Postoperative Nausea and Vomiting Following the Use of Fentanyl or Remifentanil in Ambulatory Gynecologic Laparoscopic Surgery: A Prospective Randomized Trial

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Abstract

Purpose: To test the hypothesis that using remifentanil during nitrous oxide-sevoflurane anesthetic would be associated with less postoperative nausea and vomiting (PONV) compared to a similar technique with fentanyl.

Scope: Sixty patients undergoing outpatient gynecologic laparoscopy were randomly assigned to remifentanil or fentanyl for intraoperative analgesia. The complete response rate (no PONV and no rescue) was 50% / 29 % in the remifentanil group and 37% / 12 % in the fentanyl group in the PACU and at 24 hours respectively (p=ns).

Conclusion: The use of remifentanil was not associated with a reduction in the incidence of PONV, compared with fentanyl, in patients undergoing ambulatory gynecologic laparoscopy.

This study was in part supported by a grant from Abbott Laboratories.

Keywords: postoperative nausea and vomiting, fentanyl, remifentanil, gynecologic laparoscopy, ambulatory surgery.

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Introduction

Postoperative nausea and vomiting (PONV) occur commonly after outpatient gynecologic laparoscopy with a reported incidence in the range of 56-95 % [1–3]. Short acting synthetic opioids are commonly used in ambulatory surgical patients. Opioid use is considered one of the major risk factors for PONV [4]. It is unclear if the choice of the opioid can influence the incidence of PONV. Alfentanil, a shorter acting opioid, has been associated with a lower incidence of PONV compared with fentanyl [5].

Remifentanil is a unique opioid. Its ester structure renders it susceptible to hydrolysis by blood and tissue non-specific esterases, resulting in very rapid degradation to essentially inactive metabolites. Its context-sensitive half time is rapid and relatively independent of the duration of infusion [6–8]. This rapid decline in drug effect may have advantage in being associated with a faster postoperative recovery and a lower incidence of opiate related side effects compared with other opiates.

Total intravenous anesthesia (TIVA) with propofol and remifentanil was found to result in a lower incidence of PONV compared with a technique using a propofol infusion, fentanyl, with or without nitrous oxide (N_2O) [9–11]. Similarly, TIVA with propofol and remifentanil was associated with less PONV compared to a balanced anesthesia technique with a volatile agent and fentanyl [12, 13]. The main focus of these studies was however to compare the effects of TIVA with propofol versus inhaled anesthetics on the incidence of PONV. Only one study compared PONV rates following the use of the two opiates during a volatile based technique. Apfel and colleagues reported that the use of remifentanil for intraoperative analgesia was not associated with a reduction in PONV compared to a technique using fentanyl during a volatile based anesthetic [14]. The administration of morphine at the end of surgery in the remifentanil group, however, confounded the analysis [15]. We therefore designed this study to test the hypothesis that the use of remifentanil as the intraoperative opioid during nitrous oxide-sevoflurane based anesthetic would be associated with less PONV compared to a similar technique with fentanyl.

Methods

Seventy two adult patients scheduled for outpatient gynecologic laparoscopy were enrolled in this study after obtaining institutional review board approval and written informed patient consent. Exclusion criteria were ASA physical status IV or V, antiemetic or glucocortiocosteroids use within 24 hours of surgery, allergy to ondansetron, pregnancy, breast feeding, obesity (body mass index more than 34), mental retardation, or psychiatric illness. For women of childbearing potential, a negative serum [beta]-hCG test was confirmed before enrollment.

Anesthetic technique was standardized. All patients received midazolam up to 2 mg IV as premedication. Anesthesia was induced using propofol 1.5–2.5 mg/kg and the trachea was intubated using succinylcholine 1 mg/kg. Anesthesia was maintained using 1-3 % inspired sevoflurane and 60 % nitrous oxide in oxygen. Inspired Sevoflurane was titrated to maintain a bispectral index (Aspect Medical System, Newton, MA) value between 45-60. Cisatracurium was used to maintain muscle relaxation at one twitch of the train-of-four.

Patients were randomly assigned to one of two treatment groups using a random-number table. Women were allocated using sealed opaque envelopes and randomization was grouped into blocks of 10 patients. The bolus dose of remifentanil and fentanyl was based on relative potency ratio of 1:1 [16]. In Group 1 (remifentanil group), remifentanil 1 mcg/kg was administered as a bolus at induction of anesthesia followed by an infusion at a rate of 0.05-0.3 mcg/kg/minute. The infusion was stopped at the start of skin closure. In Group 2 (fentanyl group), fentanyl 1 mcg/kg was given as a bolus at induction of anesthesia with further boluses of fentanyl 1 mcg/kg

given as needed. The opioids were given to maintain blood pressure and heart rate within 20 % of baseline. Within 20 minutes before the end of surgery, ondansetron 4 mg and ketorolac

30 mg IV were given. Local infiltration with 10-ml ropivacaine 0.5 % was administered around the trocar incision sites. Muscle relaxation was reversed with neostigmine 70 mcg/kg and glycopyrrolate 10 mcg/kg.

An independent research nurse unaware of the patients' randomization collected the data. The duration of surgery and the length of postanesthesia care unit (PACU) stay were recorded. Postoperative assessments were made at 0, 30, 60, 90,120 min, at PACU discharge, and at 24 h by telephone interview with a trained interviewer blinded to the patients' group. Nausea, emetic episodes, nausea score, sedation scores, and rescue antiemetic and analgesic use were recorded during these time intervals. The nausea score was measured as an 11 point scale ranging from 0–10 where "0" represents no nausea and "10" represents worst nausea, the concept was explained to patients preoperatively. Sedation was measured on a scale from 0-5 using the modified observer's assessment of alertness/sedation scale [7]. The time to readiness for PACU discharge, when patients were fully awake and oriented, with stable vital signs, minimal pain (<3 on a 0–10 scale) and were able to ambulate and not experiencing any side effects, was recorded. Patients rated their satisfaction with the control of PONV just before discharge from the hospital and at 24 hours, and with the control of pain at 24 h. At the 24 h follow up, patients were also asked to rate PONV control, and to indicate how well they slept. An 11 point linear numeric scale was used to rate the patients' satisfaction with the control of PONV and pain where "0" = very dissatisfied and "10" = very satisfied. A similar scale was used to rate PONV control where "0" = not effective and "10" = very effective, and to indicate how well they slept where "0" = did not sleep at all, and "10" = slept very well.

Nausea was defined as a feeling of the urge to vomit, as solicited by the investigators during assessments. Vomiting was defined as expulsion of stomach contents through the mouth. Retching was defined as an attempt to vomit, not productive of stomach contents. An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. A complete response was defined as no PONV and no need for rescue antiemetics. In the PACU, ondansetron 4 mg was used as the initial rescue medication for PONV. This was given if nausea was intractable and lasted for at least 15 minutes, if three emetic episodes occurred within 15 minutes, or at any time at the patient's request. Postoperative pain in the PACU was treated with fentanyl IV doses of 25–50 mcg. After discharge, pain was treated with ibuprofen and oxycodone 5 mg/acetaminophen 325 mg combination.

Previous studies demonstrated an incidence of PONV of 59 % in this population using intraoperative fentanyl and PONV prophylaxis with ondansetron [17]. A sample size of 30 patients per group was determined to be adequate to demonstrate a 35% difference in the incidence of PONV (from 59 % to 24 %) with $\alpha = 0.05$ and $\beta = 0.8$. Descriptive statistics were used to summarize the demographic characteristics of patients. Fisher's exact test and chi-squared procedures for categorical data, and Wilcoxon rank sum test and the Kruskal-Wallis test for continuous variables were performed for comparisons among the treatment groups. Repeated measures analysis of the variance was used to analyze pain scores. $P < 0.05$ was accepted as statistically significant.

Results

One hundred and seventeen patients were assessed for eligibility. Eighteen patients had exclusion criteria and twenty seven refused to participate. Seventy two patients were enrolled in the study. Surgery was cancelled in five patients and was converted to an open procedure in 5 patients. Two patients were excluded from the analysis in the fentanyl randomization group due to protocol violations. Data from thirty patients in each group were analyzed.

The two groups were similar with respect to age, weight, height, ASA status, history of PONV or motion sickness, smoking history, and duration of surgery (Table 1). The mean (SD) dose of the intraoperative opioid was 420 (318) mcg in the remifentanil group and 168 (71) mcg in the fentanyl group.

Table 1 Patients' demographics, risk factors for PONV, and duration of surgery.

	Remifentanil Group (n=30)	Fentanyl Group (n=30)
Age, years	32 ± 5	32 ± 6
Height, cm	166 ± 6	165 ± 5
Weight, kg	73 ± 21	76 ±19
ASA Class, I/II	12/18	9/21
History of PONV	10 (33)	5 (17)
History of motion sickness	11 (37)	13 (43)
Smoker	5 (17)	6 (20)
Duration of surgery, min	56 ± 29	58 ± 27

Values are mean ± SD or number (%). PONV=postoperative nausea and vomiting.

The duration of PACU stay was not different between the two groups (Table 2). Efficacy data are summarized in Table 2. During the first 2-h postoperatively, there was no difference between the two groups in the incidence of PONV, nausea scores, sedation scores, vital signs, need for rescue antiemetics, or complete response rate. Twenty two patients in the remifentanil group and 13 patients in the fentanyl group needed analgesia with fentanyl boluses in PACU ($p=0.035$). Significantly more fentanyl was used in PACU in the remifentanil group compared with the fentanyl group ($p=0.002$). The repeated-measures ANOVA for the pain scores over time found no significant difference in treatment overall ($p=0.3674$). However, the interaction of treatment and time was non significant ($p=0.355$), indicating no significant difference between treatments in the effect of time on pain. A non-linear effect of time was also non-significant. In this repeated-measures analysis, time to measurement was treated numerically, preserving both its order and magnitude. Patient satisfaction with PONV control was not different between the groups.

Ten patients could not be reached at the telephone number that they supplied to the study personnel and were lost to follow up, with six and four patients in the remifentanil and fentanyl groups, respectively. At 24 h postoperatively, there was no difference between the two groups in the incidence of PONV, need for rescue antiemetics, complete response, pain scores, nausea scores, or in patient satisfaction with PONV or pain control (Table 3).

Table 2 Postanesthesia Care Unit (PACU) data.

	Remifentanil Group (n=30)	Fentanyl Group (n=30)
Nausea	10 (33)	12 (40)
Vomiting including retching	6 (20)	5 (17)
Need for rescue antiemetics	13 (43)	15 (50)
Complete response	15 (50)	11 (37)
Average nausea score	0.6 ± 1.2	0.6 ± 1.2
Worst nausea score	1.5 ± 2.8	2 ± 2.7
Pain scores		
At admission	3.3 ± 3.3	2.1 ± 2.8
30 min	3.7 ± 3.4	3.1 ± 3.4
60 min	2.4 ± 2	3.1 ± 2.9
90 min	1.9 ± 1.8	2.1 ± 2.5
120 min	2.1 ± 1.6	2.1 ± 2.2
Fentanyl use in PACU, mcg	88 ± 73*	35 ± 45
Duration of PACU stay, min	155 ± 48	159 ± 55
Satisfaction with PONV control	9.4 ± 1.5	9.3 ± 1.5

Values are mean ± SD or number (%). *p=0.002.
PONV=postoperative nausea and vomiting.

Table 3 24 hours data.

	Remifentanil Group (n=24)	Fentanyl Group (n=26)
Nausea	12 (50)	17 (65)
Vomiting including retching	3 (13)	5 (19)
Need for rescue antiemetic	2 (8)	2 (8)
Complete response (0-24 h)	7 (29)	3 (12)
Nausea score	1.3 ± 1.8	3.1 ± 3.6
Pain score	3.4 ± 2.6	4.2 ± 2.5
Satisfaction with PONV contro	19 ± 1.6	8.9 ± 1.6
Satisfaction with pain control	8.9 ± 1.2	8.5 ± 2.2
Rating of PONV control	9 ± 1.9	8.8 ± 1.7
Rating of sleep	8 ± 1.9	7.7 ± 2.5

Values are mean ± SD or number (%). Nausea and pain scores represent the worst scores since discharge. PONV=postoperative nausea and vomiting.

Discussion

In this study we found no difference in the incidence of PONV following the use of remifentanil or fentanyl as part of a sevoflurane-N_2O based anesthetic, in patients undergoing outpatient gynecologic laparoscopy.

Opioids are a major cause of PONV in ambulatory surgical patients. A previous study suggested that the selection of the opioid used intraoperatively can affect the incidence of PONV following ambulatory surgery. In that study, alfentanil compared with approximately equipotent doses of fentanyl and sufentanil, was associated with a lower incidence of PONV [5]. On the other hand, the incidence of PONV was not different following the use of either remifentanil or alfentanil as part of a TIVA technique with propofol [18–21].

A number of studies have compared the incidence of PONV following the use of anesthetic regimens involving remifentanil or fentanyl. However, no conclusions could be drawn regarding the effect of the two opioids on PONV since these studies were mainly comparing balanced anesthesia versus TIVA [13]. With a propofol based technique, the use of remifentanil was associated with a significantly lower incidence of PONV compared with fentanyl [9–11].

Only one recent study compared the two opiates when used as part of a volatile based technique. Apfel and colleagues found no reduction in the incidence of PONV with the use of remifentanil compared to fentanyl with a volatile based technique in inpatients undergoing a variety of surgical procedures [14]. An accompanying editorial suggested that the use of morphine at the end of surgery in patients receiving remifentanil, was the likely explanation for the failure of the shorter acting opioid to reduce the risk of PONV [15]. In our study, no other opioids were used intraoperatively in patients receiving remifentanil.

However, similar to Apfel's study, there was no difference in the incidence of PONV between the patients who received fentanyl and those who received remifentanil, both in PACU and at 24 hours.

A possible explanation for the failure of the short acting opioid remifentanil to reduce the risk of PONV is the greater fentanyl consumption in PACU by patients in the remifentanil group. Alternatively, it is likely that prior stimulation of the opioid receptors triggers PONV and that the occurrence of the latter is not linked to the opioid plasma concentrations at the time of the symptoms [5].

The ratio of the total doses of remifentanil versus fentanyl given intraoperatively in this study was 2.5:1. The relative potency ratio of remifentanil versus fentanyl was reported as being 2:1 or 1:1 [22]. The C50 for EEG depression for fentanyl and remifentanil was 6-10 and 10–15 ng/ml respectively [22] implying that the doses used intraoperatively in this study were comparable. Furthermore, the doses used for both agents are based on an algorithm to maintain a blood pressure within 20% of baseline and reflect the doses that are routinely used in our clinical practice.

This study has its limitations. Patients in both groups received a prophylactic antiemetic with ondansetron which might have obscured the effect of the opioid used. However, given the high incidence of PONV in this patient population, we felt it was unethical not to give an antiemetic prophylaxis. Also, despite our efforts to administer adequate analgesia using a NSAID and local anesthetic infiltration, patients in the remifentanil group required more fentanyl in PACU, which might have masked any difference in emetogenic effect between the two opioids. We used fentanyl as the rescue analgesic as remifentanil is very short acting and may cause undesirable side effects such as muscle rigidity when administered in awake patients

and hence was not a suitable rescue analgesic. A study in a patient population where postoperative opioid analgesia is unlikely to be required might be able to overcome this limitation. However, there appears to be a trend of higher complete response rates in the remifentanil group in the PACU as well as at

24 hours. It did not achieve statistical significance as our sample size calculation was based on a clinically significant difference of 35%. A larger sample size of 88 per group would be needed to test this hypothesis.

In summary, the use of remifentanil as the intraoperative opioid in patients undergoing ambulatory gynecologic laparoscopic procedures was not associated with a reduced incidence of PONV, compared with fentanyl, when used as part of a sevoflurane-nitrous oxide based anesthetic.

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