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A Comparison of Remifentanyl and Morphine Sulfate for Acute Postoperative Analgesia after Total Intravenous Anesthesia with Remifentanyl and Propofol

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Background: The transition from remifentanyl intraoperative anesthesia to postoperative analgesia must be planned carefully due to the short duration of action (3–10 min) of remifentanyl hydrochloride, a potent, esterase-metabolized μ -opioid agonist. This study compared the efficacy and safety of transition regimens using remifentanyl or morphine sulfate for immediate postoperative pain relief in patients who had surgery under general anesthesia with remifentanyl/propofol.

Methods: One hundred fifty patients who had received open-label remifentanyl and propofol for intraoperative anesthesia participated in this multicenter, double-blind, double-dummy study and were randomly assigned to either the remifentanyl (R) group or the morphine sulfate (M) group. Twenty minutes before the anticipated end of surgery, the propofol infusion was decreased by 50%, and patients received either a placebo bolus (R group) or a bolus of 0.15 mg/kg morphine (M group). At the end of surgery, the propofol and remifentanyl maintenance infusions were discontinued and the analgesic infusion was started: either 0.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ remifentanyl (R group) or placebo analgesic infusion (M group). During the 25 min after tracheal extubation, remifentanyl titrations in increments of 0.025 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and placebo boluses (R group), or 2 mg intravenous morphine boluses and placebo rate increases (M group) were administered as necessary at 5-min intervals to control pain. Patients received the 0.075 mg/kg intravenous morphine bolus (R group) or placebo (M group) at 25 and 30 min after extubation, and the analgesic infusion was discontinued at 35 min. From 35 to 65 minutes after extubation, both groups received 2–6 mg open-label morphine analgesia every 5 min as needed.

Results: Successful analgesia, defined as no or mild pain with adequate respiration (respiratory rate [RR] ≥ 8 breaths/min and pulse oximetry $\geq 90\%$), was achieved in more patients in the R group than in the M group (58% vs. 33%, respec-

1996, Baltimore, Maryland. The design and execution of this study, along with data collection and analysis, were performed in cooperation with members of Glaxo Wellcome Inc. under the direction of Barbara Kirkhart. Financial support for this work was provided by a grant from Glaxo Wellcome Inc.

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tively) at 25 min after extubation ($P < 0.05$). The median remifentanyl rate for successful analgesia was $0.125 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (range, 0.05 – $0.23 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and the median number of 2-mg morphine boluses used was 2 (range, 0–5 boluses). At 35 min after extubation, $\geq 74\%$ of patients in both groups experienced moderate to severe pain. Median recovery times from the end of surgery were similar between groups. Transient respiratory depression, apnea, or both were the most frequent adverse events (14% for the R group vs. 6% for the M group; $P > 0.05$).

Conclusions: Remifentanyl provided safe and effective postoperative analgesia when administered at a final rate of 0.05 – $0.23 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the immediate postextubation period. Remifentanyl provided more effective postoperative analgesia than did intraoperative treatment with morphine (0.15 mg/kg) followed by morphine boluses (\leq five 2-mg boluses). The effects of remifentanyl dissipated rapidly after ending the infusion, and alternate analgesia was required. Further studies are underway to define transition regimens that will improve postoperative analgesia in patients receiving anesthesia with remifentanyl. (Key words: Analgesics, opioids: remifentanyl; morphine. Pain, postoperative: prevention; control. Pain management. Double-blind method.)

REMIFENTANIL hydrochloride (UltivaTM, Glaxo Wellcome, Inc., Research Triangle Park, NC) is a potent, selective 4-anilidopiperidine μ -opioid receptor agonist.^{1,2} It has a rapid onset of peak effect (blood-brain equilibration time, 1.2–1.4 min), a short duration of action independent of the duration of infusion (elimination half-life, 3–10 min), and rapid clearance ($40 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).^{3–7} The unique pharmacokinetic profile of remifentanyl is attributed to rapid metabolism of the propanoic methyl ester linkage on the parent piperidine molecule by nonspecific esterases in blood and tissues.¹ The rapid onset and short duration of action of remifentanyl permit titration of the infusion rate to response, but result in termination of analgesic effects within minutes of discontinuing an infusion. Therefore, the transition from remifentanyl intraoperative analgesia to postoperative analgesia must be carefully planned.

The transition from a total intravenous anesthesia regimen with remifentanyl and propofol to open-label remifentanyl analgesia has been previously investigated by Bowdle *et al.*⁸ In Bowdle's study, the remifentanyl dose range that provided effective postoperative analgesia was 0.05 – $0.15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. However, the analgesic regimen in study, which included bolus doses of remifentanyl, was associated with a high incidence of respiratory adverse events. The present study was designed to further investigate a remifentanyl regimen that would provide safe and effective short-term postoperative analgesia in patients who were expected to experience

moderate to severe postoperative pain after a total intravenous anesthesia regimen with remifentanyl and propofol, and to establish its effectiveness compared with a standard regimen of morphine in a double-blind comparison. Results of this study provided the guidelines and recommended doses that are included in the Food and Drug Administration-approved product information sheet for remifentanyl when continued as an analgesic into the immediate postoperative period. The use of remifentanyl and propofol in a total intravenous anesthesia regimen for induction and maintenance of anesthesia has been reported previously.⁹

Materials and Methods

Study Design

This study was performed at 10 medical centers in the United States. The protocol was approved by the institutional review boards at each center, and written informed consent was obtained from all patients. The study consisted of an open-label anesthesia phase followed by a double-blind, double-dummy, parallel-group, active-controlled postoperative analgesia phase.

Randomization was performed in accordance with a code generated using SAS version 6.08 software (SAS Inc., Cary, NC). Patients eligible for randomization were assigned the lowest available treatment number in chronological order of presentation for surgery. Each treatment number was assigned to only one patient. Solutions of remifentanyl (calculated as remifentanyl free base, $100 \mu\text{g/ml}$) and morphine sulfate were prepared by the hospital pharmacy at each center and provided in syringes. Infusion and bolus syringes were prepared for each analgesia phase treatment such that the anesthesia staff were blinded to the contents of the syringes.

Patient Selection

Enrollment was limited to patients aged at least 18 yr with American Society of Anesthesiologists (ASA) physical status I–III, who were scheduled for elective inpatient surgery (excluding cardiac, neurosurgery, and peripheral vascular surgery) during general anesthesia for up to 4 h in duration. Expected moderate to severe postoperative pain requiring parenteral analgesic treatment, and at least one overnight stay in the hospital were also required. Patients were excluded if they had a clinically significant unstable medical condition; if they had a history of substance abuse or chronic use of opioids, benzodiazepines, tricyclic antidepressants,

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or clonidine; if they had received any of these agents within 12 h before surgery; or if they were pregnant or breast-feeding.

Anesthetic Protocol

Anesthesia Phase. Two intravenous cannulae were inserted: one to administer intravenous fluids and remifentanyl, and the other for all other drugs and fluids. Standard monitors included a lead-II electrocardiogram, pulse oximetry, and capnometry. Before induction of anesthesia, approximately 5 ml/kg of crystalloid were administered intravenously. All patients were premedicated with 0.025–0.05 mg/kg intravenous midazolam.

Patients were preoxygenated for 3 min by mask with 100% oxygen, and vital signs were recorded before anesthesia induction. A single dose of 1 $\mu\text{g}/\text{kg}$ remifentanyl was followed immediately by a 0.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion. Three minutes after starting remifentanyl, 0.5 mg/kg propofol was administered by intravenous push. Additional propofol boluses (20 mg) were administered, if needed, every 30 s until loss of consciousness, followed by a 75 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ propofol infusion. Vecuronium (up to 0.15 mg/kg) was administered to facilitate endotracheal intubation. Five minutes after tracheal intubation, the remifentanyl infusion was decreased by 50% from the current rate. During surgery, remifentanyl, propofol, or both were titrated to maintain systolic blood pressure between 80 mmHg and baseline + 15 mmHg, and heart rate (HR) between 40 and 90 beats/min. Single doses of remifentanyl (1 $\mu\text{g}/\text{kg}$) and/or rate increases (0.25 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ per increase up to a maximum of 2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and 20-mg boluses of propofol or rate increases up to 125 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ were used to treat signs of light anesthesia. Rate decreases were performed at investigator discretion to treat hypotension.

Analgesia Phase. Figure 1 shows specific analgesic interventions administered to each treatment group at various predefined times. Twenty minutes before the anticipated end of surgery, the propofol infusion was decreased by 50%, and patients were randomized to receive either a placebo bolus (remifentanyl group) or a 0.15 mg/kg morphine bolus (morphine group). Residual neuromuscular blockade was reversed with neostigmine and glycopyrrolate before the anticipated end of surgery. At the end of surgery (defined as skin closure or later, such as application of a cast, and so forth), the propofol and remifentanyl maintenance infusions were discontinued, and the double-blind analgesic infusion, either 0.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ remifentanyl (remifentanyl

group) or placebo (morphine group) was started immediately. For the first 25 min of the analgesic infusion period (titration period), remifentanyl increments of 0.025 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and a placebo bolus (remifentanyl group) or 2-mg intravenous morphine bolus and a placebo rate increase (morphine group) were administered as necessary at 5-min intervals to achieve pain scores of 0–1 on a scale of 0–3. Patients verbally assessed their pain as being none, mild, moderate, or severe. Study personnel translated the patients' responses into a numeric scale: no pain = 0, mild pain = 1, moderate pain = 2, and severe pain = 3. During the titration period, patients also received supplemental oxygen (per institutional standards). Patients received 0.075 mg/kg morphine (remifentanyl group) or placebo (morphine group) in intravenous boluses 25 and 30 min after extubation, and the analgesic infusion was discontinued at 35 min. From 35 to 65 min after extubation, both groups received open-label morphine analgesia (4–6 mg for severe pain, and 2–4 mg for mild-to-moderate pain, every 5 min, as needed).

During the titration period, open-label rescue morphine was administered if two successive intermittent boluses and analgesic infusion rate increases did not provide adequate pain relief. The investigator determined the dose of morphine based on an assessment of the patient's pain level and previous analgesic requirements. After rescue morphine was administered, the analgesic infusion was continued, but no further boluses (including the scheduled morphine boluses) or increases in rate were administered. Patients who received rescue medication were excluded from subsequent analysis.

The double-blind analgesic infusion (remifentanyl or placebo) was reduced: (1) by 50% from the current rate up to two times at 5-min intervals in the event of respiratory depression (defined as a RR \leq 8 breaths/min or pulse oximetry $<$ 90%) or delayed emergence (defined as the absence of adequate respiration within 10 min after the end of surgery), and (2) by 50% or discontinued at the discretion of the anesthesiologist if respiratory depression occurred after the administration of either scheduled analgesic bolus at 25 or 30 min. If adequate respiration was not achieved after the second decrease, the analgesic infusion was discontinued, and naloxone could be administered in the case of delayed emergence. The analgesic infusion was not reinitiated after discontinuation for any reason, and postoperative pain was treated (through 65 min after tracheal extuba-

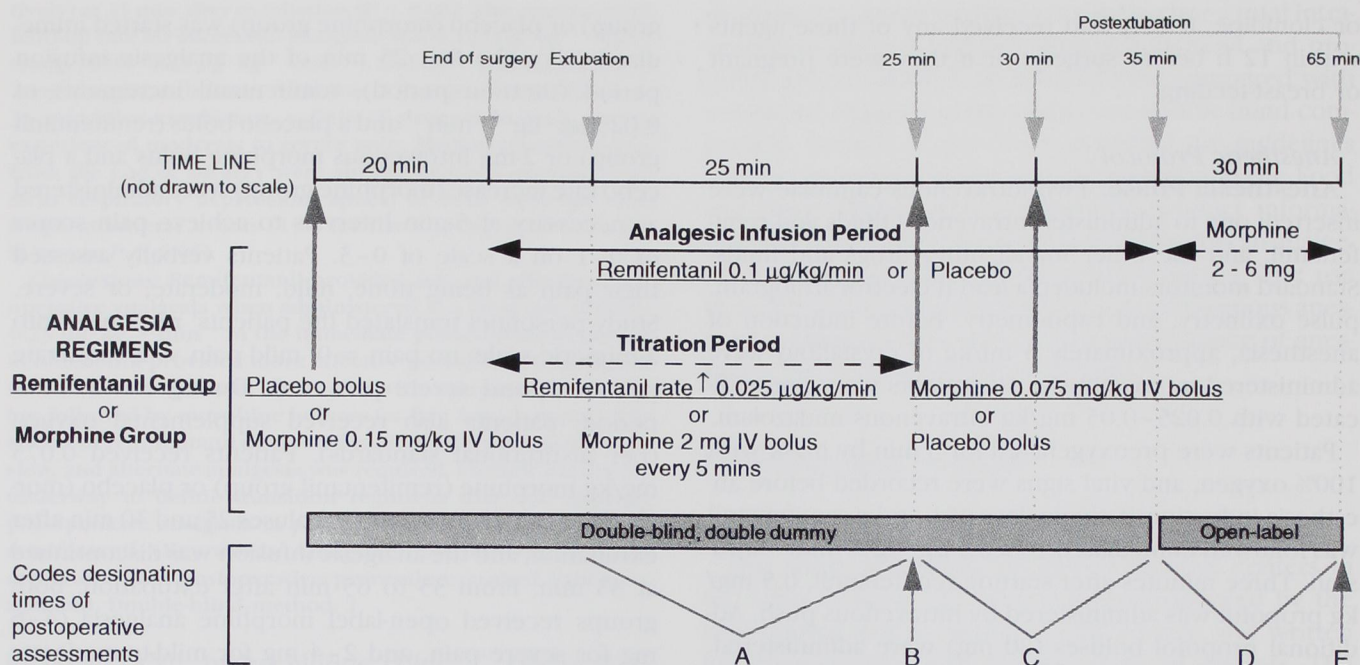


Fig. 1. Protocol applied during the postoperative period. Interventions administered to the remifentanil group are underlined. The time line is not drawn to scale.

tion) with open-label morphine at the discretion of the anesthesiologist.

Outcome Measures

Postoperative pain and hemodynamic and respiratory parameters were assessed at 3, 5, 10, 15, 20, 25, 30, and 35 min after extubation; at 5, 10, 15, 20, 25, and 30 min after discontinuation of the analgesic infusion; and every 15 min until discharge from the postanesthesia care unit (PACU).

Efficacy Assessments. Primary assessments included the proportion of patients with successful analgesia (defined as no or mild pain with RR \geq 8 breaths/min at 25 min after extubation and for the entire titration period, and the remifentanil or morphine dose requirements (mean infusion rate or number of boluses) for successful analgesia by the end of the titration period (fig. 1). Other assessments included the proportion of patients with RR \geq 8 breaths/min during the entire titration period; the proportion of patients with RR $<$ 8 breaths/min at the end of the titration period; the distribution of patients with moderate-to-severe pain at any time during treatment; the incidence of rescue morphine required during the analgesic infusion period; and the incidence of naloxone use during the initial anesthetic recovery period.

Recovery Assessments. After entry into the PACU, the Aldrete postanesthesia recovery score was determined at 5, 10, 15, 20, 25, and 30 min, and every 15 min thereafter until a score of 9 or 10 was obtained.¹⁰ Patients were qualified for discharge from the PACU when their Aldrete score \geq 9 and nausea, vomiting, and pain were adequately controlled. Recovery parameters were specifically measured from the end of surgery and included time to extubation and time to actual PACU discharge.

Safety Assessments. The incidences of all adverse events (defined as any untoward medical event, potentially drug-related or not) occurring during the study were recorded. Nausea and vomiting were specifically assessed within 15 min after extubation, at the time of discontinuation of the remifentanil/placebo analgesic infusion, and at the time of discharge from the PACU.

Data Analysis

An *a priori* power analysis was performed. A minimum of 60 patients in each treatment group was anticipated to provide approximately 80% power of detecting a difference in the success of pain control of \geq 28% between treatment groups at the end of the titration period with a significance level of 0.05. Statistical analyses were performed using SAS version 6.08. All statisti-

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cal results were two-tailed with statistical significance defined as $P < 0.05$. Data from the different centers were combined for statistical comparisons after determining that there was no treatment-by-center interaction.

The Fisher's Exact Test was used to compare differences between groups in the proportion of patients with successful analgesia (no or mild pain and $RR \geq 8$ breaths/min), and in the incidence of respiratory depression, apnea, or both. The Cochran-Mantel-Haenszel test was used to compare the distribution of pain scores between groups. Remifentanyl infusion rates, hemodynamic and respiratory parameters were summarized as weighted mean, and mean minimum and maximum values for specific periods (A, C, and D), as shown in figure 1.

For the remifentanyl infusion rate, the weighted mean was calculated as the area under the curve over time divided by the duration of the measurement, assuming a step-wise distribution. For hemodynamic and respiratory parameters, the weighted mean was calculated in a similar manner using the trapezoidal rule.

Results

Patient Accountability and Demographics

One hundred ninety-six patients were enrolled in the study, and efficacy results for 150 patients (remifentanyl, $n = 72$; morphine, $n = 78$) during the analgesia phase are presented. Forty-six patients were excluded from the efficacy analyses for the following reasons: 5 for surgical complications or changes in procedure; 18 had been treated before a protocol amendment was made to increase the morphine loading dose from 0.1 to 0.15 mg/kg; and 23 were open-label pilot patients. Safety results are presented for 191 patients (remifentanyl, $n = 93$; morphine, $n = 98$) and excluded the 5 patients who did not enter the analgesia phase due to surgical complications or changes in the procedure. Treatment groups were similar with regard to demographics and duration of anesthesia (table 1).

Eight patients receiving remifentanyl and two receiving morphine were prematurely discontinued from the study. Six remifentanyl patients were withdrawn because of adverse events (respiratory depression, $n = 4$; apnea, $n = 2$) and two for other reasons (one serious adverse event due to an accidental drug overdose and one delayed emergence). One patient receiving mor-

Table 1. Patient Characteristics

	Remifentanyl (n = 72)	Morphine (n = 78)
Male/female	19/53	29/49
Age (yr)		
Mean \pm SD (range)	43.4 \pm 14.9 (19–77)	44.4 \pm 17.2 (18–84)
ASA Physical Status (n)		
I/II/III	24/45/3	32/39/7
Anesthesia duration (min)		
Median (range)	188 (94–484)	179 (100–386)
Duration of analgesic infusion (min)		
Median (range)	39 (16–75)	NA
Types of surgery* (%)		
Urogenital/gynecological	52	53
Orthopedic	31	30
Other	17	17

SD = standard deviation; NA = not applicable.

* For total enrolled population ($n = 97$ for remifentanyl; $n = 99$ for morphine).

phine was withdrawn due to an adverse event (shivering), and another because of delayed emergence.

Efficacy Evaluations

Successful Analgesia. Twenty-eight percent of patients receiving remifentanyl and 15% receiving morphine had successful analgesia (no or mild pain with $RR \geq 8$) throughout the entire titration period. By the end of the titration period, a significantly larger proportion of patients receiving remifentanyl (58%) than those receiving morphine (33%) had achieved successful analgesia ($P < 0.05$). In addition, patients who failed to achieve successful analgesia were more likely to have had moderate or severe pain (26%) than to have $RR < 8$ breaths/min (6%).

Postoperative Pain. Figure 2 shows the distribution of patients with moderate to severe pain during the postoperative period. By the end of the analgesic infusion period, remifentanyl rate titrations resulted in a marked decrease in the proportion of patients with moderate or severe pain at 25 and 30 min after extubation. In contrast, most patients in the morphine group continued to experience moderate-to-severe pain. During the open-label period, the proportion of patients with moderate-to-severe pain increased in the remifentanyl group (whose infusion had been stopped), but showed a decrease in the morphine group (as the cumulative dose of morphine increased).

Respiratory Rate. During the entire titration period,

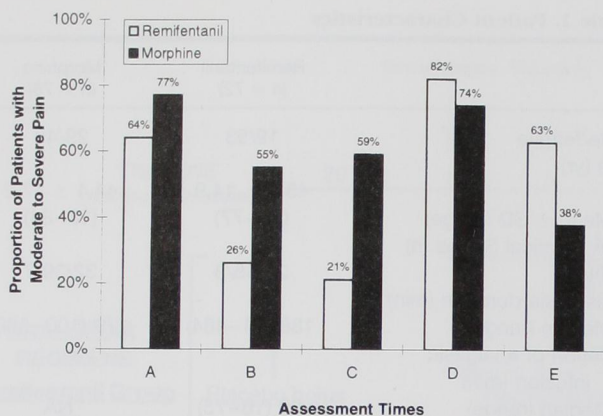


Fig. 2. The proportion of patients with moderate-to-severe pain at two time points (B, E) and at any time during three time periods (A, C, D) of the analgesia phase for the remifentanyl (n = 72) and morphine (n = 78) groups. Measurement times (see also fig. 1): titration period (A), end of titration (B), transition period (C), open-label period (D), and end of open-label period (E).

seven patients in the remifentanyl group and no patient in the morphine group had analgesic infusion rate decreases for $RR < 8$ breaths/min. Adequate respiration returned in 1–5 min after a single rate decrease in four of these patients who then completed the study. The other three patients who experienced $RR < 8$ breaths/min were withdrawn from the study before the end of the titration period because downward titration of the remifentanyl infusion did not restore adequate respiration. At the end of the titration period, most patients remaining in the remifentanyl group (97%) had $RR \geq 8$ breaths/min.

Figure 3 shows the cumulative proportions of remifentanyl patients at or below each infusion rate with no or mild pain or with $RR < 8$ breaths/min at the end of the titration period. The figure illustrates that when the infusion rate is increased to treat pain, a corresponding increase in the incidence of $RR < 8$ breaths/min does not occur.

Optimal Opioid Dosing. Most patients in the remifentanyl group (70%) had final infusion rates in the range from > 0.1 – $0.15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Successful analgesia was achieved with a mean (\pm SD) infusion rate of $0.125 \pm 0.036 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (range, 0.05 – $0.23 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) for the remifentanyl group, and a median of two 2-mg bolus doses (range, 0–5) for the morphine group. Four remifentanyl-treated patients (6%) and eight morphine-treated patients (10%) received open-label rescue morphine (approximately 12 mg) due to inadequate control of postoperative pain by the study dose regimens. At 25 and 30 min after extubation, 89% of patients in the remifentanyl group received the two scheduled double-

blind morphine transition boluses totaling 0.15 mg/kg morphine. The remaining patients had received rescue morphine (6%) or had been prematurely discontinued from the study due to adverse events (5%). During the open-label period, patients in the remifentanyl group received a total (mean \pm SD) dose of $8.8 \pm 5.3 \text{ mg}$ morphine (range, 2–25 mg), and patients in the morphine group received $7.7 \pm 5.3 \text{ mg}$ morphine (range, 2–27 mg).

Hemodynamics. The weighted mean systolic blood pressure, diastolic blood pressure, and heart rate values between the end of surgery and extubation were similar to values during the intraoperative period (fig. 4). After extubation, values returned to near baseline levels for all parameters. The hemodynamic profile remained generally stable throughout the analgesic infusion period, and during the open-label period.

Recovery Evaluations

Median recovery times were similar between groups (table 2). Two of 72 patients (3%) in the remifentanyl group and 6 of 78 patients (8%) in the morphine group were not eligible for extubation by 10 min after the end of surgery. One patient in each group was withdrawn from the study due to inability to extubate by 20 min after surgery, and naloxone was administered 23 min after the end of surgery to one 72-yr-old morphine patient. In general, patients with delayed emergence were older than the mean age for each treatment group.

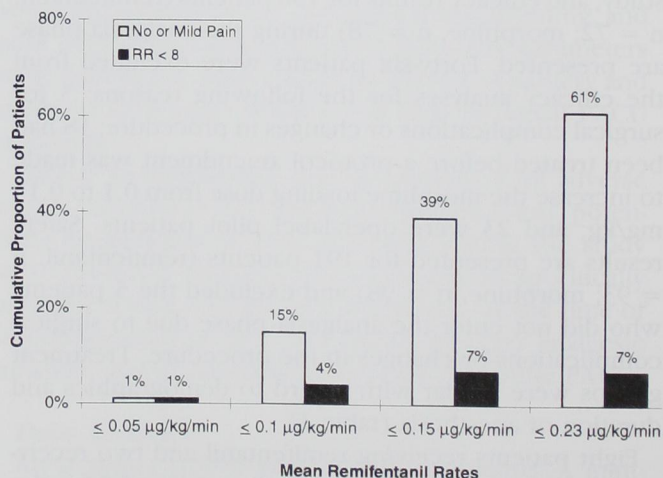


Fig. 3. Cumulative proportions of patients receiving remifentanyl with no or mild pain or with a respiratory rate < 8 breaths/min at the end of the titration period. Within the specified dose range, the remifentanyl infusion rate could be increased as required to manage pain without a corresponding increase in the proportion of patients experiencing episodes of respiratory rate < 8 breaths/min.

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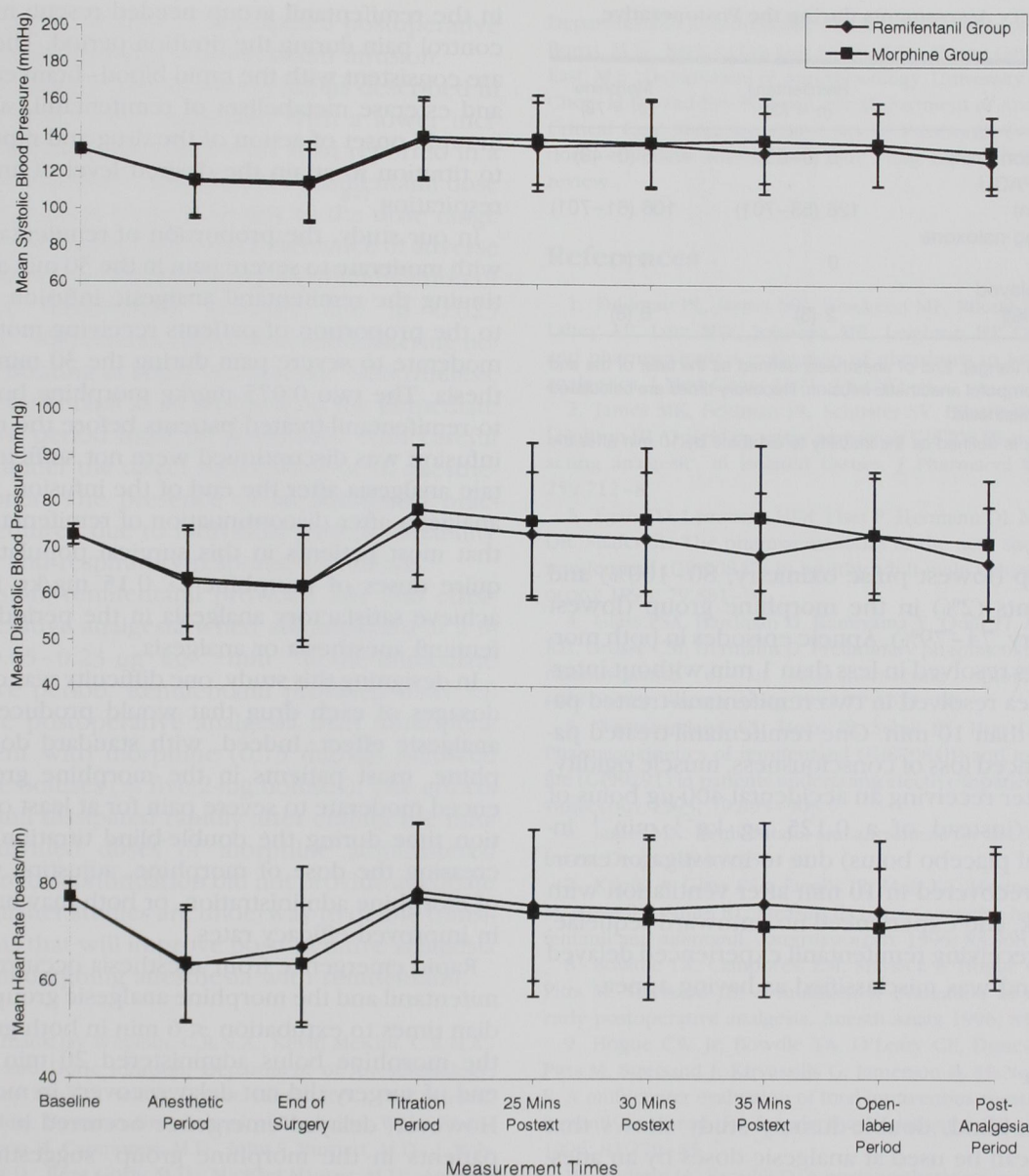


Fig. 4. Systolic blood pressure, diastolic blood pressure, and heart rate values at different stages from baseline until discharge from the postanesthesia care unit. Values are means \pm SD for baseline, and at three different postextubation (Postext) times: 25, 30, and 35 min. Remaining values are time-weighted means \pm SD values (anesthetic period = from start of intraoperative period until end; end of surgery = from skin closure until time of tracheal extubation; titration period = from tracheal extubation until 25 min after extubation; open-label period = from 35 to 65 min after extubation; postanalgesia period = from 65 min after extubation until discharge from the postanesthesia care unit).

Safety Evaluations

The most frequently reported drug-related adverse events ($\geq 5\%$) in the remifentanyl and morphine groups included transient respiratory depression and/or apnea (14% vs. 6%, respectively; $P = 0.091$), nausea (17% vs. 13%, respectively) and shivering (5% in both groups).

Respiratory depression resolved in 1–15 min without other interventions after decreasing or discontinuing study drug. After receiving 13.7 mg morphine at the end of the remifentanyl infusion, one patient became apneic and was reintubated as a precautionary measure.

Apnea was reported in four patients (4%) in the remi-

Table 2. Recovery Assessments during the Postoperative Period

	Remifentanyl (n = 72)	Morphine (n = 78)
Time to extubation (min)	5 (0–25)	6 (0–49)
Time to actual PACU discharge (min)	126 (55–701)	106 (61–701)
Patients requiring naloxone [n (%)]	0	1 (1)
Patients with delayed recovery* [n (%)]	2 (3)	6 (8)

Values are median (range). End of anesthesia defined as the later of the end of remifentanyl or propofol anesthetic infusion. Recovery times are calculated from the end of anesthesia.

* Delayed recovery is defined as the inability to extubate by 10 min after the end of surgery.

fentanyl group (lowest pulse oximetry, 80–100%) and in two patients (2%) in the morphine group (lowest pulse oximetry, 74–79%). Apneic episodes in both morphine patients resolved in less than 1 min without intervention. Apnea resolved in two remifentanyl-treated patients in less than 10 min. One remifentanyl-treated patient experienced loss of consciousness, muscle rigidity, and apnea after receiving an accidental 400- μ g bolus of remifentanyl (instead of a 0.125 μ g \cdot kg⁻¹ \cdot min⁻¹ increase + 4 ml placebo bolus) due to investigator error. This patient recovered in 10 min after ventilation with a bag or mask, and experienced no untoward sequelae. One patient receiving remifentanyl experienced delayed emergence and was misclassified as having apnea.

Discussion

This double-blind, double-dummy study shows that remifentanyl can be used at analgesic doses by an anesthesia practitioner to provide safe and effective pain relief in the immediate postoperative period after a total intravenous anesthesia regimen with remifentanyl and propofol. During the first 25 min after extubation, significantly more patients who received 0.05–0.23 μ g \cdot kg⁻¹ \cdot min⁻¹ remifentanyl achieved successful analgesia compared with patients who received morphine (0.15 mg \cdot kg⁻¹ and 2 mg intravenous boluses) administered intraoperatively and intermittently. Within the specified dose range, the remifentanyl infusion rate may be increased as required to treat pain without a corresponding increase in the proportion of patients experiencing episodes of RR > 8 breaths/min. Few patients

in the remifentanyl group needed rescue morphine to control pain during the titration period. These findings are consistent with the rapid blood–brain equilibration and esterase metabolism of remifentanyl, which result in rapid onset of action of the drug and rapid response to titration to attain the desired level of analgesia and respiration.^{1–6}

In our study, the proportion of remifentanyl patients with moderate to severe pain in the 30 min after discontinuing the remifentanyl analgesic infusion was similar to the proportion of patients receiving morphine with moderate to severe pain during the 30 min after anesthesia. The two 0.075 mg/kg morphine boluses given to remifentanyl-treated patients before the remifentanyl infusion was discontinued were not sufficient to maintain analgesia after the end of the infusion. Insufficient analgesia after discontinuation of remifentanyl suggests that most patients in this surgical population will require doses of morphine > 0.15 mg/kg in order to achieve satisfactory analgesia in the period after remifentanyl anesthesia or analgesia.

In designing this study, one difficulty was determining dosages of each drug that would produce equivalent analgesic effect. Indeed, with standard doses of morphine, most patients in the morphine group experienced moderate to severe pain for at least one observation time during the double-blind titration period. Increasing the dose of morphine, adjusting the interval of morphine administration, or both may have resulted in improved efficacy rates.

Rapid emergence from anesthesia occurred in the remifentanyl and the morphine analgesic groups, with median times to extubation \leq 6 min in both groups. Thus the morphine bolus administered 20 min before the end of surgery did not delay recovery in most patients. However, delayed emergence occurred in a few older patients in the morphine group, suggesting that the morphine dose administered should be individualized. The slightly longer median time to discharge from the PACU seen in remifentanyl-treated patients may be due to delayed transition to alternate analgesia of control postoperative pain.

As demonstrated by the present study, the rapid emergence from anesthesia made possible by using remifentanyl together with concomitant short-acting hypnotic agents such as propofol is also accompanied by rapid onset of postoperative pain in this surgical population. Thus, anesthesia practitioners who use remifentanyl as the opioid component of anesthesia must anticipate this rapid onset of pain and provide analgesia that is

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appropriate to the degree of anticipated postoperative pain before discontinuing a remifentanyl infusion.

The remifentanyl analgesic interventions described in the present study were associated with a lower incidence of respiratory adverse events than reported in a previous investigation.⁸ Although the remifentanyl dose range in the present study is similar to the dose range investigated previously,⁸ the lower incidence of adverse events supports the labeled dosing recommendation of titrating the remifentanyl infusion rate in $0.025 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ increments rather than administering bolus doses or titrating in larger increments. Nevertheless, the use of remifentanyl as an analgesic in the immediate postoperative period must be performed with careful monitoring under the direct supervision of an anesthesia practitioner. The presence of an anesthesia practitioner is required due to individual patient variability in analgesic and respiratory response to opioids.

In conclusion, remifentanyl provided safe and effective postoperative analgesia when administered at a final rate of $0.05\text{--}0.23 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the immediate postoperative period. Remifentanyl provided more effective acute postoperative analgesia than intraoperative treatment with morphine (0.15 mg/kg) followed by morphine boluses (\leq five 2-mg boluses). The effects of remifentanyl dissipated rapidly after ending the infusion. The divided doses of morphine administered shortly before discontinuation did not provide adequate analgesia. Further studies are underway to define transition regimens that will improve postoperative analgesia in patients undergoing anesthesia with remifentanyl.

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