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Randomized comparison of two anti-emetic strategies in high-risk patients undergoing day-case gynaecological surgery

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Background. Postoperative nausea and vomiting (PONV) is a significant cause of morbidity among patients undergoing general anaesthesia. The optimal strategy for prevention of PONV, however, remains unclear. This study compared two commonly used prophylactic strategies in high-risk, day-case, gynaecological surgery patients.

Methods. We conducted a randomized trial comparing sevoflurane combined with dolasetron (SD), with propofol-based total intravenous anaesthesia (TIVA) in 126 high-risk patients undergoing day-case gynaecological surgery. The primary endpoints included the incidence and severity of nausea or vomiting before discharge and the incidence of nausea or vomiting between discharge and 24 h. To identify the factors most predictive of a complete response (no PONV at any time within the 24 h period), multiple logistic regression models were fitted.

Results. Before discharge, there was no significant difference between the two treatment groups with respect to nausea and vomiting outcomes ($P=0.3$). Post-discharge nausea and vomiting (PDNV), however, were significantly more common for patients in the TIVA group (nausea, $P=0.004$ and vomiting, $P=0.03$). Type of anaesthetic, adjusted for weight and anaesthesia duration was significantly associated with complete response (odds ratio=2.7, 95% confidence interval=1.15 to 6.4).

Conclusions. Although both TIVA and dolasetron prophylaxis reduce the predicted rate of PONV in the early postoperative period, the anti-emetic effects of propofol are short-lived. A longer-acting drug such as dolasetron may therefore be necessary to prevent PDNV.

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Postoperative nausea and vomiting (PONV) is a significant cause of morbidity in patients undergoing general anaesthesia.[1] It can be particularly problematic in patients undergoing day-case surgery as it may lead to delays in discharge, unscheduled admissions, and complications such as wound dehiscence and aspiration.[2] PONV is the anaesthetic complication of most concern to patients[3] and continues to be a significant concern for the anaesthesiology profession. This is evidenced by the numerous studies, reviews, and guidelines in publication.

The risk of PONV varies from patient to patient and should be estimated preoperatively in order to initiate appropriate management. Multiple factors are associated with an increased incidence of PONV, including patient, anaesthetic, and surgical factors.[4] In order to simplify risk assessment, Apfel and colleagues developed a score-based prediction tool. The presence of two or more factors (out of a possible four) identifies a high-risk patient with an incidence of PONV ranging from 39% to 79%.[5]

The optimal strategy for preventing PONV continues to be debated. Although global prophylaxis for PONV is

generally not recommended,[6 7] it has demonstrated cost-effectiveness in high-risk groups.[8] Women undergoing day-case gynaecological surgery represent one such high-risk group.[4] Unfortunately, this subgroup of patients has been under-studied, particularly with reference to PONV after discharge from hospital.[9]

Our study aimed to compare two commonly used prophylactic strategies: sevoflurane combined with dolasetron (SD) and propofol-based total intravenous anaesthesia (TIVA) in high-risk patients undergoing day-case gynaecological surgery. Our primary endpoints were two-fold; namely, the incidence and severity of nausea or vomiting before discharge and the incidence of post-discharge nausea or vomiting (PDNV). This is defined as PONV between discharge and 24 h. Secondary endpoints included the duration of anaesthesia, the length of hospital stay, and the number of unscheduled admissions. We also aimed to identify factors predictive of PONV at any time within the 24 h postoperative period.

Methods

After ethics-committee approval, written informed consent was obtained from 126 women undergoing gynaecological day procedures at the Queen Elizabeth II Jubilee Hospital (Coopers Plains, Queensland, Australia) between July and December 2005.

Inclusion criteria stipulated patients undergo gynaecological day surgery and be considered high risk (>40%) for PONV. This was assessed according to Apfel's[5] simplified risk score that uses the following risk factors: female sex (all patients), non-smoker, previous history of PONV or motion sickness, and anticipated post operative opioid requirement. Exclusion criteria were ASA grade IV or above, age less than 18 yr, planned admission, known allergy to study drugs, pregnancy, and refusal, or inability to give informed consent.

Subjects were randomized to one of two groups: sevoflurane plus dolasetron (SD) or propofol TIVA using a computer-based random number generator with results placed into consecutively numbered, sealed opaque envelopes. The envelopes were opened before induction of anaesthesia by the anaesthetist responsible for the case, with patients blinded to their group allocation. Patient demographic data recorded preoperatively included age, ASA status, weight, and surgical procedure. A group receiving inhalation anaesthetic without dolasetron was not included, as we did not consider it ethical in high-risk patients.[10]

All patients had an i.v. line inserted and 1 litre of either compound sodium lactate or 0.9% normal saline, commencing in the preoperative holding-area. Premedications (salbutamol 5 mg nebule or sodium citrate 8.8%, 30 ml) were administered as appropriate. Patients in the TIVA group were induced and maintained using a propofol infusion with target serum concentration 2–8 $\mu g\,ml^{-1}$. This was administered by a target-controlled infusion device (Graseby-Diprifusor 3500, Smith Medical, Hythe, Kent, UK). The TIVA group did not receive any further intraoperative anti-emetic medication. Patients in the SD group were induced with propofol 1.5–2.5 $mg\,kg^{-1}$. Maintenance of anaesthesia was achieved using an oxygen/air/sevoflurane mixture. Dolasetron 12.5 mg was administered intravenously before end of surgery as the sole intraoperative anti-emetic. Clinical parameters were used to titrate both propofol and sevoflurane to an adequate depth of anaesthesia.

All patients were monitored during anaesthesia according to standards of the Australian and New Zealand College of Anaesthetists.[11] Before induction of anaesthesia, patients in both groups received i.v. midazolam 0–3 mg and fentanyl 0–200 μg at the discretion of the attending anaesthetist. After induction, airway maintenance was achieved with either a laryngeal mask airway or tracheal tube as appropriate. A neuromuscular blocking drug of the attending anaesthetist's choice facilitated endotracheal intubation and mechanical ventilation if required. Patients not requiring neuromuscular block were allowed to breathe spontaneously. Neuromuscular reversal (neostigmine 2.5 mg and either atropine 1.2 mg or glycopyrrolate 0.4 mg) was administered as necessary. All patients received analgesia with acetaminophen and an anti-inflammatory agent at the end of surgery. Adjuvant opioids were administered at the discretion of the anaesthetist.

Postoperatively, patients were transferred to the post-anaesthesia care unit (PACU). Nursing staff were not aware of allocation groups, but the anaesthetic chart could be accessed if required. The highest pain and nausea/vomiting score for each 30 min interval were recorded. Pain was scored using a visual analogue system. Nausea and vomiting were recorded according to a four-point scale routinely used in our PACU (0= no nausea, 1= occasional nausea, 2= persistent nausea requiring treatment, and 3=vomiting). Postoperative analgesia was provided with i.v. opioids and simple oral analgesics as considered appropriate by the attending anaesthetist. Rescue anti-emetics were administered according to a standardized protocol. First line rescue treatment was with ondansetron 4 mg i.v. If the patient did not respond to initial treatment this was followed by i.m. administration of prochlorperazine 12.5 mg, with third line treatment being dexamethasone 4 mg i.v. Patients were transferred to the day-surgery unit on meeting PACU discharge criteria.

Pain, nausea, and vomiting, and their necessary treatments, were recorded at 30 min intervals in the day-surgery unit until home discharge criteria were met. The time of first postoperative meal was recorded. Unplanned admissions either from PACU or the day-surgery unit were noted, as was the reason for admission.

All patients received a phone call 24 h postoperatively to determine the presence or absence of PDNV and any treatment administered.

Statistical methods

Analysis was performed by SAS, version for Windows 9.1 (SAS Institute, Cary, NC, USA). All patients were analysed on an intention to treat basis. Categorical data were compared using chi-square or Fisher's exact test. Continuous data were non-normally distributed and were compared using Wilcoxon 2-sample test. Time-to-event outcomes were compared using Kaplan–Meier survival curves and log-rank test. Logistic regression was used for multiple regression analysis of the binary outcome complete response. A patient was defined to have a complete response if they had no nausea, vomiting, or nausea medication for 24 h after surgery. Backwards elimination was used to determine the best multiple logistic model for complete response. A cutoff *P*-value of >0.05 was used to discard variables from the model. Variables considered for inclusion in the best model included treatment group and all baseline and standard treatment variables, including time-related surgery variables. A *P*-value of <0.05 is considered significant. Sample size was chosen to detect a reduction in the incidence of nausea and vomiting from 50% with inhalation anaesthesia to 25% with propofol-based TIVA, with a corrected type I error rate of 5% and power of 80%.[12]

Results

One hundred and twenty six patients were randomized to either TIVA (n=58) or SD (n=68). Four protocol violations were noted, one patient randomized to SD (no dolasetron given) and three patients randomized to TIVA [dolasetron given (two patients), dexamethasone given before prochlorperazine (one patient)].

The two groups appeared well balanced with respect to baseline characteristics and standard treatment variables (Tables 1 and 2). Intraoperative time variables and postoperative time-related outcomes were generally lower for the SD group; however, only surgical duration reached statistical significance (Tables 3 and 4). Unexpected admissions were similar for the two groups (P=0.5). There were 6 (9%) admissions in the SD and 3 (5%) in the TIVA group.

Pain scores were similar for the two groups and resolved for most patients within 2 h after surgery (Fig. 1). The maximum pain level was also comparable (P=0.2). The median (range) for the SD group was 1 (0, 10) compared with 3 (0, 10) for the TIVA group. This result was supported by a corresponding use of analgesics (Table 5).

During the period before discharge, there was no significant difference between the two treatment groups with respect to nausea and vomiting outcomes (Tables 6 and 7, Fig. 2). PDNV, however, were significantly more common in patients from the TIVA group (Tables 6 and 7). Consequently, there were significantly less patients with a complete response in the TIVA group. This effect remained significant in an adjusted-logistic regression-analysis (Table 8). The adjusted odds ratio of 2.7 suggests that patients in the SD group have 2.7 times the odds of experiencing a complete response compared with those patients in the TIVA group.

In order to compare risk factors in our population with previous studies, multiple logistic regression models were fitted. Of note is that the treatment effect estimate was similar to that estimated via an unadjusted analysis. A number of variables were associated with complete response univariately, including laparoscopic surgery and amount of morphine given. However, only the type of anaesthetic, weight of the patient, and duration of the anaesthesia were associated with complete response multivariately (Table 8).

Table 1 Comparison of baseline characteristics. IQR, inter-quartile range. *Hysteroscopy, dilation, and curettage. **Laparoscopy. ***Large loop excision of transformation zone

Variable	SD *n* (%)	TIVA *n* (%)
Procedure		
HDC*	16 (24)	20 (35)
LAP**	9 (13)	7 (12)
LAP + other	17 (25)	12 (21)
LLETZ***	12 (18)	3 (5)
Other	14 (21)	16 (27)
ASA grade		
I	36 (53)	34 (58)
II	29 (43)	23 (40)
III	3 (4)	1 (2)
Age in years median (IQR)	37 (31, 45)	39.5 (32, 48)
Weight in kg median (IQR)	71 (61, 88)	68 (57, 78)

Table 2 Drugs and devices used as part of the standard intraoperative treatment. IQR, inter-quartile range. *The number of patients receiving the drug *vs* those not receiving the drug

Variable	SD *n* (%)	TIVA *n* (%)
Morphine given*	13 (19)	14 (24)
Paralysis	26 (38)	19 (33)
Reversal	22 (32)	19 (33)
Pre-medication	8 (12)	6 (10)
Airway		
LMA	49 (72)	40 (69)
ETT	18 (27)	18 (31)
Spontaneous ventilation	36 (53)	34 (59)
Midazolam given*	65 (96)	57 (98)
Fentanyl given*	65 (96)	53 (91)
Midazolam (total dose) median (IQR)	2.5 (2, 2.5)	2.5 (2, 2.5)
Fentanyl (total dose) median (IQR)	100 (75, 100)	100 (75, 100)

Table 3 Intraoperative time variables in minutes. *Data presented as median (inter-quartile range)

Variable	SD*	TIVA*	*P*-value
Anaesthesia duration	32 (24, 50)	38.5 (26, 59)	0.09
Surgical duration	16.5 (12, 30)	22 (14, 34)	0.046
Time from end of surgery to end of anaesthetic	4 (3, 7)	4 (2, 7)	0.7

Table 4 Postoperative time related outcomes in minutes. *Data presented as median (inter-quartile range)

Variable	SD*	TIVA*	*P*-value
Time in PACU	37 (30, 45)	40 (35, 50)	0.1
Time in day surgery	85 (60, 100)	90 (60,120)	0.7
Time to first meal	100 (83, 120)	110 (85, 140)	0.15
Time from PACU till readiness for discharge	179 (152, 233)	202 (167, 253)	0.13

Table 5 Postoperative use of analgesics. *Acetaminophen and codeine

Variable	SD *n (%)*	TIVA *n (%)*	*P*-value
Fentanyl	6 (9)	5 (9)	0.9
Morphine	8 (12)	13 (22)	0.1
Panadeine forte*	7 (10)	8 (14)	0.5
Acetaminophen	1 (1)	1 (2)	0.9
NSAID	0 (0)	0 (0)	—
Other drug	3 (4)	5 (9)	0.3

Finally, in order to investigate the problems of recurrent PONV and PDNV, pooled data were examined. Of the patients who experienced PONV at any time, 39% experienced PONV both pre- and post-discharge, whereas 28% experienced PDNV alone.

Discussion

Day-case surgery is becoming more common with up to 60% of patients currently admitted on the day of surgery.[13] Despite numerous publications and guidelines, PONV is still the most common reason for poor patient satisfaction in the postoperative period.[3] There are many reasons for this; lack of understanding of the mechanisms involved, difficulties in estimating the risk in individual patients, lack of a 'gold-standard' anti-emetic intervention, and variability of dose–response relationships for current interventions. In an attempt to avoid PONV, there is an inclination to provide all patients with anti-emetic prophylaxis. This is impractical, not cost-effective and unlikely to benefit low-risk patients while placing them at risk of potential side-effects.[6 14] Another common practice is to only treat patients once they become symptomatic. Treatment of established nausea and vomiting, however, has been demonstrated as inferior to prophylaxis.[15 16]

Women undergoing day-case gynaecological surgery are at particular risk of PONV.[17] Despite these findings, few studies have investigated ambulatory gynaecological patients, with publications limited to laparoscopic procedures. Studies investigating PONV often include gynaecological patients as a subgroup and may therefore not be powered to detect significant differences in outcomes. In addition, few authors have examined PONV in ambulatory patients after discharge from hospital.[7] Tramer[9] noted the need for randomized trials of reasonable size in subgroups of patients who represent daily clinical practice. Our study was designed to reflect the day-to-day practice of clinicians who manage ambulatory gynaecological patients.

The premise of our study was that TIVA would be more effective at preventing PONV as compared with sevoflurane and dolasetron. However, our data revealed that both prophylactic regimens demonstrated equal efficacy in the early postoperative period. Other authors support this finding. Paech and colleagues[18] conducted a randomized trial comparing TIVA alone, TIVA plus dolasetron, and inhalation anaesthesia plus dolasetron in 144 patients undergoing day-case gynaecological laparoscopy. They found no difference between groups with respect to complete response and use of rescue anti-emetics in the period

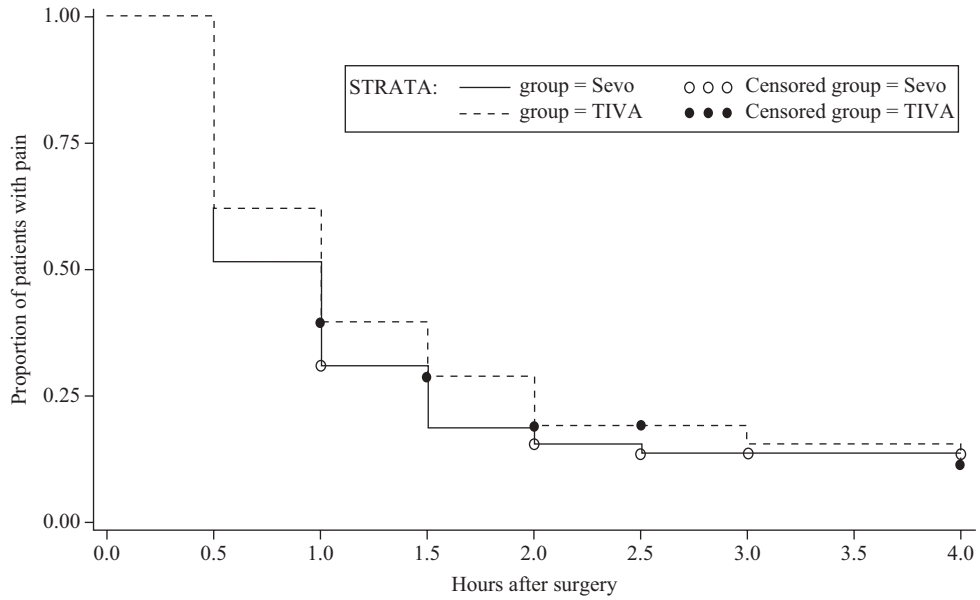

Fig 1 Number of hours after surgery to pain resolution (log-rank $P=0.3$).

Table 6 Use of nausea-relieving drugs and other nausea outcomes

Variable	SD *n* (%)	TIVA *n* (%)	*P*-value
Ondansetron	12 (18)	14 (24)	0.4
Prochlorperazine	5 (7)	3 (5)	0.6
Dexamethasone	2 (3)	5 (9)	0.2
Nausea or vomiting before discharge	16 (24)	18 (31)	0.3
Nausea only before discharge	12 (18)	12 (21)	0.7
Vomiting before discharge	4 (6)	6 (10)	0.5
Post-discharge nausea	10 (15)	21 (37)	0.004
Post-discharge vomiting	6 (9)	13 (23)	0.03
Complete response	49 (72)	30 (52)	0.019

before discharge. Habib and colleagues[19] conducted a randomized trial of 90 patients undergoing laparoscopic cholecystectomy. There was no significant difference in complete early response between the TIVA group and the group receiving inhalation anaesthesia. It should be noted that both authors included nitrous oxide as part of the inhalation anaesthesia

In one of the largest studies to date, Apfel and colleagues[20] investigated PONV in a diverse group of high-risk patients. They found that irrespective of the anti-emetic used, the incidence of PONV was similar among groups (37%). They also noted an additive effect when more than one strategy was employed. Similar results can be demonstrated with newer inhalation agents.[21] These studies suggest that TIVA and $5HT_3$ antagonists are equally efficacious in preventing early PONV.

The separation of PONV into early (pre-discharge) and late (PDNV) has not been well studied. PDNV is common (and under-reported) after anaesthesia, with an incidence of 30–50%.[22 23] In addition, our data demonstrate that many patients experience PONV for the first time after discharge. It is important to consider and prevent PDNV for two reasons: first, patients' resumption of normal activities and readiness for work may be delayed and secondly, ambulatory patients are not under direct medical supervision after their discharge.[24] Similar to early PONV, postoperative administration of anti-emetics is of limited efficacy in preventing PDNV,[15 16] highlighting the importance of considering PDNV in any PONV prophylactic strategy.

Table 7 Nausea scores by hours after surgery

Hours after surgery	Nausea score	SD *n* (%)	TIVA *n* (%)	*P*-value
0.5	0	61 (90)	51 (88)	0.7
	1	0 (0)	1 (2)	
	2	6 (9)	5 (8)	
	3	1 (1)	1 (2)	
1–1.5	0	62 (91)	48 (84)	0.2
	1	3 (4.5)	1 (2)	
	2	3 (4.5)	7 (12)	
	3	0 (0)	1 (2)	
2–2.5	0	52 (90)	42 (82)	0.6
	1	1 (2)	3 (6)	
	2	3 (5)	3 (6)	
	3	2 (3)	3 (6)	
3–4	0	10 (55)	12 (67)	0.7
	1	3 (17)	2 (11)	
	2	3 (17)	1 (5)	
	3	2 (11)	3 (17)	
Post discharge and within 24 h	0	58 (85)	37 (64)	0.002
	1	1 (2)	8 (14)	
	2	3 (4)	0 (0)	
	3	6 (9)	13 (22)	

In the past, clinicians have relied on the assumption that prophylactic strategies used to prevent PONV will also be effective in preventing PDNV. The results of our study challenge this assumption. In contrast to our results in the early postoperative period, we found a significant reduction in PDNV in the SD group compared with the group receiving TIVA. This was true for both post-discharge nausea alone, post-discharge vomiting alone, and the overall nausea or vomiting score (Tables 6 and 7).

Several other authors have investigated the question of whether PDNV needs to be considered distinct from early PONV. Apfel and colleagues[15] conducted a randomized, controlled trial of 1180 patients at high risk of PONV. Early PONV (<2 h) and late PONV (2–24 h) were examined separately. Results revealed that late PONV had different risk factors to early PONV. The only predictors of late PONV were early PONV, children compared with adults, and postoperative opioid use. In addition, anaesthetic technique (inhalation *vs* TIVA) was not a risk factor for late PONV, even though it was strongly predictive of early PONV. To further support this, Tramer and colleagues[25] performed a systematic review of 84 randomized, controlled trials comparing propofol with inhalational agents. They found that propofol infusions only had a clinically significant effect on PONV rates in high-risk patients and only for early PONV.

In contrast, Paech and colleagues[18] found post-discharge nausea to be more common after balanced inhalation anaesthesia plus dolasetron when compared with propofol TIVA with or without dolasetron. However, their inhalation group received nitrous oxide, potentially predisposing them to PONV. Interestingly, when they compared the TIVA group with the TIVA plus dolasetron group, there was a trend towards greater complete response in the TIVA plus dolasetron group, but the study was not adequately powered to detect this.

The pathophysiology of PDNV as distinct to early PONV remains an area for further investigation. However, it is clear that with different risk factors and different response to prophylaxis, PDNV deserves consideration in its own right. That propofol TIVA should be effective for early PONV but not PDNV may be explained by the pharmacokinetics of propofol infusions. It has been shown that a minimum plasma concentration of propofol is necessary to produce an anti-emetic effect.[26] As propofol has a short, context-sensitive half-time (less than 40 min for infusions up to 8 h),[27] significant plasma-levels would be unlikely after several hours. As a result, propofol may

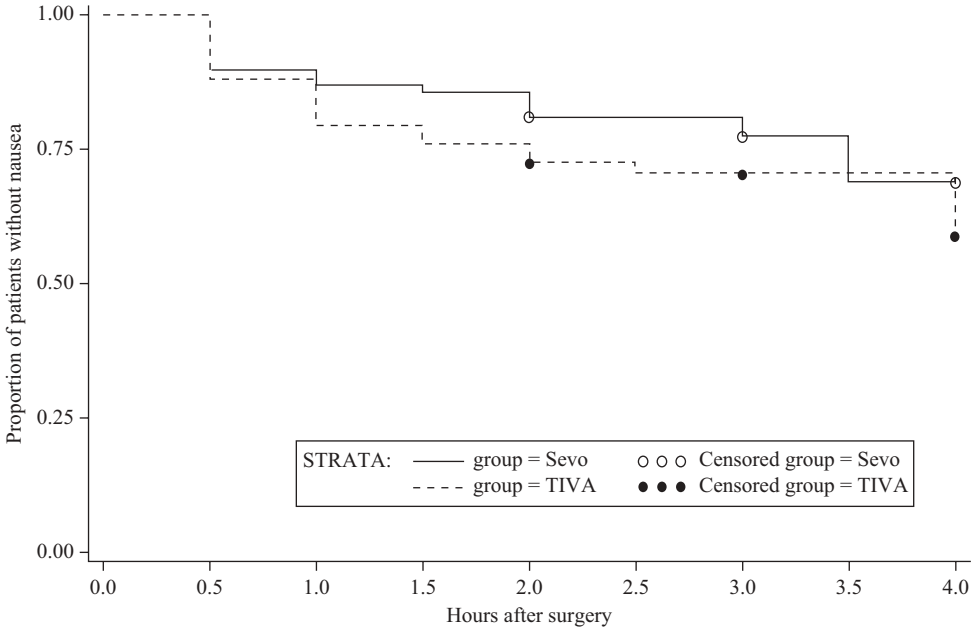

Fig 2 Number of hours after surgery until first occurrence of nausea (log-rank P=0.3).

need to be considered a prophylactic option for early PONV only.

Controversy remains over exactly which risk factors are most predictive of PONV. Other factors that have been associated with PONV include type of surgery, choice of opioid, patient-age, and length of surgery.[4 17 28] Despite the lack of high level evidence, the consensus guidelines for managing PONV suggest that a surgical duration of longer than 30 min and the type of surgery are important determinants.[6] In opposition to this, Apfel and colleagues[5 28] found that the type of surgery did not alter risk of PONV when corrected for the major risk factors. Although our study was not powered to definitively assess risk, we felt it would be of interest to compare our population with other patient populations.

Our findings in this regard were similar to other authors. Our data suggested that in addition to treatment group, weight of the patient and duration of anaesthesia were positively correlated with PONV. Evidence for duration of anaesthesia as a risk factor is supported by Apfel and colleagues[20] in their recent large, multicentre trial. They report an increased risk of PONV with every hour of anaesthesia duration with an odds ratio of 1.2. Volatile anaesthetics may be particularly significant in this respect. Another study by Apfel and colleagues[15] found that postoperative vomiting was directly related to the duration of exposure to volatile anaesthetic agents, with an odds ratio of 1.8 h^{-1} of exposure. We also noted a 32% decrease in the odds of complete response for every additional 10 kg of weight. Although often quoted as a risk factor, a systematic review by Kranke and colleagues[29] failed to demonstrate an increased risk for obese patients. Our study failed to support any correlation between type of surgery and PONV (Table 8).

In conclusion, PONV is a common complication of ambulatory gynaecological surgery with significant clinical and financial impact. Our data suggest that although both TIVA and dolasetron prophylaxis reduce the expected rate of PONV in the early postoperative period, dolasetron is significantly more effective for PDNV. The purpose of this study was to provide guidance for clinicians choosing PONV prophylaxis as part of their daily clinical management of day-case gynaecological patients. On the basis of our results, we would recommend that a longer acting 5-HT_3 antagonist be considered for PDNV prophylaxis if it is not already being used as the primary prophylactic measure for early PONV.

Table 8 Best multiple logistic-regression model for complete response

Variable	Odds ratio	95% confidence interval	P-value
Anaesthetic	2.7	1.15–6.4	0.022
Weight in 10 kg increments	0.68	0.52–0.89	0.005
Anaesthesia duration	0.62	0.49–0.79	<0.0001

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