Ambulatory Anesthesia Experience with Remifentanil

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Ambulatory anesthesia continues to increase as a percentage of the total number of anesthetic procedures performed. With this increase, there are more relatively short procedures that involve periods of brief, but significant, surgical stimulation. Deep anesthesia is often required for only a very short period. More patients undergoing outpatient surgery have serious organ system disease, particularly patients with cardiovascular disease, who require an anesthetic that provides hemodynamic stability. Patients undergoing outpatient surgery may also have respiratory disease, which raises concern about residual respiratory depression, or they may have renal or hepatic disease, which can interfere with the ability to metabolize and excrete conventional opioids. Furthermore, ambulatory anesthesia requires a fast turnover between patients and very rapid recovery. The ideal anesthetic that meets the needs of all these patients and procedures has yet to be achieved.

A μ-opioid receptor agonist meets the requirement for good control of hemodynamic responses. However, larger doses of opioid are required to provide hemodynamic control, and with traditional opioids, this may result in slower recovery and prolonged side effects. The ideal opioid for ambulatory anesthesia would therefore provide rapid onset of effect, allow rapid titratability of anesthetic depth to provide hemodynamic stability, and have rapid, consistent recovery times with few postanesthetic drug side effects, such as nausea and vomiting. The esterase-metabolized opioid, remifentanil hydrochloride, has pharmacokinetic properties that may translate into benefits for ambulatory anesthesia and recovery.

The studies that have assessed the use of remifentanil for ambulatory surgery are discussed below. There are two important caveats. In many studies, remifentanil was given in relatively larger, nonequivalent doses to assess the potential advantages of increased μ-opioid effect. In addition, remifentanil and alfentanil have different context-sensitive half-times. The duration of action of alfentanil increases with length of infusion, whereas the duration of action of remifentanil is independent of infusion length. Because of these differences, it is impossible to compare directly the responses to surgery and the rates of recovery within the individual studies. However, we can evaluate an overall combination of the intraoperative and postoperative anesthetic effects in relation to the dosages administered and the duration of administration.

In all the ambulatory studies, responses to surgical events were assessed and compared using hemodynamic, somatic, and autonomic criteria (1–4). The hemodynamic criteria were an increased heart rate >15% above the preoperative baseline or >90 bpm, or a systolic blood pressure (BP) >15% above preoperative baseline. The somatic criteria included gross purposeful movement of an extremity, eye opening, or grimacing, and the autonomic criteria were sweating or tearing.

The interaction of the remifentanil and propofol doses required to prevent patient response during surgery was studied in ASA physical status I or II patients undergoing arthroscopic surgery with a median anesthesia duration of 1 h. Specifically, this study determined the effective dose (ED50) and effective concentration (EC50) of remifentanil for lack of patient response to intubation and skin incision at three target propofol concentrations. Propofol was administered by a target controlled infusion method (1) using a target propofol concentration of 4 μg/mL for intubation, followed by 1, 2, or 4 μg/mL for the maintenance of anesthesia. These propofol concentration groups corresponded to mean propofol infusion rates of 43.7 ± 3.2, 95.3 ± 1.2, and 204.1 ± 8.2 μg · kg⁻¹ · min⁻¹, respectively, after initial propofol bolus doses

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of approximately 2 mg/kg. The remifentanil ED\textsubscript{50}/EC\textsubscript{50} (50% of patients responding) and ED\textsubscript{80}/EC\textsubscript{80} (20% responding) were assessed, and the results are listed in Table 1. As the target propofol concentration increased from 1 to 4 μg/mL, both the ED\textsubscript{50} and ED\textsubscript{80} values needed to prevent response to the criterion events decreased. This study also assessed recovery times as secondary efficacy variables. Times to spontaneous and adequate respiration and tracheal extubation were significantly longer in the 4 μg/mL propofol group. The median times to spontaneous respiration and extubation were significantly different: 1, 3, and 6 min for the 1, 2, and 4 μg/mL propofol groups, respectively. Statistically different increases in recovery for the 4 μg/mL group persisted for the times to eye opening, orientation, and ability to lift extremity on command. Times to qualify for actual discharge from phase I and phase II postanesthesia care units (PACUs) were not different among the propofol groups.

The side effects experienced by these patients were also assessed among the 1, 2, and 4 μg/mL target propofol groups. The most common side effect was shivering, which was not dose-related and which occurred in 47%–65% of patients. The incidence of nausea and vomiting decreased with increasing propofol concentrations. The incidences of nausea were 76%, 29%, and 24%, respectively, and the incidences of vomiting were 24%, 12%, and 0%. The incidence of pruritus did not differ with propofol dose (18%–29%). Dizziness (14%, 6%, and 6%, respectively) was the next most common side effect. No patient needed naloxone or experienced muscle rigidity. A significant concern was intraoperative recall. Three patients stated that they remembered some aspect of their surgery, two in the 1 μg/mL and one in the 2 μg/mL propofol group. Events related to the complexity of infusion pump usage were also noted, and included seven reports of minor pump malfunctions, as well as one reconstitution error. Based on assessments of recovery, adverse events, and hemodynamic profile, a remifentanil-propofol dose combination consisting of a remifentanil infusion of 0.25 μg · kg\textsuperscript{-1} · min\textsuperscript{-1} with propofol 2 μg/mL (100 μg · kg\textsuperscript{-1} · min\textsuperscript{-1}), with a muscle relaxant, was recommended for total IV anesthesia (TIVA) for outpatient arthroscopic surgery. The clinician must be aware of the potential for intraoperative recall when remifentanil is used with a muscle relaxant, especially with smaller doses of propofol.

Remifentanil has also been compared with alfentanil for laparoscopic tubal sterilization in ASA physical status I or II patients with an anesthesia duration of approximately 0.5 h.\textsuperscript{2} The objectives of this study were to compare the hemodynamic responses to incision (laparoscopic insertion) and to compare the need for intraoperative opioid dose titration or propofol rescue, as well as to determine the times to recovery. Patients were randomized to one of three treatment groups: alfentanil bolus dose 20 μg/kg followed by an infusion of 1 μg · kg\textsuperscript{-1} · min\textsuperscript{-1} or remifentanil 1 μg/kg followed by an infusion of 0.1 μg · kg\textsuperscript{-1} · min\textsuperscript{-1} (remifentanil-0.1) or remifentanil 1 μg/kg followed by 0.4 μg · kg\textsuperscript{-1} · min\textsuperscript{-1} (remifentanil 0.4). One minute after the opioid infusion began, propofol was given in 40-mg increments until loss of consciousness, followed by 66% N\textsubscript{2}O and intubation with mivacurium. The primary efficacy end point was the systolic BP response 1 min after trocar insertion.

Significantly fewer patients in the remifentanil 0.4 group, compared with remifentanil 0.1 or alfentaniltreated patients, responded to intubation, skin incision, and trocar insertion. Fewer remifentanil 0.4 patients (17%) required intraoperative propofol rescue (69% remifentanil 0.1, 57% alfentanil), and when required, rescue was achieved with smaller doses. However, more patients in the remifentanil 0.4 group (29%) required rate decreases to minimize hypotension (BP <80 mm Hg) and/or bradycardia (heart rate <40 bpm), compared with 3% in the other groups. At skin closure, significantly fewer remifentanil 0.4 patients responded (6%) compared with remifentanil 0.1 (17%) or alfentanil (34%) patients. The maintenance infusion of alfentanil was discontinued 5 min before the end of N\textsubscript{2}O administration to facilitate awakening at the end of surgery, whereas remifentanil was continued until the end of N\textsubscript{2}O administration at final

### Table 1. Effective Doses (ED) and Concentrations (EC) of Remifentanil to Prevent Response for 50% and 80% of Patients in Combination with Target Propofol Concentrations

<table>
<thead>
<tr>
<th>Target propofol concentration (μg/mL)</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED\textsubscript{50}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>0.44</td>
<td>0.7</td>
<td>0.18</td>
</tr>
<tr>
<td>Remifentanil (μg · kg\textsuperscript{-1} · min\textsuperscript{-1})</td>
<td>14.34</td>
<td>35.77</td>
<td>4.46</td>
</tr>
<tr>
<td>Skin incision/trocar insertion</td>
<td>0.19</td>
<td>0.26</td>
<td>0.13</td>
</tr>
<tr>
<td>Remifentanil (μg · kg\textsuperscript{-1} · min\textsuperscript{-1})</td>
<td>8.79</td>
<td>15.29</td>
<td>4.22</td>
</tr>
<tr>
<td>Remifentanil (ng/mL)</td>
<td></td>
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Data taken from Fragen et al.\textsuperscript{1}
suture. These data suggest that the higher response rate at skin closure seen in the alfentanil group was related to the need to discontinue that drug before the end of surgery. Despite the earlier discontinuation of alfentanil, no significant intergroup differences were observed for times to spontaneous respiration, adequate respiration or awakening, or later recovery times. Remifentanil provided improved anesthetic stability without detrimental effects on awakening times.

During the recovery phase of this study, significantly more remifentanil patients required postoperative fentanyl analgesia (90% vs 71%, all remifentanil versus alfentanil). Times to first analgesic are also significantly different: 10 min for remifentanil 0.1, 13 min for remifentanil 0.4, and 17 min for alfentanil. The dose of postoperative fentanyl required was also larger in the remifentanil groups: 133 and 108 μg versus 92 μg. Side effects were recorded. Rigidity occurred in all groups, usually 1 min after the opioid bolus, in one, three, and one patients, respectively. One remifentanil 0.1 patient remembered some aspect of the operation. There were no intergroup differences in the incidence of postprocedural nausea (71%–77%) or vomiting (46%–57%). These incidences are all high and may relate to the high emesis risk surgery and the need for postoperative fentanyl analgesia, as well as to the N2O/opioid infusion anesthetic techniques.

In this study, the propofol dose required for induction and the time to loss of consciousness were similar in all opioid groups. Times to discharge were also similar across treatment groups, although the remifentanil infusions were continued until the end of surgery. Remifentanil 0.4 provided more stable anesthetic conditions than the other opioid groups, as demonstrated by the lower incidence of intraoperative responses. For outpatient tubal ligation, remifentanil infusion may be started at 0.4 μg · kg⁻¹ · min⁻¹ and, after trocar insertion, decreased to as low as 0.1 μg · kg⁻¹ · min⁻¹. Postoperative analgesia will be needed by most patients.

TIVA using remifentanil with propofol is another potential option for ambulatory surgery. This combination has been studied for longer ambulatory laparoscopic procedures, with an anesthesia duration of approximately 1 h (2). Propofol was administered to all patients at a dose of 2 mg/kg, followed by 150 μg · kg⁻¹ · min⁻¹ until trocar insertion, then decreased to 75 μg · kg⁻¹ · min⁻¹. Immediately after the propofol bolus, opioid infusions were begun with either remifentanil or alfentanil. The remifentanil dose was a 1-μg/kg bolus with an infusion of 0.5 μg · kg⁻¹ · min⁻¹ until trocar insertion, and then 0.25 μg · kg⁻¹ · min⁻¹, compared with a 20-μg/kg bolus of alfentanil followed by a 2-μg · kg⁻¹ · min⁻¹ infusion, then 1 μg · kg⁻¹ · min⁻¹ after trocar insertion. The opioid dosing was titrated to hemodynamic criteria as previously described.

Of the remifentanil and alfentanil patients, 19% and 29%, respectively, responded to intubation (not significantly different). Significantly fewer remifentanil patients responded to skin incision/trocar insertion compared with alfentanil patients (11% vs 32%). With both opioids, the most common response was an increase in systolic BP. Remifentanil patients had significantly fewer responses indicating light anesthesia (53% vs 71%), and fewer needed intraoperative opioid dosage adjustments to treat the light anesthesia (20% vs 39%). This may be related to the comparatively larger remifentanil dose used. The weighted mean infusion rates were 0.29 ± 0.08 μg · kg⁻¹ · min⁻¹ for remifentanil and 1.3 ± 0.5 μg · kg⁻¹ · min⁻¹ for alfentanil.

At the end of these TIVA procedures, the alfentanil infusions were turned off a median of 10 min before the end of surgery, whereas remifentanil was continued until the end of surgery; propofol was discontinued 5 min before the end of surgery. The incidence of response to skin closure was similar in both groups (19% vs 20%). The primary efficacy end point was time to adequate respiration, defined as respiratory rate >8 breaths/minute and/or PetCO₂ <50 mm Hg. Despite the earlier discontinuation of alfentanil, there were no differences in times to spontaneous respiration, extubation, or response to verbal command. The Aldrete score was used to assess recovery during PACU phase I, and the time to first Aldrete score ≥9 was similar in both groups. The time to first analgesic use was significantly shorter for remifentanil patients (23 vs 39 min), whereas the time to qualify for phase I discharge was significantly shorter for the alfentanil patients (21 vs 42 min). The phase I delay for remifentanil patients was ascribed to the need to treat postoperative pain at that time. Times to actual phase I discharge, ambulation, and qualification for phase II discharge were not different. The time to actual phase II discharge was 174 min with remifentanil versus 201 min for alfentanil. The only significant difference in the reason for delayed phase II discharge was the incidence of nausea/vomiting: 5% for remifentanil and 19% for alfentanil.

A greater proportion of remifentanil patients required postprocedural analgesics while in the ambulatory facility (87% vs 65%). Among those patients who did receive fentanyl for postoperative pain management, the mean dose of fentanyl administered was similar and clinically acceptable in both treatment groups: 77 ± 56 vs 75 ± 65 μg for the remifentanil- and alfentanil-treated patients, respectively. The incidences of nausea and vomiting were similar: 44% and 53% for nausea and 21% and 29% for vomiting for the remifentanil- and alfentanil-treated patients, respectively. Nausea seemed to occur later in alfentaniltreated patients, which may have been related to the later administration of fentanyl analgesia. Two patients, one in each group, remembered early aspects of
the operation due to propofol infusion pump malfunctions. Two remifentanil patients experienced rigidity during the induction phase, and two alfentanil patients experienced a single episode of respiratory depression during the recovery phase. In conclusion, remifentanil used with propofol was effective as the primary opioid in TIVA for ambulatory surgery. Remifentanil can be used at relatively larger doses than alfentanil, which provides better intraoperative hemodynamic stability but maintains similar recovery. Anticipating postoperative pain and implementing appropriate analgesia before cessation of the remifentanil infusion is important. Different options for postoperative pain management after remifentanil-based anesthesia are discussed in more detail elsewhere in this supplement (3).

The use of remifentanil versus alfentanil in a balanced anesthetic technique with 0.8% isoflurane in oxygen has also been studied in patients undergoing arthroscopy, wisdom teeth extraction, or varicose vein surgery (4). In this study, alfentanil was administered as an initial bolus dose of 25 µg/kg followed by a continuous infusion of 0.5 µg·kg⁻¹·min⁻¹, and remifentanil was administered as an initial bolus dose of 1 µg/kg followed by a continuous infusion of 0.25 µg·kg⁻¹·min⁻¹. Responses to surgical stimuli were treated with one or more bolus doses of the study opioid (alfentanil 5 µg/kg, remifentanil 1 µg/kg). Neuromuscular blockade was produced by using vecuronium after induction with propofol, and anesthesia was maintained with 0.8% isoflurane in air/oxygen. Both the study drugs and isoflurane were discontinued at the end of surgery. There was no significant difference in the number of patients responding to intubation (25% and 23%) or incision (24% and 33%); however, there was a significant reduction in the number of remifentanil patients who responded during surgery (P = 0.018), required dose increases (P = 0.03), and responded during skin closure (11% vs 22%). This greater depth of anesthesia was also evident with a higher incidence of hypotension (15% vs 2%) for remifentanil patients, and three patients reported intraoperative recall postoperatively after alfentanil. Median times for achieving spontaneous respiration for alfentanil- versus remifentanil-treated patients were 5 vs 8 min, adequate respiration 6 vs 9 min, extubation 6 vs 9 min, and verbal response 7 vs 9 min. Despite the different depth of anesthesia and the slower initial recovery, the remifentanil-treated patients had better psychomotor tests 30, 60, and 90 min after surgery compared with the alfentanil patients, which suggests better overall recovery from remifentanil, although this did not result in earlier discharge from the hospital. This study highlights the clinical difficulty of providing adequate anesthesia and rapid recovery.

Two dose-finding studies have investigated the use of remifentanil during general anesthesia with spontaneous ventilation: one with isoflurane for maintenance (5) and the other with propofol as part of a TIVA (6). Both studies used similar methodology to try to identify infusion rates that would provide satisfactory anesthesia while permitting adequate spontaneous respiration (defined as Paco₂ ≤ 55 mm Hg and respiratory rate ≥ 8 breaths/min). The studies investigated four randomly allocated doses of remifentanil consisting of a loading dose of 0.125, 0.25, 0.375, or 0.50 µg/kg followed by an infusion of 0.025, 0.05, 0.075, or 0.1 µg·kg⁻¹·min⁻¹ supplemented by a small dose of the hypnotic drug. The incidences of patients moving at incision and those with respiratory depression after surgical incision were compared. After the administration of remifentanil, patients were observed for 3 min before anesthesia was induced by the administration of propofol at 10 mg/10 s until loss of verbal contact. In the inhaled drug study, isoflurane was administered to an end-tidal age-adjusted minimum alveolar anesthetic concentration (MAC), whereas in the TIVA study, hypnosis was maintained with an infusion of propofol at 100 µg·kg⁻¹·min⁻¹. Surgical incision was performed at least 5 min after laryngeal mask airway placement, after which doses of the hypnotic drug could be increased in response to inadequate anesthesia, as indicated by increases in cardiovascular responses or movement; the doses of remifentanil could be reduced in the presence of respiratory depression. Remifentanil could not be increased, nor could the dose of the hypnotic drug be reduced.

The use of remifentanil infusion in combination with isoflurane with spontaneous ventilation (5) produced dose-related respiratory depression after incision and dose-related decrease in movement (Figure 1). Respiratory depression increased from 36% at 0.025 µg·kg⁻¹·min⁻¹ to 56%, 93%, and 94% at increasing doses, with an incidence of somatic movement of 31%, 13%, 7%, and 0% at the same infusion.

![Figure 1. Remifentanil infusion in combination with isoflurane with spontaneous ventilation produced dose-related respiratory depression after incision (■) and decrease in movement (□).](image-url)
rates of remifentanil. The final infusion rates of remifentanil were 0.025–0.05 μg·kg⁻¹·min⁻¹ with final end-tidal isoflurane concentrations of 0.8%–1.3%. In the TIVA study (6), the final infusion rates of remifentanil were again 0.025–0.05 μg·kg⁻¹·min⁻¹, with final infusion rates of propofol at 120–140 μg·kg⁻¹·min⁻¹. The IV study also showed a dose-dependent increase in respiratory depression and decrease in gross movement. However, the incidence of respiratory depression was lower in the TIVA study (8%, 50%, 69%, and 79% compared with 36%, 56%, 93%, and 94%) at the same doses of remifentanil, whereas the incidence of somatic movement was higher in the TIVA study (88%, 29%, 38%, and 33% compared with 31%, 13%, 7%, and 0%). These differences may relate to the relative potency of the doses of the hypnotic drugs that were also administered; propofol at a fixed infusion of 100 μg·kg⁻¹·min⁻¹ may not provide the same depth of anesthesia as isoflurane, which was adjusted to provide an end-tidal MAC concentration. The final infusion rates of remifentanil were 0.025–0.05 μg·kg⁻¹·min⁻¹ with final end-tidal isoflurane concentrations of 0.8%–1.3%. From these studies, an infusion of remifentanil at 0.025–0.05 μg·kg⁻¹·min⁻¹ administered with isoflurane at an end-tidal concentration of 0.8%–1.3% or a maintenance propofol infusion of 120–140 μg·kg⁻¹·min⁻¹ may be used to provide adequate maintenance of anesthesia while permitting spontaneous ventilation. However, the use of a loading dose during induction may increase the incidence of respiratory depression.

The incidence of PONV was significantly lower in both spontaneous ventilation studies compared with other studies performed with remifentanil. Of 63 isoflurane patients, 5% reported nausea, versus 8% of 64 propofol patients. One patient in each study had an emetic episode. Analgesia in the form of local infiltration and NSAIDs was administered to prevent pain in these two studies, with a much lower incidence of opioid administration postoperatively as a result. The use of other opioids in the postoperative period may decrease the potential advantages of remifentanil in ambulatory anesthesia. The surgical procedures were also different. The study was not comparative, and whether the use of remifentanil in spontaneous ventilation significantly improves the quality of anesthesia remains to be investigated.

In summary, the studies of remifentanil in ambulatory anesthesia showed rapid and smooth recovery in both the dose-finding and comparative studies, in which alfentanil has been the primary comparator opioid. The common finding was that fewer patients responded to surgical stimuli with remifentanil than with alfentanil. This is because remifentanil was given at comparatively larger doses. The second common finding was that recovery times were not different—specifically, not prolonged—although remifentanil was used at a relatively larger dose and was continued to the end of surgery, whereas alfentanil was terminated earlier. The times to onset of spontaneous respiration or extubation were often not different. However, the drugs in these studies were administered according to fixed protocols, which does not accurately reflect normal clinical practice, in which doses are adjusted according to need. The dose reduction of remifentanil toward the end of surgery might further improve the rate of recovery. More importantly, recovery may also largely depend on appropriate titration of the concomitant hypnotic drug (propofol, N₂O, or potent vapor). Because the alfentanil infusions were stopped before the end of surgery to optimize recovery, this would partly explain the higher number of end of surgery responders with alfentanil. The two studies that performed psychometric tests showed more reliable recovery from remifentanil than alfentanil, as would be expected based on the drugs' pharmacokinetics.

Studies comparing remifentanil with the more commonly used opioid fentanyl have not yet been published. Therefore, the apparently high incidences of nausea/vomiting, rigidity, and recall with the remifentanil techniques cannot be compared with a conventional fentanyl-based anesthetic technique. Awareness seems to be related to the use of small doses of the concomitant hypnotic drug.

Unfortunately, these ambulatory anesthesia studies did not specifically address the issue of pain management after remifentanil-based anesthesia. Although the early recovery from remifentanil was faster in two studies, discharge from PACU phase I was delayed because of earlier requirements for pain management in the remifentanil group. Fentanyl was required earlier than after alfentanil; the dose of fentanyl was larger in one study but the same in another. Postoperative fentanyl may have contributed to the high PONV incidence of 40%–70%, with no interdrug differences, with these gynecologic laparoscopic procedures. In the two spontaneous ventilation studies, the procedures were less emetogenic, local anesthesia and NSAIDs were administered intraoperatively and no opioid analgesia was used postoperatively, and the overall incidence of PONV was much lower (7%). Anticipatory pain management is required for the successful use of remifentanil in ambulatory surgery and should include local anesthesia and nonopioid analgesics.

Remifentanil can be administered in comparatively large doses as the opioid component of ambulatory anesthesia, which will reduce patients’ responses to surgery but will not delay recovery. Remifentanil is appropriate to use for patients or procedures that require a brief, variable, or rapidly terminating intense
opioid effect. Attention must also be paid to preventing or treating the associated side effects, as well as the technical issues associated with dilution and infusion. Cost-effectiveness must be investigated. Further studies are required to identify the specific clinical uses of remifentanil and its advantages in the ambulatory setting.

References