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Antiemetic Activity of Propofol after Sevoflurane and Desflurane Anesthesia for Outpatient Laparoscopic Cholecystectomy

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Background: **Controversy exists regarding the effectiveness of propofol to prevent postoperative nausea and vomiting. This prospective, randomized, single-blinded study was designed to evaluate the antiemetic effectiveness of 0.5 mg/kg propofol when administered intravenously after sevoflurane- compared with desflurane-based anesthesia.**

Methods: **Two hundred fifty female outpatients undergoing laparoscopic cholecystectomy were assigned randomly to one of four treatment groups. All patients were induced with intravenous doses of 2 mg midazolam, 2 μg/kg fentanyl, and 2 mg/kg propofol and maintained with either 1–4% sevoflurane (groups 1 and 2) or 2–8% desflurane (groups 3 and 4) in combination with 65% nitrous oxide in oxygen. At skin closure, patients in groups 1 and 3 were administered 5 ml intravenous saline, and patients in groups 2 and 4 were administered 0.5 mg/kg propofol intravenously. Recovery times were recorded from discontinuation of anesthesia to awakening, orientation, and readiness to be released home. Postoperative nausea and vomiting and requests for antiemetic rescue medication were evaluated during the first 24 h after surgery.**

Results: **Propofol, in an intravenous dose of 0.5 mg/kg, administered at the end of a sevoflurane–nitrous oxide or desflurane–nitrous oxide anesthetic prolonged the times to awakening and orientation by 40–80% and 25–30%, respectively. In group 2 (compared with groups 1, 3, and 4), the incidences of emesis (22% compared with 47%, 53%, and 47%) and requests for antiemetic rescue medication (19% compared with 42%, 50%, and 47%) within the first 6 h after surgery were significantly lower, and the time to home-readiness was significantly shorter in duration (216 ± 50 min *vs.* 249 ± 49 min, 260 ± 88 min, and 254 ± 72 min, respectively).**

Conclusions: **A subhypnotic intravenous dose of propofol (0.5 mg/kg) administered at the end of outpatient laparoscopic cholecystectomy procedures was more effective in preventing postoperative nausea and vomiting after a sevoflurane-based (compared with a desflurane-based) anesthetic. (Key words: Anesthetics; gases; intravenous; postoperative emesis.)**

AS a result of favorable emergence profiles and minimal residual sedation,[1,2] sevoflurane and desflurane have become commonly used volatile anesthetics for ambulatory surgery. However, it has been reported that the use of these newer inhalation agents is associated with a higher incidence of postoperative nausea and vomiting (PONV) when compared with a propofol-based anesthetic technique.[3,4] It has been suggested that prophylactic antiemetics are useful for outpatients undergoing procedures associated with a high incidence of PONV.[5,6] However, there is controversy regarding the antiemetic effectiveness of propofol when administered during general anesthesia.[7–11] Unfortunately, most of these studies were inadequately powered and used the traditional volatile anesthetics rather than the newer, less soluble agents desflurane and sevoflurane.

Based on the results of a preliminary PONV study involving commonly used antiemetic drugs,[12] it was hypothesized that the use of propofol would be more effective as a prophylactic antiemetic when administered during a sevoflurane-based (rather than a desflurane-based) anesthetic. This prospective, randomized, single-blinded study was designed to compare sevoflurane with desflurane, when supplemented with a subhypnotic dose of 0.5 mg/kg propofol administered intravenously at the end of surgery, with respect to their

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effects on PONV and recovery times in outpatients undergoing laparoscopic cholecystectomy.

Methods

After we obtained institutional review board approval, we enrolled 250 female outpatients who were classified as physical status 1 or 2 by the American Society of Anesthesiologists, were 18–65 yr old, and were scheduled for laparoscopic cholecystectomy. We excluded patients with a history of PONV, motion sickness, or gastroesophageal dysfunction; patients who had received antiemetic drugs within 24 h before anesthesia; patients who had nausea or vomiting within the preceding 24 h; or patients who were more than twice their ideal body weight. Based on a computer-generated random number, patients were assigned randomly to one of the following four treatment groups: sevoflurane–control, sevoflurane–propofol, desflurane–control, and desflurane–propofol.

After premedication with 2 mg midazolam administered intravenously, anesthesia was induced with 2 μg/kg fentanyl and 2 mg/kg propofol, both administered intravenously. Tracheal intubation was facilitated using 0.6 mg/kg rocuronium administered intravenously. After intubation, anesthesia was maintained with either 1–4% sevoflurane (the sevoflurane–control and sevoflurane–propofol groups) or 2–8% desflurane (the desflurane–control and desflurane–propofol groups) in combination with 65% nitrous oxide in oxygen. Muscle relaxation was maintained using 0.15 mg/kg intravenous rocuronium boluses. In addition, supplemental intravenous bolus doses of 50 μg fentanyl were administered to treat increases in mean blood pressure more than 30% of the preanesthesia baseline and/or heart rate more than 100 beats/min, despite increasing the inspired concentrations of sevoflurane and desflurane to 4% and 8%, respectively. At the time of skin closure, patients in the two control groups were administered 5 ml intravenous saline and the two propofol groups were administered 0.5 mg/kg intravenous propofol to prevent vomiting. All patients received 60 mg ketorolac (30 mg intravenously and 30 mg intramuscularly) at the end of surgery for postoperative analgesia. When the operation was completed, residual neuromuscular block was reversed with 50–80 mg edrophonium and 0.5–0.8 mg atropine intravenously, and the maintenance anesthetics were discontinued.

Emergence times were determined at 1-min intervals from discontinuation of the volatile agent to patient awakening (*i.e.*, opening eyes at verbal command) and orientation (*i.e.*, correctly stating the date, place, and person). The times to discharge from the postanesthesia care unit were assessed at 10-min intervals. The home-readiness criteria were evaluated at 15-min intervals using the modified postanesthesia recovery score (*i.e.*, $\geq$ 18).[13] Nausea, vomiting, and requests for rescue antiemetics (*e.g.*, 10–20 mg metoclopramide administered intravenously) were assessed by direct questioning of the patient at 10-min intervals in the postanesthesia care unit and at 30-min intervals in the phase 2 (step-down) unit. Requirements for postoperative analgesic medication (intravenous fentanyl or meperidine, oral hydrocodone) were recorded. The criteria for administering analgesic medication was a patient's request for pain relief or clinically obvious distress (indicated by moaning, for example).

After the patient was discharged from the hospital, follow-up telephone calls were made 6, 12, and 24 h after surgery. If the 12-h follow-up call could not be completed before 9:00 PM, it was made at 8:00 AM the following morning to inquire about emesis during the preceding 12-h interval. If the patient was admitted to the hospital overnight ("23-hour" admission), the assessments were made at hourly intervals for 3 h at the ward and subsequently 12 and 24 h after surgery. The criteria for overnight admission of patients to the hospital included surgical considerations (bile leakage, bleeding, placement of drains, fistula to adjoining structure), severe postoperative side effects (intractable PONV lasting more than 4 h), and miscellaneous factors (procedure completed late in the day, long travel distance). All the postoperative assessments were made by an independent "blinded" observer who was unaware of the primary maintenance anesthetic and prophylactic antiemetic therapy. If intractable PONV occurred after discharge, the patient was treated with rectal prochlorperazine.

A power analysis (α = 0.05, β = 80%) was performed before the study began. This analysis suggested that 49 patients in each group should be adequate to detect a 30% decrease in emesis among the groups (assuming a 60% incidence of emesis in the control groups). Differences in the time to the first emetic episode were analyzed using Kaplan–Meier analysis. Categoric data were analyzed by the chi-squared test, and continuous data were analyzed by one-way analysis of variance. The Newman–Keuls test

Table 1. Demographic Data, Anesthesia and Operating Times, Dosages of Fentanyl and Inhalation Agents, and Intravenous Fluid Volumes in the Four Anesthetic Treatment Groups

	Sevoflurane		Desflurane	
	Control (n = 62)	Propofol (n = 64)	Control (n = 60)	Propofol (n = 64)
Age (yr)	31 ± 8	32 ± 12	35 ± 12	35 ± 13
Weight (kg)	78 ± 13	77 ± 15	75 ± 19	77 ± 19
Anesthesia time (min)	128 ± 41	123 ± 40	120 ± 27	120 ± 30
Operating time (min)	99 ± 37	96 ± 39	94 ± 27	90 ± 27
Intraoperative fentanyl (μg)	224 ± 75	217 ± 97	217 ± 93	222 ± 103
Volatile anesthetic (MAC · h)	2.3 ± 1.0	2.5 ± 1.2	2.1 ± 1.1	2.1 ± 1.0
Intravenous fluids (ml)	1,743 ± 416	1,653 ± 466	1,583 ± 414	1,609 ± 499

MAC · h = sum of end-tidal concentration divided by the MAC value multiplied by the duration of time (hour) at that concentration.

Values are mean ± SD.

was used for *post hoc* comparisons among treatment groups. A probability value < 0.05 was considered significant.

Results

There were no significant differences among the four groups with respect to demographic characteristics, duration of anesthesia and surgery, intraoperative fentanyl dosage, volatile anesthetic requirements (*i.e.*, minimum alveolar concentration hour [calculated as the sum of end-tidal concentration divided by the minimum alveolar concentration value multiplied by the duration of time (hour) at that concentration]), and intraoperative fluids (table 1). Of the patients in each treatment group, 18–21% were admitted to the hospital overnight, but none of the unanticipated admissions were because of intractable PONV (table 2). The "rescue" pain medications administered during the first 6 h after surgery are summarized in table 3. No significant differences were found among the patients in the four groups with respect to postoperative analgesic requirements.

The times to awakening and orientation in the propofol prophylaxis groups were 2–4 min more ($P < 0.05$) than in the respective control groups. Although time to discharge from the postanesthesia care unit was similar in all treatment groups, the time to home-readiness for patients discharged on the day of surgery was significantly less in the sevoflurane–propofol group (table 2).

The incidence of PONV and requests for rescue antiemetics within the first 6 h, 6–12 h, and 12–24 h after surgery are summarized in table 4. The percentiles of the

Table 2. Recovery Times and Need for Overnight Hospitalizatin after Laparoscopic Cholecystectomy in the Four Anesthetic Treatment Groups

	Sevoflurane		Desflurane	
	Control (n = 62)	Propofol (n = 64)	Control (n = 60)	Propofol (n = 64)
Awakening (min)	5 ± 3	9 ± 3*	5 ± 1	7 ± 3†
Orientation (min)	12 ± 4	15 ± 4*	10 ± 2	13 ± 5†
PACU discharge (min)	75 ± 2	81 ± 9	82 ± 8	78 ± 6
Home readiness (min)				
(same-day discharge only)	249 ± 49	216 ± 50‡	260 ± 88	254 ± 72
Hospital admission (23 h)				
Bile leak spillage (n)	7	6	8	9
Bleeding (n)	3	5	3	1
Drainage (n)	0	0	0	1
Social reasons (n)	3	1	0	2

Values are mean ± SD and numbers (n).

* $P < 0.05$ *versus* the sevoflurane and desflurane control groups.

† $P < 0.05$ *versus* the desflurane control group.

‡ $P < 0.05$ *versus* the sevoflurane control group.

Table 3. Rescue Pain Medication during the First 6 h after Laparoscopic Cholecystectomy in the Four Anesthetic Treatment Groups

	Sevoflurane		Desflurane	
	Control (n = 62)	Propofol (n = 64)	Control (n = 60)	Propofol (n = 64)
Intravenous fentanyl [n (μg)]	12 (63 ± 29)	18 (44 ± 25)	18 (54 ± 24)	16 (56 ± 25)
Intravenous meperidine [n (mg)]	7 (43 ± 12)	9 (33 ± 11)	12 (44 ± 11)	10 (40 ± 13)
Oral hydrocodone [n (mg)]	21 (7 ± 3)	16 (6 ± 3)	12 (6 ± 2)	18 (8 ± 3)
Total patient received analgesics (n)	36	39	35	34

Values are patient number (n) and average analgesic dosage (μg or mg) administered (mean values ± SD). There are no significant differences among the four groups.

Kaplan–Meier product-limit distribution of the times to the first emetic episode showed that times until 25% of patients experienced emesis were 0.7, 3.5, 0.3, and 0.7 h in the sevoflurane–control, sevoflurane–propofol, desflurane–control, and desflurane–propofol groups, respectively (fig. 1). The sevoflurane–propofol group had a significantly ($P < 0.01$) decreased incidence of PONV and fewer requests for rescue antiemetic within the first 6 h after surgery when compared with the other three treatment groups. However, there were no differences between the desflurane–control and desflurane–propofol groups with respect to the incidences of PONV or the need for antiemetic rescue during the 24-h follow-up period. Finally, there were no significant differences among the four treatment groups with respect to the incidence of PONV and use of antiemetic rescue medications from 6–24 h after surgery.

Discussion

Controversy exists regarding the antiemetic effectiveness of subhypnotic doses of propofol when used in outpatients at high risk for PONV. Although Campbell and Thomas[11] reported that a subanesthetic dose of propofol administered at the end of surgery had no antiemetic effect in patients undergoing laparoscopy using an isoflurane-based anesthetic, other studies[7–9] suggested that a low dose of propofol was effective in preventing PONV after either an isoflurane- or an enflurane-based anesthetic. Recently, Gan *et al.*[10] reported that use of propofol as an induction agent and at the end of surgery during isoflurane-based anesthesia failed to prevent PONV in patients undergoing breast surgery compared with using propofol both for induction and maintenance of anesthesia. In addition, Scuderi *et al.*[14] reported that a low-dose infusion of propofol similarly failed to show any beneficial effect in reducing PONV when used as the sole prophylactic medication in female patients undergoing outpatient laparoscopy using an isoflurane-based anesthetic technique.

In the current study, propofol had significant antiemetic activity when administered at the end of surgery with sevoflurane anesthesia but not when it was administered in conjunction with desflurane anesthesia. To detect an effect of propofol after desflurane in this patient population, a much larger group would be necessary. The failure of propofol to more effectively protect against PONV after desflurane anesthesia is consistent with the findings of Van Hemelrijck *et al.*[3] when propofol was administered for induction followed by desflurane for maintenance of anesthesia. Of interest, a previous study involving the use of sevoflurane and propofol

Table 4. The Incidence of Postoperative Nausea and Vomiting and Requests for Rescue Antiemetic Medication in the Four Anesthetic Treatment Groups during the First 24 H after Laparoscopic Cholecystectomy

	Sevoflurane		Desflurane	
	Control (n = 62)	Propofol (n = 64)	Control (n = 60)	Propofol (n = 64)
Within 6 h				
Nausea	36 (60)	20 (31)*	41 (68)	34 (53)
Vomiting	29 (47)	14 (22)*	32 (53)	30 (47)
Rescue	26 (42)	12 (19)*	30 (50)	30 (47)
6–12 h				
Nausea	19 (31)	17 (27)	26 (43)	22 (34)
Vomiting	14 (23)	12 (19)	19 (32)	16 (25)
Rescue	0 (0)	0 (0)	0 (0)	0 (0)
12–24 h				
Nausea	9 (15)	10 (16)	12 (20)	14 (22)
Vomiting	5 (8)	6 (9)	6 (10)	8 (13)
Rescue	0 (0)	0 (0)	0 (0)	0 (0)
Overall PONV	38 (61)	22 (34)*	41 (68)	37 (58)

PONV = postoperative nauseau and vomiting. Values are number (n) and percent (%) within each treatment group.

* $P < 0.05$ *versus* the other three treatment groups.

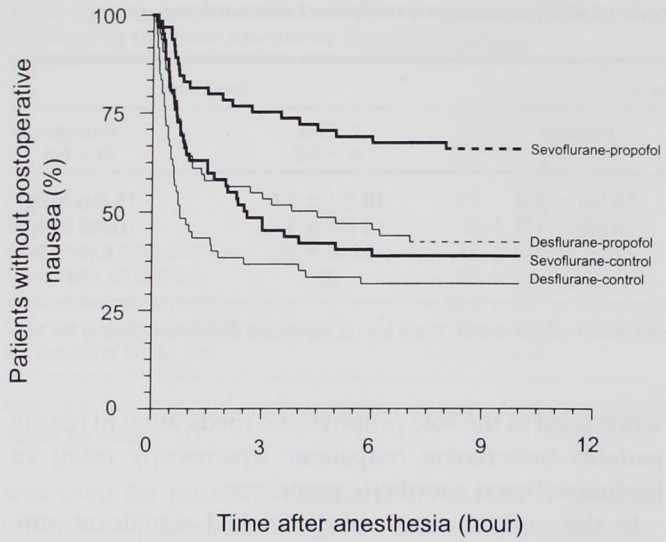

Fig. 1. Distribution of times to the first episode of postoperative nausea and/or vomiting in the four anesthetic treatment groups. Thick solid line = sevoflurane-control group; thick dashed line = sevoflurane-propofol group; fine solid line = desflurane-control group; fine dashed line = desflurane-propofol group.

showed that the use of propofol to induce anesthesia was effective in reducing PONV after sevoflurane anesthesia in outpatients undergoing laparoscopic surgery.[4] However, although the small dose of propofol (0.5 mg/kg) administered at the end of surgery prolonged the times to awakening and orientation, the time to discharge from the postanesthesia care unit was not delayed. More importantly, the times to home-readiness for discharge were decreased for patients receiving a subhypnotic dose of propofol after a sevoflurane-based anesthetic.

It has been suggested that there is little difference between sevoflurane and desflurane with respect to the intrinsic emetogenic potential compared with other inhalation anesthetics.[15,16] In a recent study, Philip *et al.*[17] reported a significantly lower incidence of postoperative nausea both in the postanesthesia care unit and in the 24-h postdischarge period after sevoflurane–nitrous oxide anesthesia compared with isoflurane–nitrous oxide anesthesia. The current study suggests that sevoflurane is more advantageous than desflurane in preventing PONV only when propofol was administered at the end of surgery. Therefore, these data suggest that a more favorable drug interaction occurs between sevoflurane and propofol than between desflurane and propofol with respect to antiemetic prophylaxis, and this combination may contribute to an earlier discharge after outpatient procedures associated with a high incidence of PONV (*e.g.*, laparoscopic cholecystectomy). Unfortunately, a scientific explanation for this difference is not available.

Decreasing the incidence of PONV after sevoflurane and desflurane anesthesia is important in facilitating early recovery after ambulatory surgery. Although prophylactic antiemetics have proven to be useful in decreasing the incidence of PONV in outpatients at high risk of PONV after desflurane anesthesia,[18] the optimal combination of antiemetic and inhalation agents is yet to be determined. Achieving a more effective outcome with respect to PONV will become increasingly important in the future as a result of increasing pressure to decrease discharge times (*i.e.*, fast track)[19,20] and to reduce unanticipated hospital admissions after ambulatory surgery.[19–21]

In conclusion, use of propofol (2 mg/kg administered intravenously) for induction followed by a second dose (0.5 mg/kg administered intravenously) after laparoscopic cholecystectomy is more effective in preventing PONV with sevoflurane than desflurane. None of the patients in either the desflurane or the sevoflurane groups required overnight hospital admission because of intractable PONV.

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