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Omission of Nitrous Oxide from a Propofol-based Anesthetic Does Not Affect the Recovery of Women Undergoing Outpatient Gynecologic Surgery

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Background: **Although nitrous oxide (N_2O) is used commonly during anesthesia, clinically relevant advantages–disadvantages of using this agent are not well established in the ambulatory setting. This study in women undergoing ambulatory gynecologic surgery compares outcomes in patients administered total intravenous anesthesia with propofol versus the propofol plus N_2O. The primary outcome was the time to home readiness. Secondary outcomes included the incidence of postanesthetic adverse events.**

Methods: **Women presenting for elective ambulatory termination of pregnancy or gynecologic laparoscopy were induced with an intravenous sleep dose of propofol and fentanyl. After induction, subjects were randomly allocated to maintenance anesthesia with propofol alone or propofol plus 65% N_2O. Patients were assessed by a blinded observer in the postanesthetic care unit at 20-min intervals to determine home readiness. Postoperative pain and nausea were measured with visual analog scales. Postoperative analgesics and antiemetics were recorded. The incidence of adverse events occurring after hospital discharge was assessed by a telephone interview 24 h postoperatively.**

Results: **A total of 740 patients received propofol alone, and 750 patients received propofol plus N_2O. Mean home readiness times were not significantly different between treatment groups. There were no significant differences between groups in pain scores, nausea scores, analgesia administration, or antiemetic administration before discharge. There were no significant differences in the frequency of adverse events for 24 h after discharge from hospital.**

Conclusions: **Omission of N_2O from a propofol-based anesthetic for ambulatory gynecologic surgery does not affect time to home readiness or the incidence of postoperative adverse events up to 24 h after discharge from hospital. (Key words: Awareness; outpatient surgery; total intravenous anesthesia.)**

AMBULATORY surgery has undergone tremendous growth over the last decade, and anesthesiologists have had to respond to this trend by adapting to the unique demands posed by ambulatory anesthesia. Patients must be adequately anesthetized for surgery yet recover quickly and with few residual effects so that they may be discharged home shortly after surgery. Propofol is now widely used to provide safe, effective, general anesthesia for ambulatory procedures.[1–5] It is currently considered the intravenous anesthetic of choice because its short duration of action allows patients to be discharged home sooner than those anesthetized with other anesthetic agents.[6–10]

Propofol is routinely administered to outpatients along with nitrous oxide (N_2O) as part of "balanced anesthesia." N_2O is popular because it is inexpensive, easily administered, and has a long history of use.[11] Despite this long history of apparently safe use, investigations over the last three decades have revealed limitations and dangers associated with this drug.[11–23] However, its use

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in outpatient settings has been somewhat controversial since harmful effects have been demonstrated in healthcare workers chronically exposed to low levels of N_2O.[15,19,24] Personnel who work in ambulatory surgical suites appear to be at highest risk.[14,18] Because the use of total intravenous anesthesia (TIVA) completely eliminates the concern of occupational N_2O toxicity, the potential benefit of N_2O to outpatients must be weighed against the current information concerning toxicity.[25]

There are relatively few studies comparing clinical outcomes of ambulatory anesthetics with and without N_2O. Data from these studies show that N_2O reduces the dosage of coadministered anesthetic drugs; however, it remains unclear whether N_2O provides any additional clinical benefit.[26] In addition, there is some evidence suggesting that N_2O may increase the incidence of adverse outpatient outcomes, such as nausea and vomiting and delayed discharge.[27,28] None of the studies that dispute this evidence have sufficient statistical power, because of inadequate sample size, to rule out definitively an association between adverse outcomes and the administration of N_2O.

These deficiencies led us to design a large, randomized, blinded, prospective study to determine the clinical utility of N_2O during propofol-based ambulatory anesthesia. Thus, the purpose of this randomized blinded trial in women undergoing ambulatory gynecologic surgery was to compare total intravenous propofol anesthesia with propofol plus N_2O. The primary clinical outcome was the time to home readiness. The secondary outcomes were the incidence and severity of postanesthetic adverse outcomes occurring over the first 24 h after hospital discharge and the delayed discharge and readmission rates.

Materials and Methods

The study was conducted at four hospitals (details of recruitment from the four hospitals are presented in the Appendix). After obtaining protocol approval by each hospital's Human Ethics Committee, written informed consent was obtained from patients undergoing termination of pregnancy or ambulatory gynecologic laparoscopy. These two surgical procedures represented the vast majority of ambulatory gynecologic surgery performed at the institutions studied. Patients undergoing other ambulatory gynecologic procedures were not studied to reduce heterogeneity in study population. Patients were American Society of Anesthesiologists status I or II and were between 18 and 55 yr of age. Patients were excluded from participation if there was a history of psychiatric disease, narcotic/sedative use, drug abuse, or morbid obesity ($>$ 30% above ideal body weight). No premedication was given.

Patients were randomly allocated by computer-generated random numbers in blocks of four to receive either total intravenous anesthesia with propofol (TIVA group) or propofol and N_2O (N_2O group). Stratification by hospital site and surgical procedure ensured that roughly equal numbers of subjects within both treatment groups were enrolled at each site. Four research assistants, blinded to treatment allocation enrolled patients into the study, obtained demographic and baseline information, and collected postoperative data. Fifteen anesthesiologists administered anesthetics, and 25 gynecologists performed the procedures. Patients were allocated to either the TIVA or N_2O group when the anesthesiologist opened the sealed opaque envelopes at induction of anesthesia. The anesthesiologists were not blinded to treatment allocation to ensure safe anesthetic care. Biased administration of the anesthetics and unblinding of the research assistants were prevented by the following: (1) preenrollment training of anesthesiologists to standardize anesthetic administration; (2) random visits by the principal investigator (R. A.) to discuss the anesthetic protocol with the anesthesiologists; (3) ongoing review of the anesthetic study sheets by the principal investigator; (4) restricting the research assistants from access to the operating rooms or patients' charts.

Patients received 500 ml of normal saline solution intravenously before arriving at the operating room. Patients were monitored with noninvasive blood pressure, electrocardiography, pulse oximeter, and end-tidal gas monitor.

At induction of termination of pregnancy, patients received fentanyl 0.7 μg/kg intravenously. After denitrogenation of the lungs with 100% O_2, 20 mg lidocaine and 2.0 mg/kg propofol were infused intravenously over 40 s with further increments of propofol titrated to loss of lid reflex. In the N_2O group, N_2O and oxygen 65%–35% were administered by mask. In the TIVA group, patients received 100% O_2. Anesthesia was maintained with intermittent bolus doses of 20 mg propofol in response to clinical signs of light anesthesia (movement, tearing, or phonation in response to surgical stimuli, or increases in blood pressure, pulse rate, or respiratory rate of $\geq$ 20%).

At induction of laparoscopy, patients received fentanyl 1.5 μg/kg and *d*-tubocurare 3 mg intravenously. After denitrogenation of the lungs with 100% O_2, 20 mg lido-

caine and 2.0 mg/kg propofol were infused intravenously over 40 s with further increments of propofol titrated to loss of lid reflex. After the administration of succinylcholine 1.5 mg/kg intravenously, subjects were intubated orally. After induction, patients were paralyzed with 0.075–0.1 mg/kg vecuronium intravenously and mechanically ventilated. In the N_2O group, patients received 65% N_2O–35% O_2, and in the TIVA group, patients received 100% oxygen. Anesthesia was maintained with an infusion of propofol 100–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ supplemented by intermittent bolus doses of 20 mg propofol in response to clinical signs of light anesthesia (movement or tearing in response to surgical stimuli or increases in blood pressure, or pulse rate of $\geq$ 20%). At the end of surgery, neuromuscular blockade was reversed with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg.

In all patients, propofol and N_2O were discontinued when the dressing was applied at the end of surgery. None of the wounds were infiltrated with local anesthetic. The anesthesiologists recorded the allocation group, induction and maintenance doses of propofol administered, duration of surgical procedure measured by stopwatch (induction of anesthesia to application of final dressing), dose and timing of all drugs, and any intraoperative anesthetic or surgical complications.

In the postanesthesia care unit, nausea, vomiting and pain were treated according to study guidelines with medications most commonly used in the study institutions. Dimenhydrinate (25–50 mg intravenously) was administered to patients who retched or vomited, could not ambulate because of nausea, or had prolonged nausea ($\geq$ 30 min). Morphine, 2–4 mg intravenously, was administered incrementally as needed for pain during the first hour of recovery by nurses in the postanesthesia care unit who were not part of the research team. Thereafter, pain was treated with acetaminophen with codeine or acetylsalicylic acid with codeine.

Nausea and pain were assessed every 20 min by a research assistant using a visual analog scale of 100 mm.[9,29] Postoperative administration of analgesia and antiemetics was recorded. To allow comparison of narcotic analgesic usage, dosages of codeine were converted to equivalent morphine dosages, and analysis of analgesic usage was made on standardized "morphine equivalents."[30] Time to home readiness was determined using the postanesthesia discharge scoring system (PADSS) based on five main criteria[31]: (1) vital signs; (2) activity and mental status; (3) pain, nausea, and vomiting; (4) surgical bleeding; and (5) liquid intake–output. Each of the five categories is assigned a value of 0–2. Patients may be discharged (*i.e.*, are home-ready) when they attain a PADSS score $\geq$ 9. Subjects were assessed by a blinded research assistant every 20 min until they reached a score $\geq$ 9. In addition, the same research assistant interviewed patients by telephone 24 h after discharge to determine the incidence of postdischarge adverse outcomes.

The incidence of perioperative dreaming and awareness during anesthesia was assessed in 649 patients 1 and 24 h after surgery by telephone interview using a questionnaire.

Statistical Analysis

We planned to recruit 1,500 patients (n = 1,000 termination of pregnancy group; n = 500, gynecologic laparoscopy group), with half the patients randomized to the N_2O group and the other half to the TIVA group. These sample sizes were identified to detect 20-min differences in time to home readiness between treatment groups with a power > 0.95 and a two-sided type I error of 0.05, based on mean ± SD time to home readiness of 111 ± 32 min (termination of pregnancy group) and 139 ± 50 min (gynecologic laparoscopy group). Data were analyzed using patient allocation by intention to treat. Descriptive statistics of continuous variables are presented as mean ± SD values, whereas discrete variables are presented as percentage ± 95% confidence intervals. Between-group comparisons were made using unpaired *t* tests for continuous variables and Fisher exact test for discrete variables. Repeated-measures analysis of variance was used to analyze continuous variables measured over time.

Results

One thousand patients undergoing termination of pregnancy (N_2O, n = 503; TIVA, n = 497) and 490 patients undergoing laparoscopy (N_2O, n = 247; TIVA, n = 243) were studied (see Appendix for institution-specific recruitment). Twenty-four hour follow-up assessments were available from nearly all randomized patients (termination of pregnancy: N_2O = 93%, TIVA = 94%; laparoscopy: N_2O = 98%, TIVA = 99%). The treatment groups were similar in terms of age, weight, American Society of Anesthesiologists status, smoking history, and history of postoperative emesis or motion sickness (table 1). Within each surgical subpopulation, there were no statistically significant differences in the duration of anesthesia or the total doses of fentanyl administered to both treatment groups. Patients in the TIVA

Table 1. Patient Characteristics

	N_2O Group	TIVA Group
Termination of pregnancy		
Age (yr)	26.2 ± 6	26.3 ± 6
Weight (kg)	58.4 ± 10	59.4 ± 10
ASA status I/II (%)	93.1/6.9	93.0/7.0
Smoker (%)	34.3	33.9
History of postoperative emesis or motion sickness (%)	17.7	18.1
Gestation (wk)	8.4 ± 2	8.7 ± 2
Laparoscopy		
Age (yr)	34.2 ± 6	34.7 ± 5
Weight (kg)	61.7 ± 12	62.2 ± 11
ASA status I/II (%)	85.4/14.6	88.9/11.1
Smoker (%)	26.0	26.7
History of postoperative emesis or motion sickness (%)	21.5	17.3
Birth control pill (%)	14.2	15.4
Menstrual (%FDLMP ≤ 8 d)*	22.8	20.0
Pregnant (%)	15.1	10.7

Where appropriate, values are mean ± SD.

* %FDLMP ≤ 8 d = percentage of patients who were within 8 days of the first day of their last menstrual period.

groups received significantly more propofol than patients in the N_2O groups. The mean dose of propofol administered to the TIVA group was 15% greater in patients undergoing termination of pregnancy (N_2O = 217.3 ± 54 mg, TIVA = 247.5 ± 68 mg; $P \leq 0.001$) and 25% greater in patients undergoing laparoscopy (N_2O = 381.1 ± 137 mg, TIVA = 456.0 ± 169 mg; $P \leq 0.001$).

Primary Outcome: Time to Home Readiness

Within each surgical subpopulation, time to home readiness was similar in both treatment groups (table 2). Among patients undergoing termination of pregnancy, the mean time between PADSS score ≥ 9 and actual patient discharge was 70 ± 55 min (N_2O group) and 70 ± 55 min (TIVA group; $P = 0.99$). Anesthesia-related causes for prolonged stay included nausea or vomiting (N_2O, n = 2; TIVA, n = 0); dizziness or headache (N_2O, n = 3; TIVA, n = 4); and other reasons (N_2O, n = 4; TIVA, n = 3). One patient in the TIVA group was admitted overnight for observation after an episode of laryngospasm, and one patient in the N_2O group was admitted for treatment of intractable pain. Mean time between PADSS score ≥ 9 and patient discharge among the group undergoing laparoscopy was 61 ± 51 min (N_2O group) and 63 ± 54 min (TIVA group; $P = 0.74$). Anesthesia-related causes for prolonged stay included nausea or vomiting (N_2O, n = 6; TIVA, n = 3); dizziness (N_2O, n = 12; TIVA, n = 17); pain (N_2O, n = 2; TIVA, n = 1); and other reasons (N_2O, n = 2; TIVA, n = 3). Two patients in each study group were admitted to hospital after surgical complications. Two patients in the N_2O group and one in the TIVA group were admitted for treatment of severe nausea and vomiting. One patient in the N_2O group was admitted for refractory pain and one from the TIVA group for severe vertigo.

Table 2. In-hospital Recovery

	N_2O Group	TIVA Group	*P*
Termination of pregnancy			
Time to home readiness (min)	113.0 ± 31.0	110.8 ± 30.1	0.24
Admitted to hospital (%)	0.2	0.2	1.00
Laparoscopy			
Time to home readiness (min)	167.2 ± 49.6	167.7 ± 49.1	0.91
Admitted to hospital (%)	1.2	1.3	1.00

Where appropriate, values are mean ± SD.

Table 3. Postoperative Pain and Analgesia Usage

	N_2O Group	TIVA Group	*P*
Termination of pregnancy			
In hospital			
Maximum pain score (cm)	2.4 ± 2.5	2.5 ± 2.6	0.46
Patients requiring analgesia (%)	18.1	21.3	0.20
Morphine equivalence dose (mg)	2.4 ± 2.1	2.4 ± 1.6	0.83
After discharge			
Pain in operative area (%)	34.6	35.2	0.83
Patients requiring analgesia (%)	20.8	21.2	0.94
Laparoscopy			
In hospital			
Maximum pain scores (cm)	5.0 ± 3.0	5.4 ± 2.8	0.15
Patients requiring analgesia (%)	75.5	80.1	0.25
Morphine equivalence dosage (mg)	5.8 ± 3.2	5.6 ± 2.7	0.54
After discharge			
Pain in operative area (%)	69.1	71.8	0.55
Patients requiring analgesia (%)	53.5	56.0	0.65

Where appropriate, values are mean ± SD.

Secondary Outcomes: Frequency of Adverse Postoperative Events

There were no differences between treatment groups in maximum visual analog scale pain scores, frequency of analgesia administration, or mean dosage of analgesia administered (morphine equivalents) before discharge from hospital (table 3).

Maximum visual analog scale nausea scores were very low, and there were no significant differences between the treatment groups (table 4). The incidence of vomit-

Table 4. Postoperative Nausea and Vomiting

	N_2O Group	TIVA Group	*P*
Termination of pregnancy			
In hospital			
Maximum nausea scores (cm)	0.4 ± 1.1	0.4 ± 1.1	0.83
Vomiting (%)	0.8	2.2	0.73
Patients requiring antiemetics (%)	2.0	4.8	0.01
Dimenhydrinate dosage (mg)	23.8 ± 8	25.0 ± 10.8	0.72
After discharge			
Nausea (%)	6.3	6.3	1.00
Vomiting (%)	2.2	1.5	0.48
Patients requiring antiemetics (%)	0.4	0.6	1.00
Laparoscopy			
In hospital			
Maximum nausea scores (cm)	0.7 ± 1.6	0.7 ± 1.6	0.72
Vomiting (%)	3.6	4.9	0.51
Patients requiring antiemetics (%)	26.1	28.9	0.54
Dimenhydrinate dosage (mg)	24.9 ± 10.6	22.6 ± 12.0	0.24
After discharge			
Nausea (%)	24.5	22.4	0.67
Vomiting (%)	11.2	10.4	0.88
Antiemetic usage (%)	1.2	1.3	1.00

Where appropriate, values are mean ± SD.

ing was not significantly different between groups. In the termination of pregnancy subgroup, antiemetics were used approximately twice as frequently by the patients who received N_2O.

Six hundred forty-nine patients were questioned postoperatively about perioperative dreams (table 5). Approximately 20% of the patients reported perioperative dreams with no significant difference in the incidence of

Table 5. Incidence of Perioperative Dreams Reported 30 min and 24 h after Surgery

	Frequency of Dreams Reported 30 min Postoperatively		Frequency of Dreams Reported 24 h Postoperatively	
Surgical Group	n/N	%	n/N	%
Termination of pregnancy				
N_2O group	50/251	20	46/235	20
TIVA group	48/242	20	39/231	17
Laparoscopy				
N_2O group	16/73	22	18/72	25
TIVA group	12/78	15	11/79	14

There was no significant difference between treatment groups in incidence of dreams.

n = number of patients reporting dreams; N = number of patients interviewed.

Table 6. Course of Patients over the First 24 h after Discharge from Hospital

	N_2O Group	TIVA Group	*P*
Termination of pregnancy			
Able to leave home (%)	86.3	84.8	0.51
Headache (%)	19.9	20.3	0.87
Drowsy (%)	19.4	18.4	0.73
Dizzy (%)	16.8	16.0	0.72
Sleep quality (%)			
Not at all good	5.6	4.8	
Somewhat good	5.6	5.2	0.96
Moderately good	14.3	15.8	
Very good	74.5	74.3	
Sought medical attention (%)	0.4	0.6	1.00
Readmitted to hospital (%)	0.2	0.2	1.00
Laparoscopy			
Able to leave home (%)	54.8	50.2	0.32
Headache (%)	15.8	19.1	0.40
Drowsy (%)	37.3	34.9	0.64
Dizzy (%)	24.9	24.9	1.00
Sleep quality (%)			
Not at all good	7.9	10.0	
Somewhat good	9.5	7.1	0.66
Moderately good	15.8	18.3	
Very good	66.8	64.7	
Sought medical attention (%)	1.2	0.4	0.62
Readmitted to hospital (%)	0.4	0.4	1.00

dreaming between treatment groups. Approximately 70% of the dreams were reported to be pleasant, while only 6–8% were considered unpleasant; 10%–15% of dreams were thought to have occurred during anesthesia, whereas the majority (53%–61%) was reported to have taken place immediately postoperatively.

Only one patient in this study reported intraoperative awareness (laparoscopy, N_2O group). The attending anesthesiologist noted that this event was likely caused by a kinked intravenous line that interrupted the flow of propofol for a short period.

Twenty-four hours after discharge, patients in both treatment groups reported similar amounts of postoperative pain and analgesia usage (table 3). Twenty-four hours after discharge, patients allocated to either treatment group experienced similar emetic symptoms and consumed similar amounts of antiemetic medication (table 4). There were no differences between treatment groups in the incidence of adverse symptoms experienced up to 24 h after discharge from hospital (table 6).

Discussion

This study demonstrates that the elimination of N_2O from a propofol-based anesthetic does not significantly

alter the rate of recovery after ambulatory gynecologic surgery. There was no difference in the incidence of vomiting or severity of nausea measured by visual analog scale between the two groups. Furthermore, we did not observe any differences in the incidence of adverse postoperative events up to 24 h after surgery. These results applied equally to patients who underwent termination of pregnancy and to those in the laparoscopy group. Therefore, these results appear to be robust and are unaffected by differences in the anesthesia protocols, patient demographics, or surgical procedures in the two surgical groups studied.

These results are similar to previous reports with smaller groups of patients undergoing outpatient or inpatient procedures.[26,32–34] Sukhani *et al.*[26] compared the recovery characteristics of two groups of patients undergoing ambulatory laparoscopy who were anesthetized with propofol alone or propofol plus N_2O. Although the time from discontinuation of propofol to eye-opening and orientation was significantly longer in patients anesthetized with propofol alone, the time to fulfilling the criteria for home readiness was not significantly different between the two groups.

Nitrous oxide causes emesis in unpremedicated human volunteers.[35] However, its significance after general anesthesia and surgery is still widely debated.[36–38] Postoperative nausea and vomiting are influenced by age, sex, date of menstrual cycle, obesity, type of operative procedure, and anesthetic technique.[36,39–45] In our study, healthy female patients undergoing ambulatory gynecologic surgery were studied to prevent confounding by these variables, and thus our results apply only to this population. Our data indicate that N_2O does not increase the incidence of postoperative vomiting. This finding is in agreement with the results of Sukhani *et al.*,[26] who investigated the effect of N_2O on postoperative nausea and vomiting in 70 patients undergoing ambulatory gynecologic laparoscopy with propofol. Our results are also consistent with the conclusions of a metaanalysis by Tramer *et al.*[27] that included studies of heterogeneous populations, surgical procedures, and anesthetic techniques. Although the odds ratios and confidence interval estimates calculated in the overall metaanalysis suggest a moderate association between postoperative nausea and vomiting and N_2O, the authors concluded that this association is only significant in patient populations with baseline postoperative nausea and vomiting rates much higher than those observed in our study.

Propofol requirements of patients who received N_2O were 20–25% lower than those who received propofol alone in both surgical groups we studied. Previous studies of N_2O using propofol or inhalational vapors as the primary anesthetic agents have demonstrated similar reductions in the dose of the primary anesthetic.[26,33–44] Although this effect of N_2O was sufficiently large to be clinically important in patients undergoing laparoscopic surgery, it was clinically insignificant in patients undergoing termination of pregnancy.

The frequency of dreaming reported 1 and 24 h after surgery was similar to the incidence reported in previous studies of women anesthetized with propofol and N_2O for termination of pregnancy.[6,46] Less than 10% of patients who dreamt described their dreams as unpleasant. Although Oxorn *et al.*[46] reported that propofol is not associated with unpleasant dreams, only 29 patients in their study were allocated to receive propofol; therefore they probably did not detect this low incidence of unpleasant dreams.

The one case of intraoperative awareness in our study was reported by a patient in the N_2O group who had a short period of intraoperative awareness during positioning for surgery. In this instance, the anesthesiologist did not notice that the intravenous tubing was kinked until after the patient had been positioned. This case illustrates that during intravenous anesthesia: (1) delivery of intravenous anesthetic drugs must be monitored at all times; (2) patients must be monitored regularly for signs of inadequate anesthesia; and (3) administration of N_2O does not guarantee unconsciousness.

We did not observe any cases of awareness in the TIVA group; thus, we can be 95% confident that the incidence of intraoperative awareness is not greater than 0.4% in patients undergoing outpatient gynecologic surgery with our TIVA protocol.[47] Miller *et al.*[48] observed a 17% incidence of awareness and recall using TIVA with propofol and alfentanil. This rate greatly exceeds the frequency of intraoperative recall commonly quoted for general anesthesia (0.1–0.2%).[49] Miller *et al.* attributed the high incidence of recall they encountered to underdosing of propofol and alfentanil (their starting infusion rates of propofol and alfentanil were 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively). It is likely that we did not encounter this unacceptably high incidence of recall as our protocol specified a starting propofol infusion rate of > 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with subsequent reductions if indicated clinically.

The aggregated incidence of awareness in the N_2O group was 0.13%. Our study has only sufficient power to detect a 20-fold difference in this rate with a power of 0.90 and an α level of 0.05. Although, on its own, our

study does not have sufficient power to determine whether N_2O reduces the risk of awareness during intravenous anesthesia, it provides data from a large number of patients that may be combined with data from future prospective randomized studies in a metaanalysis to resolve this issue. In their metaanalysis, Tramer *et al.*[27] reported that the risk of intraoperative awareness is greatly increased in the absence of N_2O (odds ratio, 4.5; 95% confidence interval, 1.1–18). However, this assessment is probably highly biased because (1) their metaanalysis selected studies that evaluated the effect of N_2O-free anesthetics on postoperative nausea and vomiting rather than selecting studies aimed at investigating the incidence of intraoperative recall *per se* (only 7 of the 24 trials that Tramer *et al.* evaluated reported intraoperative recall as an outcome); and (2) six of seven cases of intraoperative awareness during N_2O-free anesthetics were reported from one study in which it is evident that not all patients received adequate levels of anesthesia.[34]

Nitrous oxide is a well-described analgesic agent that is thought to interact with opioid receptors in the central nervous system.[50,51] Although data from animal studies suggest that N_2O may have properties leading to "preemptive analgesia,"[52,53] we found no evidence of this. There were no differences in pain visual analog scale scores in hospital or in the reported incidence or severity of pain up to 24 h after hospital discharge. Eger *et al.*[34] also found no evidence of residual analgesia after surgery with N_2O.

The major finding of this study in patients undergoing ambulatory gynecologic surgery is that elimination of N_2O from a propofol-based anesthetic does not significantly alter the time to discharge. There was no difference in the postoperative incidence of vomiting or severity of nausea between treatment groups. In addition, there was no difference in 24-h postoperative adverse outcomes. Thus, these results indicate that the clinical outcome of women undergoing outpatient gynecologic surgery is largely unaffected by omission of N_2O from a propofol-based anesthetic.

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Appendix

Patient Recruitment Log

	N_2O Group	TIVA Group
Termination of pregnancy		
Toronto General Hospital	277	274
Toronto Western Hospital	226	223
Laparoscopy		
Toronto General Hospital	88	84
Toronto Western Hospital	81	84
North York General Hospital	63	62
Women's College Hospital	15	13

Time to Home Readiness at Each Study Institution

	Time to Home Readiness (min)		
	N_2O Group	TIVA Group	*P*
Termination of pregnancy			
Toronto General Hospital	127 ± 30	125 ± 29	0.25
Toronto Western Hospital	95 ± 22	94 ± 21	0.41
Laparoscopy			
Toronto General Hospital	195 ± 54	190 ± 53	0.56
Toronto Western Hospital	164 ± 38	165 ± 38	0.81
North York General Hospital	130 ± 28	135 ± 36	0.35
Women's College Hospital	203 ± 50	196 ± 53	0.70

Values are mean ± SD.