioids, it was not possible to administer alfentanil infusions at an equipotent dose to remifentanil because of the risk of delayed recovery and prolonged respiratory depression at higher infusion doses of alfentanil. The remifentanil and propofol infusion rates were chosen based on effective anesthesia in a previous study (6,7). This study also evaluated the interaction between propofol and remifentanil, and the results showed that as the dose of remifentanil increased, propofol dose requirements for anesthesia decreased. The pharmacokinetic difference in offset with remifentanil compared to

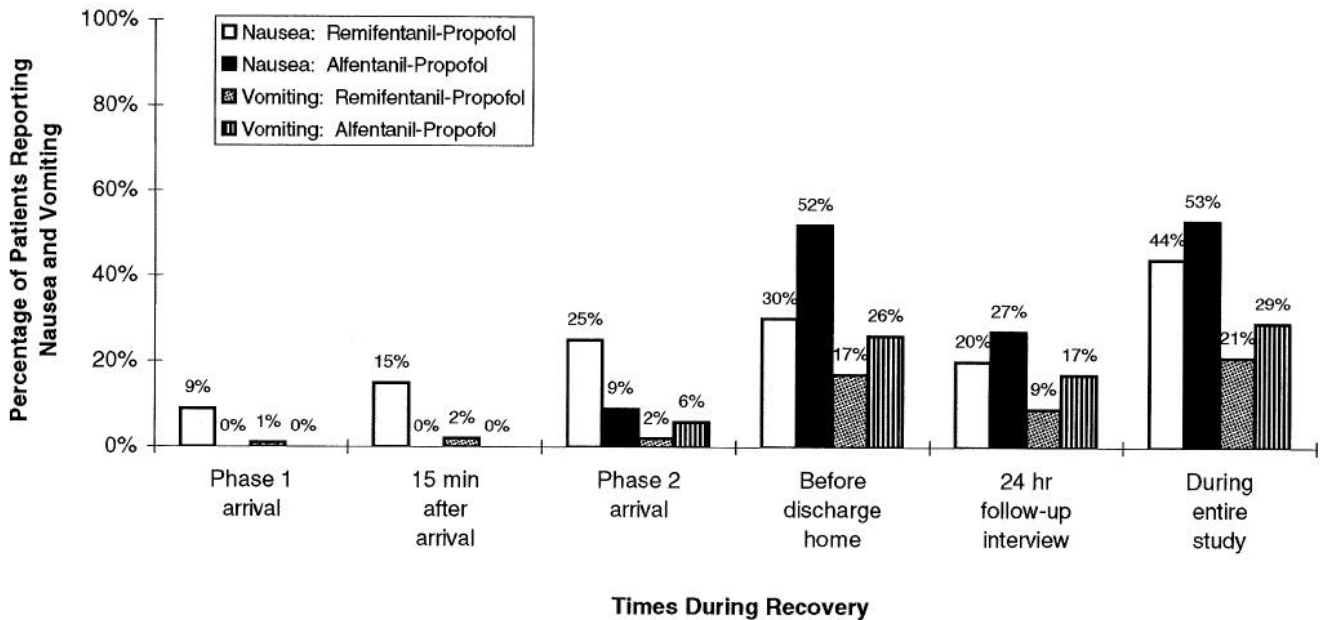


Figure 1. Percentage of patients reporting nausea and vomiting during recovery after remifentanil-propofol or alfentanil-propofol infusions for total intravenous anesthesia for ambulatory laparoscopic surgery. *n* = 133 for remifentanil-propofol; *n* = 66 for alfentanil-propofol.

alfentanil suggests areas of appropriate use in clinical practice. Since remifentanil can be administered until the end of surgery, it may be useful for procedures where high levels of surgical stimulation persist until the end of surgery and for surgery of unknown duration.

A larger proportion of remifentanil patients received fentanyl for analgesia in PACU Phase I (77%) compared with alfentanil patients (35%), and they needed it sooner (23 vs 39 minutes). These factors may have contributed to the delay in qualifying for Phase 1 discharge. The earlier occurrence of pain in remifentanil patients is consistent with more alertness, as measured by the lower sedation scores. Nausea and vomiting occurred earlier with remifentanil and later with alfentanil; this may have been due to the differences in timing of the administration of fentanyl for analgesia. In the 24-hour period after discharge from the ambulatory center, the incidence of analgesic use for pain was similar between groups (82% for remifentanil; 77% for alfentanil). The earlier occurrence of pain can be a disadvantage of an ultra-short-acting analgesic such as remifentanil. However, the administration of analgesics early in the postoperative period (15–20 minutes after the end of surgery) rather than in response to pain should provide appropriate patient comfort after remifentanil-based anesthesia for these ambulatory procedures.

The times to awakening after remifentanil or alfentanil infusions were not different. This is due to the study design, since alfentanil was discontinued 10 minutes before the end of surgery to avoid delayed awakenings. This study design makes it impossible to assess the effect of the opioid on decreasing operating

room utilization times. This study did evaluate discharge readiness times from PACU Phase 1, and discharge readiness occurred earlier in the alfentanil group. This is of concern since PACU Phase 1 is a labor-intensive, expensive care area. The delay experienced by the remifentanil patients may be related to the treatment of postoperative pain, as discussed in the paragraph above, and more proactive management of postoperative pain before symptoms appeared might reduce the Phase 1 stay. The cost of remifentanil relative to alfentanil has not yet been determined.

In a retrospective analysis, the reasons for delay from PACU Phase 2 discharge were identified. This delay is defined as actual discharge occurring >30 minutes after meeting eligibility criteria (16). The main reason for delay was the lack of transportation home (38% for remifentanil; 28% for alfentanil). Other reasons for delay were protocol requirement for two-hour stay (17% for remifentanil; 12% for alfentanil), and hospital requirement for patients to void (9% for remifentanil, 16% for alfentanil). The only significant difference in reason for delayed discharge was in nausea/vomiting: 5% for remifentanil; 19% for alfentanil (*P* < 0.05).

Two cases for intraoperative awareness were reported in this study. Both patients (one remifentanil and one alfentanil) received inadequate doses of propofol until after trocar insertion due to infusion pump malfunctions. As has been previously reported for TIVA techniques, the most common reasons for intraoperative awareness involve technical problems such as infusion pump malfunctions or disconnections

of the intravenous tubing (17,18). Results also indicate that similar percentages of patients in both groups responded to skin closure. Although no patient reported awareness of skin closure, the percentage of patients with a response to skin closure in both groups is relatively large. A higher infusion rate of propofol, $>75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, for anesthesia maintenance may have reduced the response rate.

For this study, the protocol mandated the use of naloxone if adequate respiration did not occur 10 minutes after the end of surgery. In clinical practice, the incidence of naloxone use among remifentanil patients may be lower with less stringent guidelines governing the timing of naloxone administration.

Two remifentanil patients experienced muscle rigidity during the induction phase. One patient from the open-label, pilot study experienced muscle rigidity that may be attributed to administering remifentanil before propofol. One patient experienced muscle rigidity during an opioid bolus overdose. In both cases, muscle rigidity involved some extremity and abdominal wall stiffness and was resolved within three to four minutes without any ventilation problems.

In conclusion, remifentanil used with propofol was effective as the primary opioid in TIVA for ambulatory surgery. In this study, remifentanil provided better intraoperative hemodynamic stability than alfentanil, because remifentanil was dosed to higher levels of opioid effect, with similar recovery. Postsurgical pain occurred earlier with remifentanil, and early, prospective pain management is needed.

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References

1. Pandit SK, Green CR. General anesthesia techniques. *Int Anesthesiol Clin* 1994;32:55-79.
2. Hughes MA, Glass PSA, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992;76:334-41.
3. Westmoreland CL, Hoke JF, Sebel PS, et al. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 1993;79:893-903.
4. Feldman PL, James MK, Brackeen MF, et al. Design, synthesis, and pharmacological evaluation of ultrashort- to long-acting opioid analgesics. *J Med Chem* 1991;34:2202-8.
5. James MK, Feldman PL, Schuster SV, et al. Opioid receptor activity of GI87087B, a novel ultra-short acting analgesic, in isolated tissues. *J Pharmacol Exp Ther* 1991;259:712-8.
6. Fragen RJ, Randel GI, Librojo BS, et al. The interaction of remifentanil and propofol to prevent response to tracheal intubation at the start of surgery for outpatient knee arthroscopy [abstract]. *Anesthesiology* 1994;81:A376.
7. Hogue CW, Bowdle TA, O'Leary C, et al. A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery. *Anesth Analg* 1996;83:279-85.
8. Deleted in proof.
9. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg* 1970;49:924-33.
10. Chung F. Are discharge criteria changing? *J Clin Anesth* 1993; 5:64S-68S.
11. Newman MG, Trieger N, Miller JC. Measuring recovery from anesthesia. A simple test. *Anesth Analg* 1969;48:1-5.
12. Beck AT, Feshback S, Legg O. The clinical utility of the digit symbol test. *J Consult Clin Psychol* 1962;26:263-8.
13. Koch GG, Edwards S. Clinical efficacy trials with categorical data. In: Peace KE, ed. *Biopharmaceutical statistics for drug development*. New York: Marcel Dekker, 1988:428-33.
14. Landis RJ, Heyman ER, Koch GG. Average partial association in three-way contingency tables: a review and discussion of alternative tests. *Int Stat Rev* 1978;46:237-54.
15. Breslow NE. Covariance analysis of censored survival data. *Biometrics* 1974;30:89-99.
16. Chung F, Skinner EP, Jamerson B, Reese PR. Recovery and reasons for discharge delay after remifentanil vs alfentanil in outpatient surgery [abstract]. *Anesth Analg* 1996;82:S65.
17. Sandin R, Nordstrom. Awareness during total i.v. anaesthesia. *Br J Anaesth* 1993;71:782-7.
18. Kelly D, Brull SJ. The cost of modern technology. *J Clin Anesth* 1995;7:80-1.