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Remifentanil versus *Remifentanil/midazolam for Ambulatory Surgery during Monitored Anesthesia Care*

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Background: **This study was designed to define the appropriate dose of remifentanil hydrochloride alone or combined with midazolam to provide satisfactory comfort and maintain adequate respiration for a monitored anesthesia care setting.**

Methods: **One hundred fifty-nine patients scheduled for outpatient surgery participated in this multicenter, double-blind study. Patients were randomly assigned to one of two groups: remifentanil, 1 μg/kg, given over 30 s followed by a continuous infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (remifentanil); remifentanil, 0.5 μg/kg, given over 30 s followed by a continuous infusion of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (remifentanil + midazolam). Five minutes after the start of the infusion, patients received a loading dose of saline placebo (remifentanil) or midazolam, 1 mg, (remifentanil + midazolam). If patients were not oversedated, a second dose of placebo or midazolam, 1 mg, was given. Remifentanil was titrated (in increments of 50% from the initial rate) to limit patient discomfort or pain intraoperatively, and the infusion was terminated at the completion of skin closure.**

Results: **At the time of the local anesthetic, most patients in the remifentanil and remifentanil + midazolam groups experienced no pain (66% and 60%, respectively) and no discomfort (66% and 65%, respectively). The final mean (± SD) remifentanil infusion rates were 0.12 ± 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (remifentanil) and 0.07 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (remifentanil + midazolam). Fewer patients in the remifentanil + midazolam group experienced nausea compared with the remifentanil group (16% *vs.* 36%, respectively; $P < 0.05$). Four patients (5%) in the remifentanil group and two patients (2%) in the remifentanil + midazolam group experienced brief periods of oxygen desaturation ($Sp_{O2} < 90\%$) and hypoventilation (< 8 breaths/min).**

Conclusions: **Remifentanil alone or combined with midazolam provided adequate analgesia and maintained adequate respiration at the doses reported. The low dose of remifentanil combined with 2 mg midazolam, compared with remifentanil alone, resulted in fewer side effects, slightly greater sedation, and less anxiety. (Key words: Anesthetics, intravenous: remifentanil; midazolam. Analgesics, opioids: remifentanil. Anesthesia adjuvants: midazolam. Ambulatory care. Anesthesia recovery period. Anesthetic, local.)**

The new μ-opioid receptor agonist, remifentanil hydrochloride, is rapidly metabolized by hydrolysis of the methyl ester linkage by nonspecific esterases in blood and tissues.[1] Unlike other opioids, remifentanil has a short elimination half-life of 3-10 min,[2,3] and the duration of action does not increase with increasing duration of administration because of rapid clearance (40 $ml \cdot kg^{-1} \cdot min^{-1}$) and lack of drug accumulation.[2-5] The pharmacokinetic properties of remifentanil suggest that it may be useful for the monitored anesthesia (MAC) setting and may allow for a titratable balance between analgesic and respiratory depressant effects. The objective of this study was to define the appropriate dose of remifentanil hydrochloride alone or in combination with midazolam to provide satisfactory comfort and to maintain adequate respiration for MAC.

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Methods and Materials

Study Design

This double-blind, randomized study was approved by the institutional review boards at each of the seven institutions scheduled to enroll patients. Written informed consent was obtained from all patients scheduled to undergo superficial ambulatory surgeries during monitored anesthesia care. Randomization was performed according to a code generated using SAS version 6.08 (SAS Inc., Cary, NC). Patients eligible for randomization were assigned the lowest available treatment number in chronologic order of presentation to the anesthesiologist. Each treatment number was assigned to only one patient. Solutions of remifentanil hydrochloride (calculated as remifentanil free base, 100 μg/ml) were prepared by the hospital pharmacy at each center. Blinding was achieved by providing the remifentanil, midazolam, and placebo in coded syringes identified only with the treatment number and patient's initials.

Patient Selection

Screening procedures (*i.e.*, medical history, 24-h drug history, and physical examination) were completed and evaluated before patient enrollment. Enrollment was limited to patients who were aged 18 years or older, American Society of Anesthesiologists' (ASA) physical status I–III, and less than 100% over ideal body weight. Patients were excluded if they had any of the following conditions: uncontrolled hypertension (diastolic blood pressure > 100 mmHg), ischemic heart disease, congestive heart failure, renal or hepatic dysfunction, severe chronic respiratory disease, conduction disorder, ventricular arrhythmia, drug or substance abuse, hepatitis, psychiatric illness that may impair the patient's ability to provide informed consent, or were pregnant or breast-feeding. Patients were also excluded if they had any condition that may place them at a greater than normal risk to taking midazolam, *i.e.*, patients with myasthenia gravis or acute narrow-angle glaucoma. Patients were also excluded if they had anesthesia or opioid use within 2 days before study participation, if they had a history of chronic benzodiazepine use, or if they had received an injection of a benzodiazepine within 12 h before surgery.

Anesthetic Protocol

This study was divided into three periods: a preoperative period, an intraoperative period, and a recovery period. In the preoperative period, patients blindly received one of two treatment regimens: remifentanil, 1 μg/kg, given over 30 s followed by a continuous infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (remifentanil group), or remifentanil, 0.05 μg/kg, given over 30 s followed by a continuous infusion of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (remifentanil + midazolam group). Five minutes after the start of the remifentanil infusion, a series of measurements, including heart rate, blood pressure, respiratory rate, oxygen saturation, end-tidal CO_2, and verbal assessments of pain, discomfort, anxiety, and sedation were recorded. Once these were completed, the first dose of placebo (remifentanil group) or midazolam, 1 mg, (remifentanil + midazolam group) was administered in a blinded manner over 30 to 60 s. If patients were not oversedated, a second dose of placebo or midazolam, 1 mg, was given for anxiety at least 2 min after the first dose. All scheduled safety and efficacy assessments were recorded at 3 min after the last placebo or midazolam bolus, and hemodynamic and respiratory measurements were repeated every 5 min until the local anesthetic was administered. The local anesthetic injection was administered at least 3 min after the last dose of placebo or midazolam.

The intraoperative period began after the local anesthetic injection. Hemodynamic, respiratory, and efficacy measurements were performed at specified times from the local anesthetic injection until the end of surgery (*i.e.*, placement of last suture). Pain level was assessed 1 min after the local anesthetic injection. Hemodynamic and respiratory measurements and discomfort, anxiety, and sedation assessments were recorded at 1, 5, and 10 min after the local anesthetic injection and were repeated every 10 min until the end of surgery. Starting 1 min after the local anesthetic injection, the remifentanil infusion rate was adjusted based on patient discomfort or hemodynamic and respiratory values. At 3 and 5 min after each change in the remifentanil infusion rate, the hemodynamic and respiratory measurements were repeated. Open-label midazolam (0.5 mg) could be administered as a rescue medication at this time for anxiety in either group, if needed.

The remifentanil infusion rate could be increased (in 50% increments from the initial rate) if the discomfort score was greater than 4 on an 11-point scale (see **Study Parameters** section) or if the patient complained of discomfort or pain or had a somatic response such as grimacing or movement or required additional sedation, analgesia, or anxiolysis. The maximum remifentanil infusion rate allowed was 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remifentanil group or 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remifen-

tanil + midazolam group. The remifentanil infusion rate could be decreased by 50% if the patient experienced respiratory depression, defined as a respiratory rate < 8 breaths/min for ≥ 1 minute, or O_2 saturation < 94% on O_2 supplementation; hypotension, defined as systolic blood pressure 15 mmHg below baseline or < 80 mmHg for ≥ 1 min; or bradycardia, defined as heart rate < 40 beats/min for ≥ 1 min.

The recovery (last) period began with the termination of the remifentanil infusion at the end of surgery (skin closure) and continued until the patient was discharged from the hospital. Pain, discomfort, anxiety, and sedation scores and hemodynamic and respiratory function measurements were recorded at 1, 3, 5, 10, 20, and 30 min after the termination of the remifentanil infusion and were repeated every 15 min thereafter until the patient qualified for discharge. Nausea and vomiting were assessed and recorded on arrival in recovery, after 15 min, and just before discharge. Antiemetics were administered if deemed clinically necessary.

Immediate recovery was assessed using the modified Aldrete score.[6] Patients who had two successive Aldrete scores of 9 or more, no or mild nausea, and no vomiting were transferred from the operating room directly into the postanesthesia care phase II recovery area (step-down unit) after bypassing the phase I recovery area. Patients qualified for discharge from the phase II recovery area when they met phase I discharge criteria, had a postanesthesia discharge score (PADS) of 9 or 10,[7] and were walking unassisted.

Study Parameters

The primary efficacy measures were pain and discomfort scores assessed at 1 min after the local anesthetic injection and the remifentanil infusion dose, which provided adequate comfort (discomfort score ≤ 4) and maintained adequate respiration (≥ 8 breaths/min). Patients were asked to verbally rate their level of pain (on a descriptive scale, with 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). Patients also were asked to verbally rate their level of discomfort, sedation, and anxiety on an 11-point numerical rating scale (where 0 = none and 10 = extreme). The patient's level of sedation was also assessed by the investigator using the 5-point Observer's Assessment of Alertness/Sedation (OAA/S) scale[8] (modified by reversing the order of the scores such that 0 = alert and 5 = deep sleep).

Recovery times were measured from the end of surgery and included time to ambulate unassisted and times to qualify for and actual discharge from phase I and phase II. The incidence of adverse events (defined as any untoward medical event, potentially drug-related or not) was recorded throughout the study.

Statistical Analysis

An *a priori* power analysis was performed. A minimum of 50 patients in each treatment group was anticipated to provide approximately 80% power of detecting a difference of 30% in the proportion of patients experiencing none or mild *versus* moderate or severe pain 1 min after the local anesthetic injection at a significance level of 0.05. Statistical analyses were performed using SAS version 6.08 (SAS Inc.). All statistical tests were two-tailed, with statistical significance defined as $P < 0.05$. After determining that there was no overall treatment-by-site interaction, data from the different centers were combined for statistical comparisons.

Discomfort scores were grouped for the proportion of patients who had no discomfort (score = 0), mild discomfort (score = 1-4), and moderate-to-severe discomfort (score = 5-10). Pain and discomfort scores were compared between groups using logistic regression adjusted for site. Recovery times were compared between groups using Cox's proportional hazard modeling adjusted by site.[9] For the infusion rate of remifentanil, the weighted mean was calculated as the sum (Σ) of the individual rates (X) at each measurement time (t) divided by the total duration of measurement (T) (*i.e.*, $\Sigma\ X_n\ (t_n - t_{n-1})/T$ for $n = 1, 2, \ldots, N$ where N is the number of observations). For the hemodynamic and respiratory parameters, the weighted mean was calculated as the sum of the individual parameter (X) values at each measurement time (t) divided by the total duration of measurement (T) (*i.e.*, $\Sigma\{[(X_n + X_{n-1})/2](t_n - t_{n-1})\}/T$ for $n = 1, 2, \ldots, N$ where N is the number of observations). The weighted means obtained were compared between groups using the analysis of variance, adjusted for site and baseline.

Results

Patient demographics were similar between the two study groups (table 1). The median time from the start of remifentanil administration to the local anesthetic injection for both groups was 12 min (range, 7-42 min for the remifentanil group and 7-29 min for the remifentanil + midazolam group). During the preoperative period, 93% (75/81) and 91% (71/78) of patients in the remifen-

Table 1. Demographic Data

	Remifentanil	Remifentanil + Midazolam
No. of patients	78	81
Gender distribution [no. (%)]		
Female	49 (63)	50 (62)
Male	29 (37)	31 (38)
Age* (yr)	44 ± 13	45 ± 16
Height* (in)	65 ± 5	66 ± 5
Weight* (kg)	73 ± 17	73 ± 18
Surgical types† [no. (%)]	28 (36)	28 (35)
Breast biopsy		
Lumpectomy	2 (3)	4 (5)
Skin/subcutaneous tissues	10 (13)	15 (19)
Urogenital	5 (6)	7 (9)
Vascular	5 (6)	6 (7)
Orthopedic	6 (8)	4 (5)
Peripheral nerves, muscles	4 (5)	6 (7)
Head and neck	4 (5)	4 (5)
Thoracic	5 (6)	3 (4)
Abdominal	4 (5)	0

* Age, height, and weight are shown as mean ± SD.

† Patients may have had more than one surgical procedure performed and can be counted more than once.

tanil and remifentanil + midazolam groups, respectively, received the second blinded syringe containing either placebo or midazolam, 1 mg. Thus, the mean (± SD) dose of midazolam used was 1.93 ± 0.26 mg.

Efficacy Evaluations

The majority of patients (≥ 60%) in both groups experienced no pain (fig. 1A) and no discomfort (fig. 1B) with local anesthetic injection. Similar proportions of patients in both groups experienced moderate-to-severe pain with local anesthetic injection (16% in the remifentanil group and 20% in the remifentanil + midazolam group; $P = 0.54$; fig. 1A).

The final remifentanil infusion rate (mean ± SD) was 0.12 ± 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remifentanil group and 0.07 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remifentanil + midazolam group. The majority of patients in the remifentanil and remifentanil + midazolam groups (71% and 68%, respectively) required at least one remifentanil rate change, with more patients requiring rate increases than rate decreases in both groups.

When compared with the remifentanil + midazolam group, fewer patients in the remifentanil group were sedated (OAA/S score ≥ 3) before (4% *vs.* 22%) and within 1 min after the local anesthetic injection (0% *vs.* 10%; $P < 0.05$). No patient in any group had an OAA/S score of 5. More patients in the remifentanil group (13%) experienced anxiety (anxiety score ≥ 5) compared with the remifentanil + midazolam group (2%; $P < 0.05$) before the local anesthetic injection.

Clinically significant decreases from baseline in the weighted mean systolic (fig. 2A) and diastolic (fig. 2B) blood pressure values were noted in the remifentanil + midazolam group during and after the local anesthetic. The weighted mean heart rate values were also significantly lower in the remifentanil + midazolam group than in the remifentanil group (fig. 2C). The weighted mean respiration rate before the local anesthetic was significantly lower in the remifentanil + midazolam group compared with the remifentanil group ($P = 0.003$). Respiratory rates returned to ≥ 8 breaths/min in a median time of 3 min (range, 0–6 min) after the infusion rate decrease

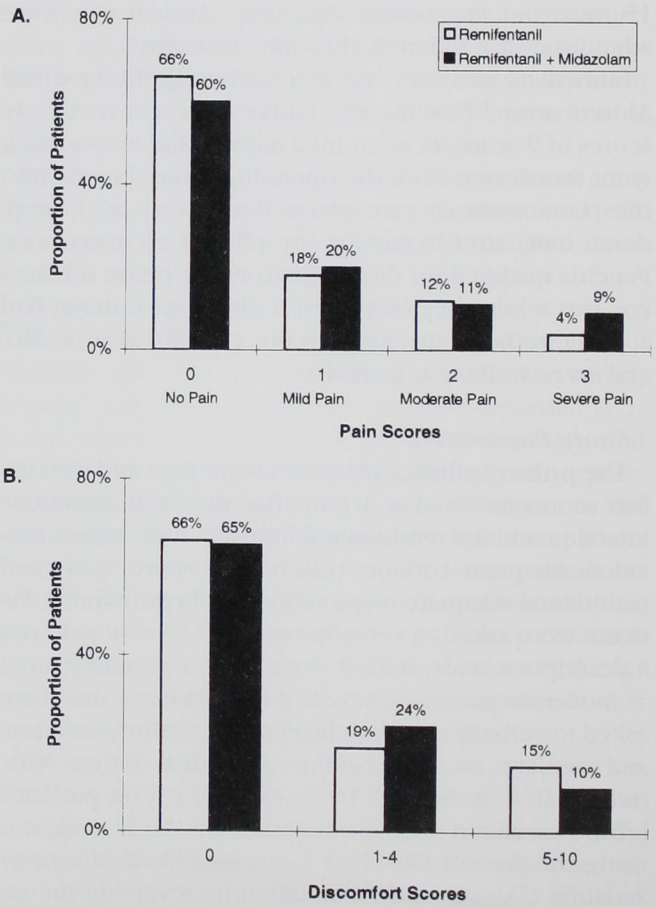

Figure 1. The distribution of pain (*A*) and discomfort (*B*) scores obtained within 1 min after the local anesthetic injection for the remifentanil and remifentanil + midazolam groups. Similar proportions of patients in both groups experienced no pain (score = 0) and no discomfort (score = 0).

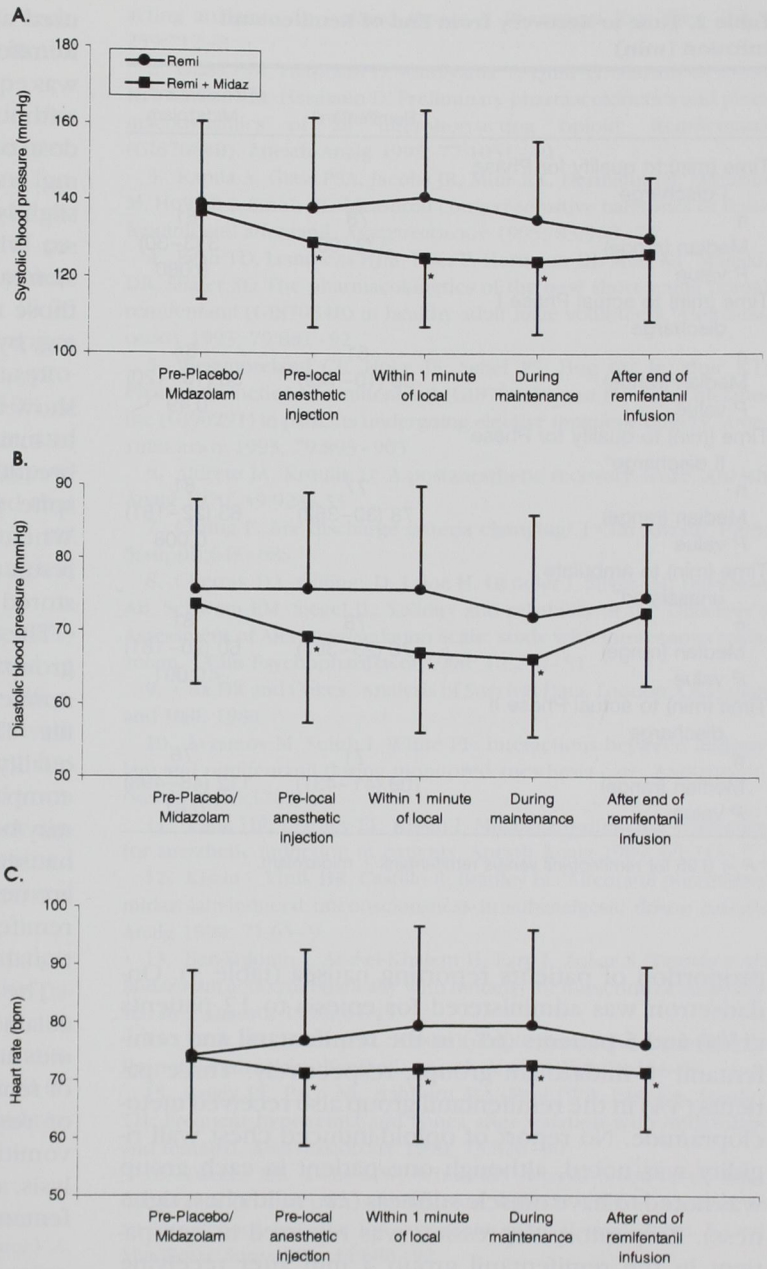

Figure 2. Weighted mean (± SD) systolic blood pressure (*A*), diastolic blood pressure (*B*), and heart rate (*C*) at five measurement times for the remifentanil and remifentanil + midazolam groups. *Weighted mean values for the remifentanil + midazolam group were significantly lower compared with those in the remifentanil group at several times ($P < 0.05$).

in both study groups. No patient required a rate adjustment for hypertension or hypotension. Four patients (5%) in the remifentanil group and two patients (2%) in the remifentanil + midazolam group experienced brief periods of oxygen desaturation ($Sp_{O2} < 90\%$) and hypoventilation (< 8 breaths/min).

Recovery Evaluations

Patients were qualified for discharge from the phase I recovery area in a median time of 3 min in both groups. Patients in the remifentanil + midazolam group were able to ambulate sooner (60 min) and were qualified for discharge from the phase II recovery area earlier than patients in the remifentanil group (76 min; $P < 0.05$; table 2). There was no difference in the time the patients were actually discharged from the hospital (table 2).

Safety Evaluations

The only significant difference noted between study groups in the incidence of adverse events was in the

Table 2. Time to Recovery from End of Remifentanil Infusion (min)

	Remifentanil	Remifentanil + Midazolam
Time (min) to qualify for Phase I discharge		
n	78	81
Median (range)	3 (2–90)	3 (3–30)
P value		0.080
Time (min) to actual Phase I discharge		
n	61	64
Median (range)	58 (10–149)	50 (10–120)
P value		0.49
Time (min) to qualify for Phase II discharge*		
n	77	81
Median (range)	78 (30–352)	63 (22–181)
P value		0.008
Time (min) to ambulate unassisted*		
n	78	81
Median (range)	76 (23–397)	60 (20–181)
P value		<0.001
Time (min) to actual Phase II discharge		
n	71	76
Median (range)	109 (41–437)	112 (48–498)
P value		0.61

* $P < 0.05$ for remifentanil *versus* remifentanil + midazolam.

proportion of patients reporting nausea (table 3). Ondansetron was administered for emesis to 12 patients (15%) and 5 patients (6%) in the remifentanil and remifentanil + midazolam groups, respectively. Three patients (4%) in the remifentanil group also received metoclopramide. No report of opioid-induced chest wall rigidity was noted, although one patient in each group was noted to have muscle stiffness (*i.e.*, mild chest tightness). Respiratory depression was reported in one patient in the remifentanil group 4 min after receiving the initial infusion. The episode resolved 2 min after interruption of remifentanil infusion. The infusion was reinitiated at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without further incident.

Discussion

This double-blind study identifies the mean dose of remifentanil required to provide adequate analgesia and comfort while maintaining adequate respiration when used alone or in combination with midazolam, 2 mg. Remifentanil, when used with or without midazolam, was equally effective in providing analgesia and comfort without compromising respiratory function. A lower dose of remifentanil in combination with midazolam, 2 mg, was associated with a reduced incidence of anxiety, slightly greater sedation, and a lower incidence of nausea while maintaining efficacy. The remifentanil infusion rates used in the present study are consistent with those reported in a previous study with midazolam, 2 mg, by Avramov.[10]

Results from the intraoperative period of this study show that remifentanil has a rapid response to titration to maintain adequate respiration (respiratory rate > 8 breaths/min). Respiratory profiles remained stable despite frequent infusion rate increases or decreases. When remifentanil infusion rates were decreased as a result of hypoventilation, adequate respiration was restored in a median time of 3 min.

The similarity in early recovery times for both study groups is consistent with the rapid offset of action of remifentanil that provides a predictable recovery profile. The longer times to ambulate unassisted and to qualify for phase II discharge in the remifentanil group compared with the remifentanil + midazolam group may be related to the higher incidence of postoperative nausea in the former group of patients. Further studies are needed to evaluate the recovery times and costs of remifentanil-based techniques *versus* the use of conventional narcotics in identical patient populations.

The use of decreased doses of remifentanil and midazolam is based on the known interaction between opioids and benzodiazepines.[11–14] Overall, the combination of remifentanil and midazolam decreased the incidence of respiratory depression, postoperative nausea, and vomiting while still providing effective analgesia, anxiolysis, and sedation. These findings suggest that the remifentanil-midazolam technique may be a significant im-

Table 3. Number (%) of Patients Reporting the Most Common Adverse Events

	Remifentanil (n = 78)	Remifentanil + Midazolam (n = 81)
Overall	44 (56)	29 (36)
Nausea*	28 (36)	13 (16)
Pruritus	17 (22)	10 (12)
Headache	8 (10)	6 (7)
Vomiting	8 (10)	2 (2)

* $P < 0.05$ for remifentanil *versus* remifentanil + midazolam.

provement in the armamentarium of anesthetic techniques available to patients undergoing surgery in the MAC setting.

Remifentanil in combination with midazolam in this study produced less adverse respiratory events than previously reported for fentanyl or a combination of fentanyl and midazolam or diazepam.[15,16] In our study, no patient experienced apnea, and fewer than 5% of patients had $Sp_{O2} < 90\%$. In a study of unstimulated volunteers, Bailey *et al.* found that midazolam alone (0.05 mg/kg) produced no hypoxemia ($SpO_2 < 94\%$) or apnea in contrast to two other regimens: fentanyl alone produced no apnea but did lead to hypoxemia in 50% of the patients, and the combination of midazolam and fentanyl produced apnea in 50% of patients and hypoxemia in 92% of patients.[15] Tucker *et al.* also found that combining midazolam or diazepam with fentanyl resulted in the development of hypoxemia in surgical outpatients.[16]

The incidence of nausea (16%) and vomiting (2%) with the remifentanil-midazolam regimen reported in our study is lower than incidences reported for alfentanil regimens after ambulatory surgery.[17-21] A disadvantage with alfentanil use in the outpatient setting has been the high incidence of nausea (45-68%) and vomiting (38%).[17,18] The incidence of nausea was not significantly altered (32%) when midazolam was combined with alfentanil in patients undergoing extracorporeal shock-wave lithotripsy.[19,20]

In conclusion, remifentanil provided effective analgesia and maintained adequate respiration in healthy patients undergoing superficial surgeries during MAC at a mean infusion rate of 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$ when administered alone, or at a mean infusion rate of 0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in combination with 2 mg of midazolam.

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