Anesthesiology 2001; 95:616–26

Randomized Controlled Trial of Total Intravenous Anesthesia with Propofol versus *Inhalation Anesthesia with Isoflurane–Nitrous Oxide*

Postoperative Nausea and Vomiting and Economic Analysis

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Background: **To assess the incidence of postoperative nausea and vomiting after total intravenous anesthesia (TIVA) with propofol *versus* inhalational anesthesia with isoflurane–nitrous oxide, the authors performed a randomized trial in 2,010 unselected surgical patients in a Dutch academic institution. An economic evaluation was also performed.**

Methods: **Elective inpatients (1,447) and outpatients (563) were randomly assigned to inhalational anesthesia with isoflurane–nitrous oxide or TIVA with propofol–air. Cumulative incidence of postoperative nausea and vomiting was recorded for 72 h by blinded observers. Cost data of anesthetics, antiemetics, disposables, and equipment were collected. Cost differences caused by duration of postanesthesia care unit stay and hospitalization were analyzed.**

Results: **Total intravenous anesthesia reduced the absolute risk of postoperative nausea and vomiting up to 72 h by 15% among inpatients (from 61% to 46%, $P < 0.001$) and by 18% among outpatients (from 46% to 28%, $P < 0.001$). This effect was most pronounced in the early postoperative period. The cost of anesthesia was more than three times greater for propofol TIVA. Median duration of stay in the postanesthesia care unit was 135 min after isoflurane *versus* 115 min after TIVA for inpatients ($P < 0.001$) and 160 min after isoflurane *versus* 150 min after TIVA for outpatients ($P = 0.039$). Duration of hospitalization was equal in both arms.**

Conclusion: **Propofol TIVA results in a clinically relevant reduction of postoperative nausea and vomiting compared with isoflurane–nitrous oxide anesthesia (number needed to treat = 6). Both anesthetic techniques were otherwise similar. Anesthesia costs were more than three times greater for propofol TIVA, without economic gains from shorter stay in the postanesthesia care unit.**

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Received from the Departments of Anesthesiology and Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. Submitted for publication April 28, 2000. Accepted for publication March 22, 2001. Supported by a Fund for Investigative Medicine (project code OG96-038) from the Dutch Health Insurance Council, College voor Zorgverzekeringen, Amstelveen, The Netherlands. Presented at the annual meeting of the American Society of Anesthesiologists, Dallas, Texas, October 11–12, 1999.

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SEVERAL studies have suggested that total intravenous anesthesia (TIVA) with propofol reduces the incidence of postoperative nausea and vomiting (PONV) and results in shorter emergence times.[1–5] However, a meta-analysis showed that most studies were smaller, did not have follow-up beyond 6 h postoperatively, and were often sponsored by industry. Results were difficult to combine as a result of heterogeneous definitions of PONV.[6,7]

At present, propofol TIVA is more expensive than inhalational anesthesia with isoflurane and nitrous oxide (N_2O). However, some investigators have suggested that TIVA could be cost-effective because the costs of treating PONV and of increased recovery room stay after inhalational anesthesia offset the additional drug acquisition costs of propofol TIVA.[8,9]

We compared the incidence of PONV up to 72 h postoperatively in a large group of unselected elective surgical inpatients and outpatients who were randomized to receive either inhalational anesthesia with isoflurane–N_2O or TIVA with propofol–air. The primary hypothesis was that propofol TIVA would reduce the incidence of PONV compared with a conventional inhalation anesthetic technique. In addition, we hypothesized that the results might reveal subgroups with a high baseline risk for PONV, such as females and patients undergoing certain types of surgery, who would benefit more from TIVA than patients with a low baseline risk. This would allow identification of subgroups for whom TIVA could be especially advantageous. In addition, we performed an economic evaluation of the two techniques, testing the hypothesis that propofol TIVA would be an economically viable alternative to isoflurane in both inpatients and outpatients undergoing a broad array of surgical procedures. Because cost–benefit analysis requires that a dollar value be placed on PONV, and these data are not available, TIVA was considered economically viable if the additional drug acquisition cost for TIVA was balanced by the financial gains from reduced recovery time.

Materials and Methods

The study was conducted at the Academic Medical Center of the University of Amsterdam and was approved by its institutional medical ethics committee. All

patients gave written informed consent before being included in the study.

Patients

From April 1997 to January 1999, 1,447 inpatients and 563 outpatients scheduled to undergo elective surgery with general anesthesia were enrolled in the study. Exclusion criteria were emergency, cardiac, or intracranial surgery; American Society of Anesthesiologists physical status classification greater than III; age less than 18 yr or more than 80 yr; (possible) pregnancy; renal or liver disease precluding use of either anesthetic technique; use of antiemetic or proemetic medication in the 2 weeks before surgery; body weight greater than 120 kg; previous enrollment in the same study; and insufficient command of the Dutch language. Patients receiving regional anesthetic techniques were not included in the study, except in the case of upper abdominal surgery, for which epidural analgesic supplementation was permitted.

Study Anesthetics

The two anesthetic regimens consisted of (1) inhalational anesthesia with isoflurane and 60% N_2O in oxygen (isoflurane group) for maintenance of anesthesia after induction with thiopental (inpatients) or propofol (outpatients), and (2) TIVA with propofol and air–oxygen for anesthesia induction and maintenance (TIVA group). Propofol dosage and isoflurane concentration were determined by the attending anesthesiologist. Prophylactic antiemetics were not permitted. Anesthesiologists were free to choose the type and dose of muscle relaxants and (opioid) analgesics as well as other drugs for supplementation of anesthesia, as deemed necessary. Postoperative analgesics were given as ordered by the responsible anesthesiologist. Administration of antiemetic therapy was the responsibility of postanesthesia care unit (PACU) and day care unit (DCU) nurses. The protocol prescribed intravenous metoclopramide (0.15 mg/kg) as the primary antiemetic therapy, followed by intravenous droperidol (15 μg/kg) if necessary.

Randomization and Blinding.

Patients were randomized (unstratified) to either isoflurane or TIVA by an electronic randomization program running on a protected server. Medication for both anesthetic techniques was brought into the operating room on a covered tray, concealing the randomization from the attending anesthesia staff until directly before induction of anesthesia.

Personnel in the PACU and DCU, including the physician on duty, remained blinded to the randomization. Intravenous lines and stopcocks were flushed with saline to remove visible traces of propofol before transportation of patients to the PACU–DCU. Strict measures were taken to rule out exchange of information between blinded and nonblinded personnel. All patients received oxygen by mask for at least 30 min after arrival in the PACU–DCU. This served to camouflage any odor of residual isoflurane in expired air.

Research nurses who made intraoperative and postoperative observations were not involved in the care-giving process. During stay in the PACU, the anesthesia record was kept in a sealed envelope to be opened only in case of emergency by the research nurse who had performed the intraoperative observations. Patients were blinded to the anesthetic technique at all times during the study.

Measurement Protocol

Preoperative Measurements. A research nurse recorded baseline characteristics of consenting patients, including information on previous PONV and motion sickness. Patients completed a questionnaire covering general health (Short Form-36).[10,11]

Intraoperative Measurements. Intraoperatively, the following data were recorded: type and dose of premedication, duration of induction, airway management (endotracheal tube or laryngeal mask airway), type and doses of all medication administered intraoperatively, surgical time, and anesthetic time. Time to awakening (response to verbal command) and time to extubation after discontinuation of anesthesia were also recorded.

The surgical procedures were categorized into superficial, upper abdominal, lower abdominal, laparoscopic, inner ear, and strabismus surgery. The superficial surgery category included all procedures in which body cavities were not opened, *e.g.*, orthopedic, plastic, oral, and nasal surgery.

Postoperative Measurements. Routine monitoring was initiated on arrival in the PACU or DCU. Every 15 min, a research nurse recorded PONV, analgesic, and antiemetic medication. Nausea, retching, and vomiting were scored separately. Times to permission for discharge and actual discharge from the PACU or DCU (no step-down unit) were also recorded.

Approximately 24 h after surgery (range, 20–28 h), a research nurse visited inpatients at the ward or telephoned outpatients at home to record occurrence of PONV, use of antiemetics or analgesics, and the presence of possible postoperative complications and side effects subsequent to discharge from the PACU. Patients were asked to quantify discomfort caused by nausea, retching, and vomiting and to rate their anesthetic experience (scale of 0 to 10). Similar information was collected 72 h postoperatively with reference to the previous 48 h. All measurement procedures were tested in a pilot study.

Fourteen days postoperatively, patients received a questionnaire by mail regarding PONV experience from 72 h to 14 days, ratings of anesthesia, and general health as measured by the Short-Form 36.[10]

Primary and Secondary Outcome Measures. Primary outcome was the cumulative incidence of PONV at 72 h. PONV was defined as the occurrence of nausea or retching or vomiting and was combined from separate observations of nausea, retching, and vomiting (scored on seven occasions). Secondary outcomes were subjective ratings of the severity of PONV (from 0 = no discomfort from PONV, to 10 = worst discomfort possible), ratings of the anesthetic experience, and use of antiemetic drugs. Subgroup analysis was scheduled for type of surgery and gender.

We performed an evaluation of the two anesthetic techniques from an economic perspective. Costs for both anesthetic strategies were specified. Health outcomes were measured in terms of PONV incidence in the 72 h postoperatively and in terms of general health (Short Form-36) at 14 days postoperatively. As the study was based on data from individual patients, economic evaluation of consequences on the setting level (*e.g.*, the efficiency of hospital-wide adoption of either of the anesthetic techniques) required extrapolation.

Cost Data. Individual cost registration started at the time of induction. Detailed volume data on intraoperative medication, anesthesia time, and other time-related variables, postoperative medication (antiemetics and analgesics), length of stay in the PACU or DCU, and length of stay in the hospital were recorded in the case report form. For the last 753 patients, time to return to work was recorded at 14 days postoperatively.

Intraoperative use of isoflurane was measured by weighing the vaporizer on an electronic precision scale preoperatively and postoperatively (Vibra HG-10 K, accuracy 0.05 g, Ridderkerk, The Netherlands). The volume of N_2O was calculated from the fresh gas flow and the fraction of N_2O during steady state anesthesia. Use of antiemetics during stay in the PACU or DCU was recorded by a research nurse.

The variable and fixed-cost components and their corresponding prices are shown in the Web Enhancement (table 1). The costs of drugs and resources were based on the actual acquisition costs to the center and calculated according to the number of opened packages, *i.e.*, including the "spill" of drugs (any drugs left over in an opened vial or syringe at the end of a procedure were not used for a subsequent patient, but were discarded; this waste was termed "spill") . For propofol, the costs of spill were calculated separately. Costs of equipment were composed of the depreciation, maintenance, and repair of devices specific for isoflurane and TIVA (vaporizer, oxygen–N_2O fail-safe device, gas analyzer, gas evacuation equipment on the ventilator, scavenging equipment in the operating room, and infusion pumps).

Sample Size. Power calculations were performed for inpatients and outpatients separately. For inpatients, the expected baseline event rate in the control group (isoflurane) was estimated at 25%, the weighted average of approximately 25% high-risk procedures (55% PONV; abdominal, laparoscopy, middle ear, strabismus[12–16]) and approximately 75% low-risk procedures (15% PONV; superficial). For outpatients, the baseline rate was estimated at 12.5%. Targeting detection of a 7.5% risk reduction for both inpatients and outpatients, an α of 0.05 and a β of 0.10, and anticipating 10% postrandomization loss caused by organizational constraints, sample size was set at 700 inpatients and 300 outpatients per treatment arm.

Data Management. Missing individual data from the multiple observation points were not substituted except during analysis of primary outcome, which was conducted both with and without substitution of missing data (imputation). Data were imputed drawing at random from the combined PONV distribution of TIVA and isoflurane patients.

Statistical Analysis

All data were analyzed according to the intention-to-treat principle. All comparisons between isoflurane and TIVA were performed for inpatients and outpatients separately, unless stated otherwise. Data are presented as mean ± SD or median with 10th–90th percentiles for nonnormally distributed variables. The number needed to treat (NNT) was calculated as 1/absolute risk reduction. Variables were compared using parametric and nonparametric tests as appropriate. Conventional survival time analysis was used to compare cumulative incidence of PONV with standard test statistics (log rank) for differences according to anesthetic treatment. Subgroup analyses were scheduled for type of surgery and gender. In addition, multivariate logistic regression analysis with 72-h cumulative incidence of PONV as the dependent variable was conducted to determine the relative role of baseline characteristics and to determine interaction, if any, between anesthetic technique and other characteristics. All statistical analyses were performed using SPSS version 9.0 for Windows (SPSS Inc., Chicago, IL).

Economic Analysis. Direct cost analysis was performed by comparing hypnotic and total anesthetic drug costs, the latter including opioids, muscle relaxants, and antagonists. In addition, direct costs of antiemetics were calculated. Return to work was used as an indicator for indirect nonmedical costs, excluding persons aged 65 yr and older and persons without a paid job.

Economic evaluation was performed using cost-effectiveness analysis, in which the NNT was used to calculate the cost of averting PONV in one patient. Economic consequences for the hospital under study regarding the budget of the anesthesiology department (based on cost reservations for anesthetics and antiemetics), assuming implementation of one technique only, were also calculated. These calculations were based on mean costs. Because no reliable data are available to value the impact

of suffering from PONV in monetary terms, we refrained from cost–benefit analysis.

Length of stay in the PACU was recorded to assess the effect of technique on recovery time and PACU utilization. We evaluated the difference in time until readiness for discharge and actual discharge (log-rank statistics). From the study data (including data on variance per patient subgroup) and data on the number of surgical procedures performed per year in the hospital under study, we intended extrapolation of the economic effects on the PACU level, assuming hospital-wide implementation of either of the two anesthesia strategies.

Results

Patient Inclusion, Randomization, and Follow-up

A total of 2,010 patients were included and randomized to receive either isoflurane or TIVA (563 outpatients and 1,447 inpatients). Figure 1 shows inclusion and reasons for dropout in both treatment arms. The pattern of withdrawal was similar across TIVA and isoflurane groups. Complete 72-h follow-up was obtained in 1,952 patients (97%). Postoperative questionnaires were returned by 1,803 patients (90%). Information on complications up to 14 days postoperatively was obtained for all 2,010 patients in the study, either directly from patients or from medical records and letters of discharge.

Baseline Characteristics and Intraoperative Data

Baseline patient characteristics were similar across allocation groups (table 1). The average age of inpatients and outpatients was 45 and 38 yr, respectively. Slightly more women underwent surgery. A majority of patients reported previous surgery (83% of inpatients, 76% of outpatients). General health (Short Form-36) was lower than healthy population norms.[11] Table 2 shows intraoperative data. Outpatients seldom received premedication. Endotracheal tubes and muscle relaxants were used significantly more often for inpatients than for outpatients. Among inpatients, laryngeal mask airways were used more often in the propofol group than in the isoflurane group (12% *vs.* 8%, $P = 0.005$). Conversely, more isoflurane inpatients were intubated. All patients received opioids intraoperatively. Average use of propofol for anesthesia maintenance was 8.9 mg · kg^{-1} · h^{-1} (inpatients) and 10.2 mg · kg^{-1} · h^{-1} (outpatients). Isoflurane use was 13.2 ml/h (inpatients) and 14.4 ml/h (outpatients). There were no statistically significant differences in the duration of inpatient anesthesia across techniques and in the time from discontinuation of anesthesia until response to a verbal command in outpatients after TIVA or isoflurane (median, 9 min). For inpatients, the times until response to a verbal command were 11 and 12 min after isoflurane and TIVA, respectively ($P = 0.036$).

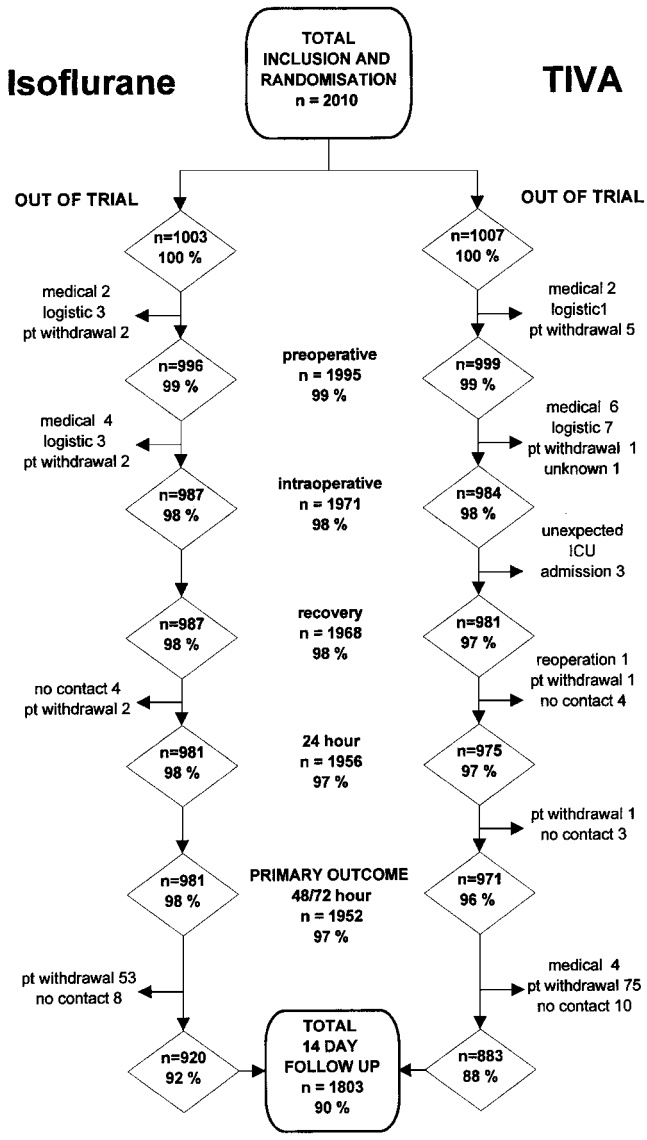

Fig. 1. Flow chart of randomization and follow-up. Isoflurane patients received inhalational anesthesia with isoflurane–nitrous oxide after induction with thiopental (inpatients) or propofol (outpatients); total intravenous anesthesia (TIVA) patients received total intravenous anesthesia with propofol–air for induction and maintenance. ICU = intensive care unit.

Postoperative Nausea and Vomiting

The cumulative 72-h incidence of PONV among inpatients was 61% in the isoflurane group compared with 46% in the TIVA group (relative risk, 1.32; 95% confidence interval [CI], 1.20–1.46; imputed dataset). In outpatients, the cumulative incidence of PONV was 47% after isoflurane and 29% after TIVA (relative risk, 1.61; 95% CI, 1.29–2.02; imputed dataset). Figure 2 shows the cumulative incidence PONV up to 72 h as survival curves. After 24 h, the relative risk for PONV in isoflurane was 1.43 (95% CI, 1.28–1.59) for inpatients and 1.83 (95% CI, 1.42–2.34) for outpatients. Table 3 shows the development of PONV in the various postoperative time periods. The difference between isoflurane and

Table 1. Patient Characteristics at Baseline*

	Inpatients		Outpatients	
	Isoflurane (N = 706)	TIVA (N = 711)	Isoflurane (N = 281)	TIVA (N = 273)
Age (yr)	45 ± 15.5	45 ± 15.2	38 ± 11.0	39 ± 12.3
Female gender	415 (59)	403 (57)	156 (56)	148 (54)
Ethnic origin				
White	622 (88)	616 (87)	226 (81)	211 (78)
African	30 (4.3)	30 (4.2)	20 (7.2)	21 (7.7)
Mediterranean	13 (1.8)	11 (1.6)	5 (1.8)	6 (2.2)
Asian	20 (2.8)	26 (3.7)	14 (5.0)	16 (5.9)
Other	20 (2.8)	25 (3.5)	14 (5.0)	18 (6.6)
ASA physical status				
I	410 (58)	448 (63)	217 (77)	209 (77)
II	268 (38)	242 (34)	64 (23)	61 (22)
III	27 (3.8)	20 (2.8)	0	2 (0.7)
Type of surgery				
Superficial	535 (76)	513 (73)	219 (79)	217 (80)
Intraabdominal	58 (8.2)	79 (11)	0	0
Laparoscopic	52 (7.4)	54 (7.7)	51 (18)	45 (17)
Strabismus	10 (1.4)	2 (0.3)	2 (0.7)	1 (0.4)
Middle ear	45 (6.4)	54 (7.7)	6 (2.2)	5 (1.8)
Body mass index (kg/m^2)	25 ± 4.3	25 ± 4.1	24 ± 3.6	25 ± 3.8
Previous anesthesia				
No	135 (19)	111 (16)	65 (23)	68 (25)
Yes, without PONV	394 (56)	406 (57)	137 (49)	141 (52)
Yes, with PONV	167 (24)	175 (25)	71 (25)	55 (20)
Yes, PONV unknown	9 (1.3)	17 (2.4)	8 (2.8)	8 (2.9)
History of motion sickness	148 (21)	129 (18)	60 (21)	61 (23)
SF36 general health†				
Physical summary score	47 ± 11.3	47 ± 12.5	50 ± 9.6	49 ± 9.5
Mental summary score	48 ± 11.3	48 ± 11.1	50 ± 8.7	51 ± 8.6

* All values are shown as numbers of patients followed by rounded percentages in parentheses (values below 10% not rounded). Because of rounding, percentages may not total 100. Plus–minus values are mean ± SD. Baseline characteristics are shown for study patients who actually underwent surgery and anesthesia. There were no significant differences in baseline characteristics between treatment groups. † Short Form-36 (SF36) Health Survey values are scored on a continuous scale from 0 (worst) to 100 (best).[20,21]

Isoflurane group = inhalational anesthesia with thiopental, isoflurane, and nitrous oxide for inpatients, and propofol induction, isoflurane, and nitrous oxide for outpatients; TIVA group = total intravenous anesthesia with propofol–air; ASA = American Society of Anesthesiologists; PONV = postoperative nausea and vomiting.

TIVA was apparent at PACU discharge. Beyond 24 h, PONV development was similar in both treatment arms. Results were identical using the imputed dataset or using the dataset of patients with 21 complete observations for PONV (88%).

Venn diagrams (fig. 3) show the individual contributions of nausea, retching, and vomiting to the combined PONV end point with the two anesthetic techniques. The percentage of patients who had all three emetic symptoms decreased from 26.5% to 14.8% for inpatients (relative decrease, 44%) and from 12.1% to 6.2% for outpatients (relative decrease, 49%).

Secondary Outcome Measures

Antiemetics were administered more often in patients who received isoflurane (inpatients: 36% *vs.* 18%, $P < 0.001$, relative risk 2.06, 95% CI 1.71–2.49; outpatients: 20% *vs.* 8%, $P < 0.001$, relative risk 2.65, 95% CI 1.65–4.24). Subjective ratings of discomfort from nausea at 24 h were lowest in the TIVA group. The percentage of patients reporting "no discomfort" from nausea after 24 h was 58% *versus* 70% among inpatients and 70% *versus* 80% among outpatients for TIVA and isoflurane, respectively. After 24 h, ratings of the anesthetic experience in general were significantly higher for TIVA inpatients than for isoflurane inpatients. After 14 days, ratings of the anesthetic experience were significantly higher for all TIVA patients (data on patient ratings of PONV and anesthetic experience can be found in the Web Enhancement, table 2).

Complications. One outpatient in the TIVA group and two in the isoflurane group (incidence, 0.5%) were admitted to the ward because of intractable PONV. In the structured 24-h postoperative interview, seven patients reported awareness for the anesthetic period, an incidence of 0.4% (isoflurane, n = 4; TIVA, n = 3). Two outpatients in the TIVA group had memories of pain and sounds during anesthesia, and one isoflurane inpatient and one isoflurane outpatient remembered sounds and inability to move. The remaining three patients remembered being aware of sounds.

Table 2. Intraoperative and Postoperative Data*

	Inpatients			Outpatients		
	Isoflurane (N = 706)	TIVA (N = 711)	*P* Value	Isoflurane (N = 281)	TIVA (N = 273)	*P* Value
Sedative premedication	565 (80)	580 (82)	0.460	8 (2.8)	9 (3.3)	0.759
Airway management						
Laryngeal mask airway	53 (7.5)	84 (12)	0.005	94 (34)	99 (37)	0.501
Endotracheal intubation	649 (93)	619 (88)	0.005	180 (66)	168 (63)	0.501
Muscle relaxants	681 (97)	647 (91)	< 0.001	220 (79)	205 (76)	0.370
Muscle relaxant reversal	110 (16)	112 (17)	0.604	30 (14)	29 (15)	0.858
Temperature at end of surgery (°C)†	36.1 ± 0.68	36.0 ± 0.68	0.232			
Median duration anesthesia (min) (10th–90th percentile)	122 (61–225)	115 (59–230)	0.162	62 (36–119)	64 (39–125)	0.116
Median time to awakening (min)‡ (10th–90th percentile)	11 (5–25)	12 (5–27)	0.036	9 (4–18)	9 (4–20)	0.237
Intraoperative protocol violations						
Prophylactic antiemetics	5 (0.7)	9 (1.3)	0.289	2 (0.7)	1 (0.4)	1.0
Nonprotocol induction agent	20 (2.8)	11 (1.5)	0.098	2 (0.7)	2 (0.7)	1.0
Nonprotocol antiemetic	2 (0.3)	2 (0.3)	1.0	0	0	
Other protocol violations§	35 (5.0)	55 (7.7)	0.032	11 (3.9)	22 (8.1)	0.039
Postoperative medication						
Analgesics up to 72 h			0.645			0.479
None	24 (3.6)	29 (4.5)		22 (8.3)	16 (6.3)	
NSAIDs	378 (57)	357 (55)		223 (84)	224 (88)	
Opioids ± NSAIDs	262 (40)	262 (40)		20 (7.5)	15 (5.9)	
Antiemetics up to 72 h	255 (36)	124 (18)	< 0.001	57 (20)	21 (7.7)	< 0.001

* All values are shown as numbers of patients followed by rounded percentages in parentheses (values below 10% not rounded). Because of rounding, percentages may not total 100. Plus–minus values are mean ± SD. Differences between isoflurane and total intravenous anesthesia (TIVA) groups tested according to Mann–Whitney, Pearson chi-square, or Fisher exact test, as applicable. † Temperature at end of surgery was not measured in outpatients. ‡ Time to awakening = time from discontinuation of anesthesia until response to a verbal command. § Other protocol violations = violations considered to be of minor importance to the patient and to the study question (*e.g.*, briefly adding nitrous oxide to TIVA; using sevoflurane instead of isoflurane).

Isoflurane group = inhalational anesthesia with thiopental, isoflurane, and nitrous oxide for inpatients, or propofol induction, isoflurane, and nitrous oxide for outpatients; TIVA group = total intravenous anesthesia with propofol–air; NSAIDs = nonsteroidal antiinflammatory drugs.

Per-protocol Subgroup Analysis

Total intravenous anesthesia reduced the incidence of PONV most in the subgroup of patients undergoing superficial surgical procedures (absolute risk reduction, 20%). TIVA reduced PONV after middle ear surgery but not after abdominal and laparoscopic surgery (table 4). Because of the small number of patients undergoing strabismus surgery (n = 15), no conclusions could be drawn on the effect of TIVA in these patients.

Female patients suffered substantially more PONV than male patients (women at 72 h: isoflurane 65% *vs.* TIVA 50%; men: isoflurane 46% *vs.* TIVA 31%; $P < 0.001$). Survival curves depicting PONV development for men and women separately can be found in the Web Enhancment (fig. 1.) Multiple logistic regression confirmed the effect of anesthetic technique (odds ratio for inpatients: 2.03 [95% CI, 1.57–2.59], for outpatients: 2.30 [95% CI, 1.52–3.49]) when corrected for baseline characteristics such as age, gender, and previous PONV.

Economic Evaluation

Postanesthesia Care Unit Discharge Times. For inpatients, length of stay in the PACU until readiness for discharge was 135 min with isoflurane *versus* 115 min with TIVA ($P < 0.001$). For outpatients, length of stay in the DCU until readiness for discharge home was 160 min

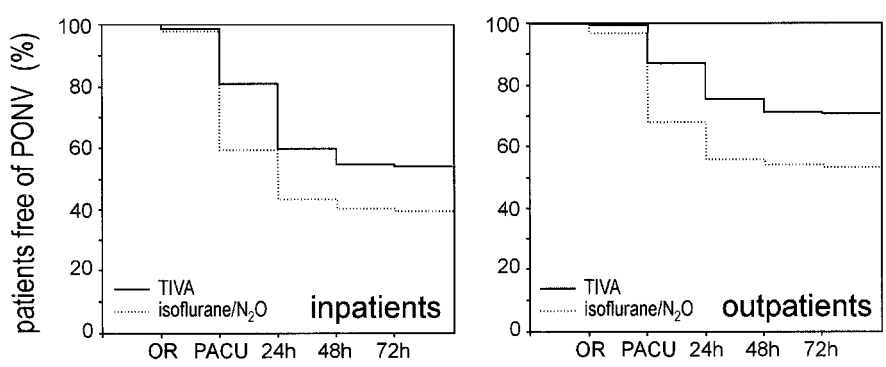

Fig. 2. Survival without postoperative nausea and vomiting (PONV) according to anesthetic technique ($P < 0.001$, log-rank test for inpatients and outpatients). Isoflurane patients received inhalational anesthesia with isoflurane–nitrous oxide after induction with thiopental (inpatients) or propofol (outpatients); total intravenous anesthesia (TIVA) patients received total intravenous anesthesia with propofol–air for induction and maintenance. OR = operating room directly after emergence from anesthesia; PACU = postanaesthetic care unit or day care unit, as applicable; 24 h = 24 h postoperatively; 48 h = 48 h postoperatively; 72 h = 72 h postoperatively.

Table 3. Number of Patients with Nausea, Retching, or Vomiting*

	Inpatients			Outpatients		
	Isoflurane (N = 706)	TIVA (N = 711)	*P* Value	Isoflurane (N = 281)	TIVA (N = 273)	*P* Value
Nausea, retching, or vomiting†						
Directly after anesthesia	14 (2.0)	9 (1.3)	0.302	8 (2.8)	1 (0.4)	0.038
Discharge PACU/DCU	284 (40)	129 (18)	< 0.001	86 (31)	35 (13)	< 0.001
24 h	284 (40)	223 (31)	0.001	81 (29)	46 (17)	0.001
48 h	106 (15)	99 (14)	0.597	25 (8.9)	26 (9.6)	0.883
72 h	68 (9.6)	52 (7.3)	0.127	17 (6.1)	11 (4.0)	0.334
Retching or vomiting‡						
Directly after anesthesia	14 (2.0)	9 (1.3)	0.302	8 (2.8)	1 (0.4)	0.038
Discharge PACU/DCU	157 (22)	35 (4.9)	< 0.001	41 (15)	12 (4.4)	< 0.001
24 h	227 (32)	170 (24)	0.001	45 (16)	20 (7.4)	0.001
48 h	32 (4.5)	44 (6.2)	0.167	6 (2.1)	8 (2.9)	0.551
72 h	21 (3.0)	19 (2.7)	0.751	3 (1.1)	3 (1.1)	1.000

* All values are shown as numbers of patients followed by rounded percentages (for values greater than 10%) in parentheses. Because of rounding, percentages may not total 100. Each patient with postoperative nausea and vomiting (PONV) is counted in the time period when PONV occurred, irrespective of previous PONV (*i.e.*, each patient can contribute several times to the PONV endpoint). Differences between isoflurane and total intravenous anesthesia (TIVA) tested for each time period according to Pearson chi-square or Fisher exact test, as applicable. † Nausea, retching, or vomiting, or any combination of these three emetic events (100% minus percentage of patients with no PONV). ‡ Retching or vomiting, irrespective of the presence of nausea.

Isoflurane group = inhalational anesthesia with thiopental, isoflurane, and nitrous oxide for inpatients, or propofol induction, isoflurane, and nitrous oxide for outpatients; TIVA group = total intravenous anesthesia with propofol–air; PACU = postanesthetic care unit (inpatients); DCU = day care unit (outpatients).

with isoflurane and 150 min with TIVA ($P = 0.039$). Times until actual discharge varied accordingly (data not shown). The difference between isoflurane and TIVA remained the same throughout the entire range of discharge percentiles. (The distribution of time to readiness for discharge with both strategies is shown in fig. 2 of the Web Enhancement). Significant differences in times until readiness for discharge between randomization arms were also observed in the subgroup of patients who did not experience PONV in the PACU or DCU. The median (10th–90th percentile) times until readiness for discharge for inpatients without PONV were 125 min (75–239) after isoflurane *versus* 110 min (65–210) after TIVA ($P = 0.001$). For outpatients without PONV, these times were 155 min (95–230) after isoflurane *versus* 145 min (85–219) after TIVA ($P = 0.03$).

On average, 18 adult inpatients and 12 outpatients per day are eligible for either isoflurane or TIVA in our center. Extrapolation of recovery time data to these patients could lead to efficiency gains along the following lines. In the scenario in which all patients receive TIVA, the reduction in PACU time in the most optimistic situation would be 15 min per inpatient and 10 min per outpatient (based on median time to readiness for discharge after TIVA *vs.* isoflurane). Patient time saved in the PACU and DCU in the course of 1 day could theoretically be 4.5 h (18 patients times 15 min) and 2 h (12 patients times 10 min), respectively.

Direct Cost Analysis. Detailed drug acquisition costs at the time of the study can be found in the Web Enhancement, table 1). Table 5 shows the intraoperative volumes of anesthetics. For inpatients (median duration of anesthesia = 2 h) median costs (10th–90th percentile) of induction with thiopental and maintenance with isoflurane were $10.84 (5.67–22.64) *versus* $39.53 (19.89–75.74) for propofol TIVA. In outpatients (median duration of anesthesia = 1 h), these amounts for induction with propofol and maintenance with isoflurane were $13.10 (8.51–20.18) *versus* $28.31 (19.89–47.69) for propofol TIVA.

Use of antiemetics was twice as high in the isoflurane group (36% *vs.* 18%). The total costs of antiemetics comprised less than 2% of total drug costs. No differences in the use of analgesics were observed. The actual costs of all anesthetic drugs in the study groups can be found in the Web Enhancement, table 3).

Median length of hospitalization was 3 days in both randomization arms (10th–90th percentiles: 1–9 days after isoflurane and 1–10 days after TIVA; difference not significant). Sixty percent of the inpatients and 77% of the outpatients had a paid job. There was no statistically significant difference in the number of days to return to work with both strategies (median, 14 days for inpatients and 10 days for outpatients).

After 14 days, Short Form-36 general health scores showed no differences between patients in the isoflurane and TIVA groups. Therefore, as intended, we conducted a cost identification analysis that focused on overall cost differences given equivalent clinical outcome. The additional cost per surgical session for TIVA when compared with isoflurane was $28.98 for inpatients and $14.87 for outpatients.

If we were to consider the transient reduction of PONV as a clinical end point, then cost-effectiveness analysis would be justifiable (with cost per additional patient free of PONV as the outcome measure). To avoid PONV in the first 24 h after surgery in one inpatient who would have suffered from PONV after isoflurane, six

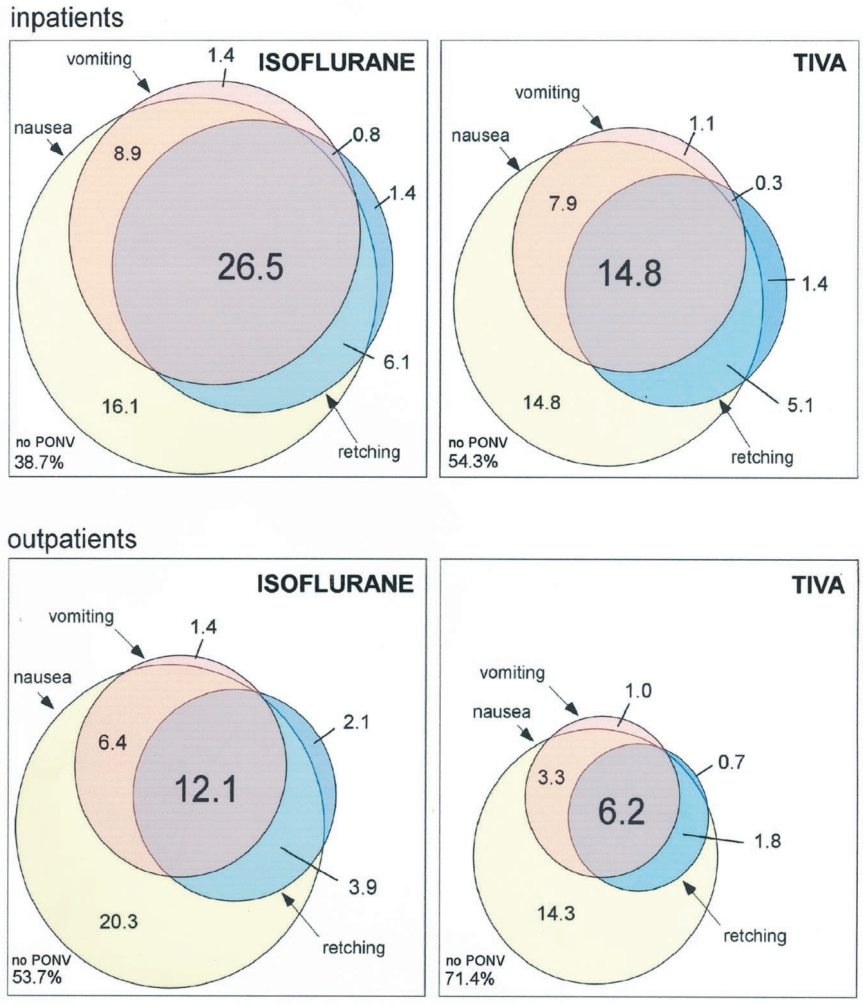

Fig. 3. The relative contribution of nausea, vomiting, and retching to the cumulative incidence of postoperative nausea and vomiting (PONV) at 72 h postoperatively. The area of each circle in the Venn diagrams corresponds to the frequency of the individual PONV component. Yellow circles = nausea; pink circles = vomiting; blue circles = retching. The total area of the square box surrounding each Venn diagram represents 100%. Note that the circles representing vomiting or retching are almost completely contained within the circle representing nausea, *i.e.*, vomiting without nausea is extremely rare. The combined outline of the three circles represents the cumulative incidence of PONV (nausea or vomiting or retching). Isoflurane patients received inhalational anesthesia with isoflurane–nitrous oxide after induction with thiopental (inpatients) or propofol (outpatients); total intravenous anesthesia (TIVA) patients received total intravenous anesthesia with propofol–air for induction and maintenance.

patients would have to receive TIVA (absolute risk reduction, 17; NNT = 6), totaling \$174 (\$29 × 6). Accordingly, to avoid PONV until 24 h in one outpatient, five patients would have to receive TIVA (absolute risk reduction, 20; NNT = 5), amounting to \$75.

Economic Implications for the Hospital. In 1998, 15,590 patients underwent surgery in the hospital under study. Approximately 7,770 of these patients were older than 18 yr and eligible to receive either isoflurane or TIVA. If all patients would have received TIVA, the additional cost of propofol for 1998 would have been \$225,218. The additional costs for TIVA are lower when the decreased use of antiemetics after TIVA is taken into account. When either metoclopramide or droperidol are used as primary antiemetic therapy, savings resulting from decreased use of antiemetics would amount to \$2,220 after TIVA, equaling 1% of the additional drug acquisition cost for propofol. If ondansetron, a more expensive antiemetic, would have been the first-choice antiemetic therapy, decreased use of antiemetics after TIVA would save \$6,324 in the cost of antiemetics.

Discussion

The cumulative incidence of PONV was significantly lower after TIVA than after isoflurane. Absolute risk reduction with TIVA was between 15 and 20% (NNT = 7–5) depending on duration of follow-up. Moreover, from the patients' perspective, TIVA was superior. The PONV reduction in the current study is in agreement with results from two recent metaanalyses that pooled data from several smaller studies comparing propofol with inhalational agents. Tramer *et al.*[6] and Sneyd *et al.*[7] found an NNT with propofol TIVA of 6 and 7, respectively, to prevent one early PONV incident (< 6 h). Our follow-up period was long compared with other PONV studies. The effect of the anesthetic technique was most prominent in the first 24 h after surgery (early PONV), whereas beyond that point the incidence of PONV increased equally in both groups. This suggests that anesthetic-induced PONV is most important in the first 24 h after surgery, whereas PONV resulting from the surgical procedure and postoperative analgesics dominates thereafter.

Power analysis was based on PONV incidences from the literature available at the time of study design.[12–16] The

Table 4. Number of Patients with Postoperative Nausea, Retching, or Vomiting, According to Surgery Type*

	Inpatients			Outpatients		
	Isoflurane	TIVA	*P* Value	Isoflurane	TIVA	*P* Value
Superficial surgery	n = 546	n = 516		n = 213	n = 216	
Discharge PACU/DCU	210 (39)	78 (15)	< 0.001	64 (29)	19 (8.8)	< 0.001
24 h	219 (40)	146 (28)	< 0.001	62 (28)	34 (16)	0.002
48 h	67 (12)	56 (11)	0.470	18 (8.2)	20 (9.2)	0.701
72 h	43 (7.9)	31 (6.0)	0.232	12 (5.5)	8 (3.7)	0.377
Intraabdominal surgery†	n = 64	n = 87				
Discharge PACU/DCU	26 (41)	26 (30)	0.170			
24 h	23 (36)	38 (44)	0.338			
48 h	21 (33)	25 (29)	0.591			
72 h	15 (23)	12 (14)	0.126			
Laparoscopic surgery	n = 52	n = 54		n = 51	n = 45	
Discharge PACU/DCU	22 (42)	14 (26)	0.075	21 (41)	16 (36)	0.572
24 h	18 (35)	15 (28)	0.447	17 (33)	9 (20)	0.142
48 h	9 (17)	11 (20)	0.687	7 (14)	5 (11)	0.765
72 h	4 (7.4)	4 (7.7)	1.000	5 (9.8)	2 (4.4)	0.442
Middle ear surgery	n = 45	n = 54		n = 6	n = 5	
Discharge PACU/DCU	26 (58)	10 (19)	< 0.001	1 (17)	0	1.0
24 h	24 (53)	23 (43)	0.287	2 (33)	3 (60)	0.567
48 h	9 (20)	6 (11)	0.219	0	1 (20)	0.455
72 h	6 (13.3)	4 (7.4)	0.505	0	1 (20)	0.455

* All values are shown as numbers of patients followed by rounded percentages (for values greater than 10%) in parentheses. Due to rounding, percentages may not total 100. Each patient with postoperative nausea and vomiting (PONV) is counted in the time period when PONV occurred, irrespective of previous PONV (*i.e.*, each patient can contribute several times to the PONV endpoint). Differences between isoflurane and total intravenous anesthesia (TIVA) tested using Pearson chi-square or Fisher exact test, as applicable. † No (intra)abdominal procedures were performed in outpatients.

Isoflurane group = inhalational anesthesia with thiopental, isoflurane, and nitrous oxide for inpatients, or propofol induction, isoflurane, and nitrous oxide for outpatients; TIVA group = total intravenous anesthesia with propofol–air; PACU = postanesthetic care unit; DCU = day care unit.

higher-than-expected PONV incidence increased the power of the study to detect a difference in PONV between TIVA and isoflurane. Moreover, the large sample size strengthens the results of subgroup analyses and the inference regarding the lack of difference in the incidence of complications between the TIVA and isoflurane groups.[17]

As expected, type of surgery was a major determinant of PONV frequency in both groups, and it modified the effect of the anesthetic technique on PONV. Patients undergoing superficial surgical procedures benefited most from TIVA (absolute risk reduction = 18%; NNT = 6). An unexpected finding was that, in the patients undergoing abdominal procedures, TIVA was unable to suppress the occurrence of PONV, although the number of intraabdominal procedures was relatively low. We cannot exclude that TIVA may suppress early PONV for intraabdominal procedures. For laparoscopic procedures, we were unable to detect a protective effect from TIVA. This finding has not been previously reported and refutes results from previous studies.[5] Demographic characteristics also affected the probability of PONV, with female gender and younger age predisposing toward higher incidence in both groups.

Various definitions of PONV have been used in studies on the effects of anesthetics and antiemetics, *e.g.*, nausea

Table 5. Median Intraoperative Volumes of Anesthetics (10th–90th Percentiles)*

	Inpatients		Outpatients	
	Isoflurane	TIVA	Isoflurane	TIVA
Minutes of anesthesia	122 (61–225)	115 (59–230)	62 (36–119)	64 (39–125)
Use of anesthetics				
Total use of propofol (mg)	NA	1,400 (700–2700)	200 (200–400)	1,000 (700–17)
Induction	NA	200 (140–330)	200 (160–300)	200 (150–36)
Maintenance	NA	980 (410–2,230)	NA	540 (270–11)
Spill†	NA	180 (30–400)	20 (0–150)	185 (40–410)
% of patients with spill > 200 mg (1 vial)	NA	42	1	40
Thiopental (mg)	440 (325–500)	NA	NA	NA
Isoflurane (g)	29.7 (13.2–67.0)	NA	15.15 (7.7–35.0)	NA
Nitrous oxide (l)	223.8 (81.0–578.6)	NA	96.69 (41.70–236.5)	NA

* Inpatients and outpatients in the total intravenous anesthesia (TIVA) groups received induction and maintenance of anesthesia with propofol–air. Inpatients in the isoflurane group received anesthesia induction with thiopental; maintenance was performed with isoflurane and nitrous oxide. Outpatients in the isoflurane group received anesthesia induction with propofol and maintenance with isoflurane and nitrous oxide. † Any propofol left in the infusion pump/syringe after completion of an anesthetic was not reused for the next patient but was thrown away. This "wasted" propofol was termed "spill."

only, nausea and vomiting, or vomiting only.[18,19] This has hampered interstudy comparability.[18] Because we scored nausea, retching, and vomiting independently, our data allowed for alternative end-point definitions. The Venn diagrams in figure 3 show that PONV is primarily determined by the presence of nausea. When vomiting and retching are combined and taken as one end point, the incidence of PONV is lower, but similar differences between isoflurane and TIVA remain. Accordingly, the results of the various possible PONV end points are comparable, provided that nausea is included.

The incidence of PONV in the current study was high. The reported incidence of PONV varies widely in the anesthesia literature, depending on setting and case mix (from $< 5\%$ to $> 50\%$).[16,20] Diversity in methods of data collection may also account for some of the observed differences. Emetic symptoms can be quantified as retrospective self-report, established through explicit questioning, or observed on site by a third party. As a consequence of the effects of both suggestion and increased detection, repeatedly questioning patients about PONV might result in a higher percentage of patients reporting PONV and receiving antiemetic therapy than would be the case in normal practice. In our study, blinded trial nurses did not communicate PONV findings to PACU nurses caring for patients, and PONV scores in the case report form were unavailable to PACU nurses.

One hypothesis at the outset of the study was that the results might reveal subgroups of patients who would benefit more from TIVA. This would allow identification of subgroups for whom TIVA could be especially advantageous. However, except for abdominal and laparoscopic procedures, TIVA proved beneficial to the same extent for all patient groups. Therefore, the practice of reserving TIVA for high-risk patients only seems unjustified.

Among inpatients, the study anesthetics consisted of induction with either propofol or thiopental, followed by TIVA or isoflurane. All outpatients received propofol for induction. If propofol used for anesthesia induction only were antiemetic, irrespective of the maintenance regimen, the magnitude of the reduction in relative risk among outpatients would have been less than actually occurred among outpatients in the current study. This finding supports results from a metaanalysis by Tramer *et al.*,[6] who showed that propofol for anesthesia induction followed by a nonpropofol maintenance technique did not result in PONV reduction.

The difference in airway management among the inpatients (more laryngeal mask airways in the propofol group) is probably caused by the fact that the ultimate selection of airway management may have been determined or altered after disclosure of the anesthetic allocation (TIVA is recommended in combination with the laryngeal mask airway). A recent study by Joshi *et al.*[21] showed that PONV was similar for patients with endotracheal tubes and laryngeal mask airways when an identical anesthetic technique was used. Therefore, the difference in airway management in the current study is not likely to be a confounding factor.

Many anesthesiologists add N_2O to propofol anesthesia because the additive effect allows for lower infusion rates, which reduces cost.[22,23] Furthermore, it has been suggested that supplementing TIVA with N_2O would reduce the incidence of awareness and recall (equal for both techniques in this study).[24] However, N_2O may increase the incidence of PONV.[25] A recent metaanalysis showed a pooled odds ratio for omitting N_2O of 0.63 (0.53–0.75, 95% confidence interval).[26] The current trial was not designed to determine to what extent PONV after inhalational anesthesia is caused by N_2O or isoflurane. If the treatments had consisted of propofol–N_2O *versus* isoflurane–N_2O, the treatment effect of TIVA might have been smaller.

The shorter length of stay at the PACU or DCU after TIVA (approximately 15 min) has also been reported by other investigators.[9,27,28] Patients without PONV were discharged from the PACU–DCU sooner after TIVA than after isoflurane. Our protocol required patients to remain in the PACU for at least 1 h. The observed 15-min shorter PACU times will probably not hold for procedures in which a patient can be discharged to the ward after 30 min. Although it would appear that faster recovery times directly decrease costs, it is difficult to convert these shorter PACU and DCU stays into economic gains. The flow through the operating rooms and PACU–DCU is a chained process; Dexter and Tinker[29] stated that "the major determinant of PACU costs is, by far, the distribution of admissions." Furthermore, a system of flexible staffing would be a necessity.[8,29] Therefore, in the setting of this study, it is unlikely that the PACU time with TIVA can be used to recover one additional patient or to reduce the number of PACU nurses by one. In a more homogeneous population with respect to type of surgery, and in case of brief standardized procedures, translation of shorter recovery after TIVA into economic gains is more likely. This could probably be best achieved in an office-based anesthesia setting or an ambulatory surgicenter.

At the time of the study, TIVA with propofol was two to three times more expensive than conventional anesthesia with isoflurane and N_2O when considering intraoperative costs only. Using the NNT, the costs of preventing PONV in one additional patient by using TIVA instead of isoflurane were \$174 in inpatients and \$75 in outpatients. A reduction of propofol acquisition cost by 65% would make TIVA equally expensive as isoflurane–N_2O in outpatients. For inpatients, a propofol cost reduction of 75% would make the cost of TIVA similar to that of isoflurane–N_2O. The patent on the current propofol emulsion (Diprivan, AstraZeneca Nederland, Zoetermeer, The Netherlands) has recently expired in The

Netherlands, resulting in a steep decrease of propofol acquisition cost (up to 75% reduction, depending on the formulation [1% *vs.* 2%] and type of packaging [prefilled syringes or glass vial]). With this unanticipated large cost decrease, several cost considerations have lost relevance (university setting, case mix, drug waste caused by the forced use of prefilled 50-ml syringes when using target controlled infusion pumps).

Because this study was conducted in a single academic institution, external validity (ability to generalize) is an issue. However, the study population comprised a large heterogeneous group of unselected patients and surgical procedures of varying duration, although very brief procedures were underrepresented. In addition, the design of this trial, apart from random assignment of TIVA or isoflurane and strict blinding procedures, did not interfere with current practice patterns. Therefore, our study patients and surgical procedures are comparable to those in other teaching institutions.

In conclusion, we have shown that propofol TIVA results in a reduction of PONV, particularly in the early postoperative period. TIVA increases patient comfort and patient ratings of anesthesia., while slightly reducing PACU and DCU discharge times. However, anesthesia costs were greater, and no clear economic gains were found.

The authors thank Wilco E. van Genderen, M.D. (Anesthesiologist, Medical Center Alkmaar, The Netherlands), and Lucilla E. Overdijk, M.D. (Anesthesiologist, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands), for constructive input in the design of this study, the team of research nurses for their enthusiasm and dedication, and the anesthesiologists and anesthesiology residents of the Academic Medical Center, University of Amsterdam, for their support and help with patient inclusion. Many thanks also to John Hartung, Ph.D. (State University of New York Health Science Center, Brooklyn, NY), whose careful editing of the manuscript was invaluable.

References

1. Borgeat A, Wilder-Smith OH, Saiah M, Rifat K: Subhypnotic doses of propofol possess direct antiemetic properties. Anesth Analg 1992; 74:539–41
2. Kalman SH, Jensen AG, Ekberg K, Eintrei C: Early and late recovery after major abdominal surgery: Comparison between propofol anaesthesia with and without nitrous oxide and isoflurane anaesthesia. Acta Anaesthesiol Scand 1993; 37:730–6
3. Raftery S, Sherry E: Total intravenous anaesthesia with propofol and alfentanil protects against postoperative nausea and vomiting. Can J Anaesth 1992; 39:37–40
4. Oddby-Muhrbeck E, Jakobsson J, Andersson L, Askergren J: Postoperative nausea and vomiting: A comparison between intravenous and inhalation anaesthesia in breast surgery. Acta Anaesthesiol Scand 1994; 38:52–6
5. Klockgether-Radke A, Piorek V, Crozier T, Kettler D: Nausea and vomiting after laparoscopic surgery: A comparison of propofol and thiopentone/halothane anaesthesia. Eur J Anaesth 1996; 13:3–9
6. Tramer M, Moore A, McQuay H: Propofol anaesthesia and postoperative nausea and vomiting: Quantitative systematic review of randomized controlled studies. Br J Anaesth 1997; 78:247–55
7. Sneyd JR, Carr A, Byrom WD, Bilski AJ: A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents. Eur J Anaesth 1998; 15:433–45
8. Marais ML, Maher MW, Wetchler BV, Korttila K, Apfelbaum JL: Reduced demands on recovery room resources with propofol (Diprivan) compared to thiopental-isoflurane. Anesth Rev 1989; 16:29–40
9. Wetchler BV, Alexander CD, Kondragunta RD: Recovery from the use of propofol for maintenance of anesthesia during short ambulatory procedures. Semin Anesth 1992; 11:20–2
10. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473–83
11. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E: Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51:1055–68
12. Lerman J: Surgical and patient factors involved in postoperative nausea and vomiting. Br J Anaesth 1992; 69:24S–32S
13. Bodner M, White PF: Antiemetic efficacy of ondansetron after outpatient laparoscopy. Anesth Analg 1991; 73:250–4
14. Green G, Jonsson L: Nausea: The most important factor determining length of stay after ambulatory anaesthesia. A comparative study of isoflurane and/or propofol techniques. Acta Anaesthesiol Scand 1993; 37:742–6
15. Hovorka J, Korttila K, Erkola O: Nitrous oxide does not increase nausea and vomiting following gynaecological laparoscopy. Can J Anaesth 1989; 36:145–8
16. Koivuranta M, Laara E, Snare L, Alahuhta S: A survey of postoperative nausea and vomiting. Anaesthesia 1997; 52:443–9
17. White PF, Watcha MF: Has the use of meta-analysis enhanced our understanding of therapies for postoperative nausea and vomiting? Anesth Analg 1999; 88:1200–2
18. Korttila K: The study of postoperative nausea and vomiting. Br J Anaesth 1992; 69:20S–3S
19. Andrews PL: Physiology of nausea and vomiting. Br J Anaesth 1992; 69:2S–19S
20. Sinclair DR, Chung F, Mezei G: Can postoperative nausea and vomiting be predicted? ANESTHESIOLOGY 1999; 91:109–18
21. Joshi GP, Inagaki Y, White PF, Taylor-Kennedy L, Wat LI, Gevirtz C, McCraney JM, McCulloch DA: Use of the laryngeal mask airway as an alternative to the tracheal tube during ambulatory anesthesia. Anesth Analg 1997; 85:573–7
22. Davidson JA, Macleod AD, Howie JC, White M, Kenny GN: Effective concentration 50 for propofol with and without 67% nitrous oxide. Acta Anaesthesiol Scand 1993; 37:458–64
23. Raeder JC: Total intravenous anaesthesia- free from nitrous oxide, free problems? Acta Anaesthesiol Scand 1994; 38:769–70
24. Tramer M, Moore A, McQuay H: Omitting nitrous oxide in general anaesthesia: Meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. Br J Anaesth 1996; 76:186–93
25. James MFM: Nitrous oxide: Still useful in the year 2000? Curr Opin Anaesthesiol 1999; 12:461–6
26. Divatia JV, Vaidya JS, Badwe RA, Hawaldar RW: Omission of nitrous oxide during anesthesia reduces the incidence of postoperative nausea and vomiting: A meta-analysis. ANESTHESIOLOGY 1996; 85:1055–62
27. Boldt J, Muller M, Uphus D, Hempelmann G: [Cost aspects in anesthesia: Propofol versus isoflurane anesthesia]. Anaesthesist 1996; 45:731–6
28. Phillips AS, Mirakhur RK, Glen JB, Hunter SC: Total intravenous anaesthesia with propofol or inhalational anaesthesia with isoflurane for major abdominal surgery: Recovery characteristics and postoperative oxygenation—An international multicentre study. Anaesthesia 1996; 51:1055–9
29. Dexter F, Tinker JH: Analysis of strategies to decrease postanesthesia care unit costs. ANESTHESIOLOGY 1995; 82:94–101