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Predictors of nausea and vomiting risk factors and its relation to anesthesia

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Abstract
This is the first study to investigate risk factors for PONV after xenon-based anesthesia. While the incidence of PONV was significantly lower than predicted by Apfel Score, female sex, young age, and long duration of anesthesia predicted PONV after xenon-based anesthesia. A history of PONV or non-smoking status failed to reach statistical significance, probably because of lower power associated with smaller effect size. The lack of efficacy of 5-HT3 receptor antagonists is reasonable because xenon antagonizes these receptors itself, yet needs to be interpreted carefully and warrants confirmation by a sufficiently powered randomized controlled study.

Keywords: Nausea, vomiting, anesthesia

Introduction
Postoperative nausea and vomiting (PONV) are and their clinical implications, based on published a common complication following both in- and out- data of randomized controlled trials (RCTs) and patient surgery. Meta-analyses [1]. The overall incidence of nausea and vomiting following surgery ranges from 12% to 26% and 22% to 38%, respectively, Risk Factors figures may reach 70% in patients at high risk of Risk factors for PONV may be based on character- PONV [2]. Possible consequences of PONV include teristics relating to the patient, anesthetic or type of patient discomfort, unplanned hospital admission surgery. Specific risk factors for PONV in adults are after outpatient surgery, delayed discharge after presented in table I [2].

Although the relationship patient surgery, strain or tearing of sutures, wound between patient-related risk factors and PONV are dehiscence, bleeding, increased intracranial peculiar, such a relationship with surgical risk factors sure, dehydration, electrolyte imbalance, and plume- (e.g. duration and type of surgery) is less clear. Nary aspiration of vomitus [3]. In one survey, anesthesiologists responded that patients reported that incision-site pain was the most undesirable outcome when, in actuality, the chief concern of the patients was postoperative vomiting.

Patients have been reported as willing to spend an additional $US100 out of their own pocket for an effective antiemetic [4]. The definition of PONV varies within studies and articles, with nausea and vomiting often being listed separately or as a single entity. Early PONV is generally defined as occurring from 0 to 2 hours postoperatively, while late PONV is generally defined as occurring from 2 to 24 hours postoperatively [5]. Understanding the mechanisms of PONV enhances the chances of prevention and effective management of this problem. The latest comprehensive reviews of the mechanisms of PONV are more than a decade old and do not include recent guidelines for the prophylaxis and/or treatment of PONV or contemporary areas of research [6].

Postoperative nausea and vomiting (Ponv) are one of the most frequent side effects after anesthesia, occurring in 30% of unselected inpatients and up to 70% of “high-risk” in patients During the 24 h after emergence. Its incidence following ambulatory surgery is not uncommonly reported as lower than in inpatient surgery, but PONV may be under-recognized in the outpatient setting, where patients quickly leave direct medical oversight [7].

For the ambulatory patients, Post Discharge Nausea and Vomiting (PDNV) must also be acknowledged. Even though predischarge PONV predicts PDNV some patient does not experience emetic sequelae until after discharge. Nausea and vomiting may start and persist up

to days after anesthesia and thus strategies providing long-lasting protections should be sought. Q2 the present paper aims at providing an overview around PONV with a focus on prediction and factors that influence the risk for and severity of PONV in the patient scheduled for ambulatory surgery and anesthesia. Postoperative nausea and vomiting (PONV) is not only common but is one of the most distracting side effects after surgery/anesthesia [8]. Avoiding pain and PONV is highly prioritized.

Background

Nausea and vomiting are distinctly unpleasant sensations that may occur after surgery and anesthesia. Prevention and treatment of these symptoms are of particular importance in ambulatory anesthesia. Although rarely the cause of major morbidity, they occur relatively frequently and may result in the prolonged recovery room or hospital stays or unanticipated admission, adding cost and inconvenience to a patient's experience [9].

Patients who become nauseated or vomit stay on average an extra 20–25 minutes in the post anesthetic care unit (PACU). In the ambulatory population, nausea and vomiting may occur or recur following discharge when patients have limited access to effective treatment. For patients, prevention of postoperative nausea and vomiting (PONV) ranks as high as pain control as a health care priority after surgery [10].

Prevention of PONV is one of the extensively studied areas in perioperative medicine, and numerous interventions, pharmacological and Nonpharmacological, are proven by double-blind placebo-controlled randomized trials to reduce but unfortunately not eliminate the incidence of these symptoms. The established clinical practice encourages clinicians to identify patients at risk of PONV and use a multimodal approach to prevent its occurrence. This review focuses on current approaches to risk prediction and reduction. Prediction of risk is important as not all patients will experience PONV even if not given antiemetic prophylaxis, and therefore, it is of clinical importance to identify patients who might benefit from interventions. In this way, patients who are not at risk of PONV would not receive medications that they have little likelihood of benefitting from, and they would also avoid the risk of possible side effects. The ability to accurately predict PONV coupled with an effective prophylactic or treatment strategy would result in avoidance of symptoms, faster recovery, and increased patient satisfaction, limit the occurrence of side effects, and improve resource utilization [11].

Post-discharge nausea and vomiting

Post-discharge nausea and vomiting (PDNV) is experienced by 35%–49% of patients and may continue for up to one week [12]. Pain may be an additional risk factor for late PDNV. PDNV is particularly concerning, as patients may have limited access to effective therapies, and untreated symptoms have a significant impact on quality of life, functional status, and satisfaction [13]. The ability to accurately predict PDNV would be arguably more valuable than PONV as it would allow clinicians to provide easier access to interventions, EG, longer-acting agents and oral or transdermal preparations. In a multicenter study of 2,170 adults undergoing ambulatory anesthesia, Apfel identified a number of risk factors for PDNV, such as female sex, age >50 years, a history of nausea or vomiting, and opioid administration or nausea in the post anesthesia care unit. Depending on the number of risk factors, the patient's risk for PDNV was predicted as 7%, 20%, 28%, 53%, 60%, and 89%, broadly in keeping with PONV prediction (Figure 1). [14] The area under the receiver operating characteristic curve (AUC ROC) was 0.72.

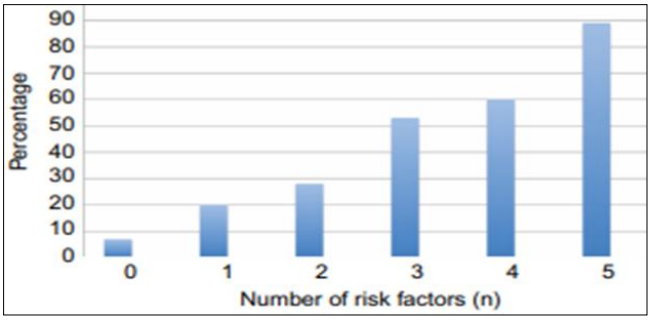

Fig 1: Projected incidence of post discharge and vomiting using the using the Apfel score.

The physiology of PONV is complex and not fully understood. The centers for coordinating vomiting are located throughout the pons and medulla. The chemoreceptor trigger zone (CTZ) and the nucleus tractus solitaries (NTS) receive input, which can contribute to nausea and vomiting. The CTZ then projects to the NTS, which triggers vomiting by stimulating multiple other nuclei (rostral nucleus, nucleus ambiguous, ventral respiratory group, and the dorsal motor nucleus of the vagus). The CTZ receives input from vagal afferents in the gastrointestinal tract. As it is located in the area postrema of the fourth ventricle outside the blood-brain barrier, it can also be stimulated by emetogenic drugs, toxins, and metabolites in the blood and cerebrospinal fluid. The NTS receives input from vagal afferents and from the vestibular and limbic apparatus; therefore, it is sensitive to motion sickness. It also appears to receive input directly from the cerebral cortex in anxiety-induced nausea. There are multiple neurotransmitter pathways involved in transmitting these signals: 5HT3 is the principal neurotransmitter for vagal afferents to the CTZ, dopamine-2 transmits from the CTZ to the NTS, and the vestibular apparatus uses histamine-1 and acetylcholine as its neurotransmitters. PONV can be triggered by various stimuli acting on different neurotransmitter [15].

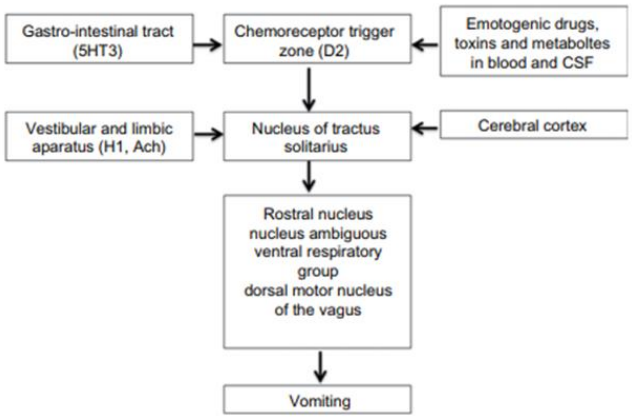

Fig 2: Pathophysiology of nausea and vomiting after anesthetic and surgery.

Pathways, including anxiety, pain, drugs, and motion. There are several different classes of antiemetic medications available targeting these different pathways (vide infra).

Antiemetics: risks and benefits

A large number of drugs have been shown in well-designed

trials to prophylactically reduce PONV with numbers needed to treat ranging from 2 to 9 [16]. It is estimated that even the most effective agents reduce the symptoms in only 25%–30% of those who receive them. Since a patient is likely to experience simultaneous activation of multiple emetogenic pathways, the use of drugs that act on different pathways is logical. Used in combination, antiemetic agents from different classes have greater efficacy than used alone [17]. Although in theory, the use of multiple drugs at lower individual doses is more effective than single therapy, evidence for antagonism between some antiemetic agents is evolving. Available antiemetic agents include 5HT3 receptor antagonists, corticosteroids, neurokinin-1 receptor antagonists, butyrophenones, antihistamines, anticholinergics, benzodiazepines, alpha-2 agonists, and phenothiazines. More recently, investigated interventions include gabapentin and mirtazapine that act at 5HT3 and histamine receptors [18]. Other drugs can influence PONV through omission or substitution, eg, opioids, volatile anesthetic agents, nitrous oxide, and reversal agents. Given the range of options and dose variations, it is perhaps unsurprising that no optimal combination of agents has been determined. In a Cochrane review of 737 studies involving 103,237 patients, Carlisle and Stevenson 21 studied eight proven antiemetics and estimated that in a population experiencing a 30% incidence of PONV, administration of a proven antiemetic would benefit only 10%. The remainder would not benefit but would be exposed to side effects [19]. A study aiming to investigate all possible combinations of single fixed doses of eight drugs would require 256 groups. Overall, side effects are usually mild and are estimated to be experienced by 4% of those who receive them. [20] The side effects of the drug classes are as follows: 5HT3 receptor antagonists: headache, elevated liver enzymes, constipation, and QTc prolongation in higher doses; corticosteroids: hyperglycemia, shortened duration of rocuronium-induced neuromuscular blockade, perineal pruritus, and bradycardia, [21] the incidence of postoperative wound infections does not appear to increase following the use of dexamethasone; 27 NK-1 receptor antagonists: dizziness, headaches, and constipation [22] butyrophenones: sedation, hypotension, and extrapyramidal symptoms, pathological QTc prolongation does not occur with doses used for PONV prophylaxis;30 antihistamines: sedation, dry mouth, and constipation; anticholinergic agents: dry mouth, drowsiness, and visual disturbances; benzodiazepines: sedation; alpha-2 agonists: hypotension and sedation; phenothiazines: sedation; gabapentin: somnolence and dizziness; PC6 acupoint stimulation: skin irritation, blistering, redness, and pain [23].

A practical issue encountered by clinicians using current risk scores is that certain risks cannot be evaluated when assessing risk factors. Although certain risk factors are binary, eg, male versus female, others are not. A patient who has never had an anesthetic before clearly does not have a history of PONV but may well be in a high-risk group. Alternatively, a patient who had a previous anesthetic but did not have PONV may not have experienced symptoms because they received antiemetics. Patients may also confuse delayed opioid-induced nausea with PONV. Additionally, neither the likelihood of postoperative opioid administration nor the duration of surgery can be known with absolute certainty. It is also unclear whether infrequent smokers should be categorized identical to heavy smokers. Similar issues relate to quantification of motion sickness. Thus, arguably, in a proportion of patients, many elements of a scoring system cannot be used with confidence [24].

The average PONV rate in contemporary practice is thought to be ~20%–30%.61 Examination of control groups in recent randomized controlled trials representing "usual care" in academic institutions shows even higher incidences. In a recent study of 1,483 patients, the incidence of PONV in the patient group who were subject to risk assessment and the therapeutic recommendation was 42%. The "care as usual" group had an overall incidence of PONV of 50%. This ranged from 23% to 82% depending on risk profile. 62 A prior study from the same investigators yielded a 42% incidence of PONV in the "care as usual" group.63 Ziemann-Gimmel *et al* 64 recently reported an incidence of 37.3% of PONV in bariatric patients who had volatile-based general anesthesia all of whom who received triple prophylaxis. White *et al*. 65 reported a 45% requirement for rescue antiemetics in patients who had a minimum of two Apfel risk factors [25].

A number of well-conducted studies have investigated the effect of intravenous fluids in PONV [26]. McCaul *et al* [27] failed to find any benefit of balanced crystalloid in quantities targeted to replace fasting volume-deficit patients undergoing gynecological laparoscopy. In a similar patient population, larger quantities of fluid (30 mL/kg) did, however, reduce PONV substantially. Pulmonary function was not adversely affected at these volumes, but it should be recognized that the patients in these studies did not have the cardiorespiratory disease, and equivalent volumes of fluid may not be appropriate to all patient populations and surgeries. [28] Intravenous fluid administration has also been shown to reduce pain after laparoscopic surgery [29]. The results of the studies investigating colloids are conflicting. Preoperative oral carbohydrate drinks taken 2 hours preoperatively have been shown to reduce PONV [30]. Acustimulation A recent Cochrane review assessed the literature regarding stimulation of the wrist acupuncture point PC6 for preventing PONV and found the technique to be no inferior to pharmacological antiemetics.36 Implementation gaps There is ample evidence that antiemetic prophylaxis is underutilized by providers [31].

In Scotland, Brampton *et al* 76 reported only a 67% adherence to local PONV guidelines and a 58% incidence of PONV. In the US, 61% and 52% compliances were reported for prophylaxis and rescue medication, respectively, in accordance with the American Society of Anesthesiologists and American Society of Peri-Anesthesia Nurses clinical practice guidelines. In that study, conducted in an academic teaching center, 8% of patients did not receive any prophylactic antiemetic agents despite each having a high-risk profile. Compliance with institutional protocols is improved somewhat by educational strategies and decision prompting. Kappen *et al* [32] recently reported their investigation into the failure of risk-prompting strategy for PONV to influence patient outcome. The reluctance of the clinicians to change practice was based in part on risk management, ie, the lack of risk-benefit consideration for drugs. Additional factors were the low priority given to PONV as an important health care outcome and the reliance on intuition to make decisions regarding prophylaxis [33].

Methods

Eligible patients were aged 18 yr or older and were scheduled to receive general anesthesia for surgery that included a skin incision and that was anticipated to exceed 2 h. Patients undergoing cardiac surgery or thoracic.

Surgery requiring one-lung ventilation, or in whom N2O was contraindicated in the opinion of the anesthetist (e.g. past history of severe postoperative emesis and current bowel obstruction), were excluded. The primary hypothesis of the ENIGMA trial was that avoidance of N2O in the gas mixture for anesthesia

may decrease the duration of hospital stay. The current paper presents an analysis of one of the secondary outcomes of the trial. This secondary analysis was prospectively planned.

Preoperative demographic characteristics and details of patient medical and surgical history were recorded. A past history of PONV or motion sickness and postoperative opioid use were not recorded. Severe PONV was defined as: (i) two or more episodes of expulsion of gastric contents at least 6 h apart; (ii) received at least three doses of antiemetic medication for treatment of PONV, within the first 24 h after surgery; or both. Severe PONV was assessed at 24 h post-surgery by an interview and medical record review. Statistical analyses all randomized patients were considered as comprising the intention-to-treat population for all primary and secondary analyses. Continuous data were graphed to assess their distribution. Data were summarized using mean (SD) (symmetrically distributed data), median (range) (interquartile range) (skewed data), and number (%) (Categorical data). Groups were compared using unpaired, two-tailed t-tests (symmetrically distributed data), Wilcoxon rank-sum tests (skewed data), x 2 tests (categorical data), or log-rank tests (survival data). Because of the expected possibility of interactions between two or more covariates, including effect modifiers, we chose to explore the confounding effect of those variables found to have a significant (P,0.20) association with severe PONV in multivariate logistic regression models. We thus developed a parsimonious model of independent predictors of risk of severe PONV. We used receiver operating characteristic (ROC) analysis on our logistic regression model. These statistical analyses were conducted using Stata 8.2 (Stata Corporation, College Station, TX, USA). In addition, we applied a recursive partitioning or classification and regression tree analysis (CART). Whereas logistic regression is used to define overall relationships between potential risk factors and outcomes, CART is used to examine local or subgroup relationships. For example, CART, or similar procedures, has been used to identify high-risk groups for harmful alcohol use14 and patients at high risk of atrial fibrillation after cardiac surgery.15 we used the CART 6 (2006) binary tree-building procedure (Salford Systems, San Diego, CA, USA). All of the variables used in the logistic regression analysis were available for selection by CART. BIS monitoring and N2O were entered into CART first because a significant interaction between them was identified during logistic regression modeling. We began with the full data set (n¼2012). Although CART includes cross-validation procedures, we further tested the methodology by randomly splitting the sample into a training sample to create the CART tree (n¼1509; 75%) and a testing sample (n¼503; 25%) to test it both subsamples were highly similar on the composition of the outcome variable. The classification accuracy obtained for each subset was compared using an x 2 test, if not significantly different, the two samples were combined and the tree reconstructed on the total sample. Finally, the final subgroups (or 'terminal nodes') of the CART tree were entered into a logistic regression analysis, adjusting for the effects of possible risk factors available to, but not chosen by, CART (i.e. age, 45 yr, and abdominal surgery).14 All reported P-values are two-sided and not adjusted for multiple comparisons.

Results

Assessment of postoperative nausea and vomiting Subjects were followed for 24 h after extubation by study physicians. The incidence of nausea, vomiting, or both within the 24 h period was assessed by medical chart inspection followed by a personal patient interview and recorded as a binary variable. The requirement for postoperative antiemetic medication ('rescue medication') was assessed from medical charts. The incidence of postoperative nausea and vomiting and quantification of independent predictors the observed incidence of PONV was compared with the expected incidence predicted by Apfel Score. The initial Apfel Score was corrected for the administered postoperative opioids. This comparison was performed only in subjects who did not receive antiemetic prophylaxis to determine the unimpeded emetic activity of xenon-based anesthesia. We assessed predictors for PONV or rescue medication after xenon-based anesthesia by logistic regression analysis. A recent, large meta-regression identified female sex, history of PONV or motion sickness, non-smoking status, younger age, duration of anesthesia, use of postoperative opioids, and certain types of surgery as independent predictors for PONV after propofol or inhaled anesthetic-based anesthesia.8 Therefore, we decided a priori to include these variables in the model. The comparison of postoperative opioid consumption was facilitated by calculation of morphine equivalents. In addition, different classes of medical antiemetic prophylaxis and study centers were also included as single binary variables in the model a priori. The aim of the next step was to identify further potential predictors by testing remaining variables (height, weight, body mass index, amount of intraoperative fluids, type of intraoperative opioid, and use of regional anesthesia) for association with PONV or rescue medication by Univariate analysis. As no statistically significant associations were found, we did not include these variables in our logistic regression analysis. Variables within the model were tested for collinearity using the Collin extension of Stata (P. Ender, University of California, and Los Angeles, CA, USA). The goodness of fit was assessed using the Homer–Lemeshow test with 10 groups. The effectiveness of medical antiemetic prophylaxis the effect of prophylactic antiemetics was part of the logistic regression analysis. However, we additionally performed a propensity score-matched analysis so that subjects who did or did not receive prophylactic antiemetics were comparable. To this end, a binary variable was generated indicating whether a subject received medical antiemetic prophylaxis or not. Then, a logistic regression model including sex, age, smoking status, history of PONV or motion sickness, regional anesthesia, duration of anesthesia, anticipated postoperative opioid use, and study center was used to calculate the propensity for receiving medical antiemetic prophylaxis. Finally, subjects with prophylaxis were matched on a one-to-one basis with patients without prophylaxis on the logic of the propensity score using calipers of 0.2 of the logit. Univariate analyses were performed to verify that groups were balanced on the variables used for calculation of the propensity score (i.e. that matching was successful). Additionally, standardized differences were calculated to quantify the balancing of groups. 10 the sample size estimation of the underlying study was carried out based on the primary endpoints depth of anesthesia and incidences of hypertension and anesthesia. However, when comparing an overall PONV incidence associated with general anesthesia of 38%11 and a previously reported PONV incidence of 27.5% after xenon-based anesthesia, a minimal sample size of 364 patients would be required. On this basis, we considered the available number of 500 patients included in this study to be sufficient.

Table 1: Shows the results of the correlation between the variables of the study variables and their significance

Predictor	Adjusted odds ratio	95% Confidence interval	P-value
Subject-related factors			
Female sex	1.76	1.08-2.89	0.025
Age (per 10 yr)	0.82	0.69-0.97	0.023
Non-smoking status	1.48	0.87-2.51	0.15
History of PONV or motion sickness, or both	1.44	0.83-2.50	0.19
Anaesthesia-related factors			
Duration (per hour)	1.36	1.17-1.59	<0.001
Postoperative morphine equivalent (per mg)	1.02	0.99-1.05	0.13
Prophylaxis			
Dexamethasone	0.72	0.32-1.60	0.41
5-HT_3 antagonist	1.39	0.65-2.98	0.40
Other	1.06	0.41-2.76	0.91
Prophylaxis *per se'*	0.98	0.54-1.77	0.93

Duration of anesthesia was a strong predictor for PONV and need for rescue medication; the incidence of PONV was roughly doubled with every additional 2 h of exposure. This relationship has also been known for other inhaled anaesthetics17 and nitrous oxide and appears to be independent of the targeted receptors. Given that xenon has a very low blood–gas partition coefficient of 0.11518 and does not accumulate, [34] it is questionable whether it can directly trigger PONV several hours after anesthesia. However, xenon has been traced in human blood and urine up to 24 h after anesthesia, probably because of storage in fatty tissue. Rather than triggering PONV by direct mechanisms, alterations in gene expression and protein function may contribute to PONV after xenon inhalation. For example, xenon facilitates preconditioning by inducing hypoxia-inducible factor-1α. It also up regulates a variety of genes involved in neuronal signaling, [35] alters the excitability of brain cells by increasing neuronal Ca2+ concentration, [36] and interferes with neuronal norepinephrine re-uptake.

However, given that the molecular mechanisms of PONV have yet to be elucidated, it remains highly speculative whether these xenon-induced cellular alterations contribute to PONV. Not all items of the Apfel Score were predictive in our patient population. The confidence intervals for non-smoking status and history of PONV, motion sickness, or both were too wide to reach statistical significance, and effect sizes for those two factors were smaller than after 'traditional' anesthesia.8 It seems reasonable that PONV after anesthesia with 'classic' inhaled anesthetics or propofol does not necessarily predict PONV after xenon-based anesthesia because of different mechanisms of action. However, we cannot completely rule out the possibility that in a larger sample, non-smoking status and history of PONV/motion sickness may be detected as significant predictors. Postoperative nausea and vomiting have been widely attributed to postoperative opioid use. [37]

In our model, the dose of postoperative opioids was not predictive for PONV. It is known that administration of postoperative opioids is correlated with the duration of anaesthesia.7 29 When testing for collinearity, we found a positive correlation between postoperative morphine equivalent use and duration of anesthesia (Pearson's r=0.21).

Table 2: Shows the results of the significance of each variable and the probability values of the study

	Total cohort (n=488)			Propensity-matched cohort (n=182)			Standardized difference
	Prophylaxis (n=155)	No prophylaxis (n=333)	P-value	Prophylaxis (n=91)	No prophylaxis (n=91)	P value	
Age (yr)	47 (16)	56 (16)	<0.001	50 (17)	SO (15)	0.89	0.02
Female	111 (72)	116 (35)	<0.001	49 (54)	42 (46)	0.37	0.14
Non-smoking status	123 (79)	241 (72)	0.12	74 (81)	71 (78)	0.71	0.07
History of PONY or motion sickness, or both	36 (23)	58 (17)	0.14	20 (22)	16 (18)	0.58	0.10
Postoperative opioid use	100 (65)	276 (83)	<0.001	59 (65)	65 (71)	0.43	0.12
Duration of anaesthesia (min)	160 (96)	171 (93)	0.22	165 (96)	173 (95)	0.56	0.09
Additional regional anaesthesia	19 (12)	92 (28)	<0.001	13 (14)	12 (13)	0.99	0.03
Percentage expected risk according to Apfel	48 (16)	42 (17)	0.002	44.3 (16)	43.0 (20)	0.93	0.08
Score							
24 h PONY	44 (28)	92 (28)	0.91	27 (30)	31 (34)	0.63	0.09
24 h nausea only	22 (14)	56 (17)	0.51	11 (12)	14 (15)	0.67	0.09
24 h vomiting only	11 (7)	15 (5)	0.28	8 (9)	9 (10)	0.99	0.03
24 h nausea and vomiting	11 (7)	21 (6)	0.84	8 (9)	8 (9)	1.0	0
24 h need for rescue medication	43 (28)	81 (24)	0.44	25 (28)	27 (30)	0.87	0.04

The data reported were obtained in a prospective cohort study investigating adverse events during xenon-based anesthesia so that prophylaxis was not protocolized, but administered at the discretion of the attending anesthetist. Thus, it would not have been appropriate to compare the raw incidences of PONV in patients who did or did not receive prophylactic antiemetics. This issue was addressed by controlling for other factors in the logistic regression analysis. Furthermore, we conducted a thorough propensity score matching with the objective of creating two groups of patients, with or without antiemetics, which were similar in all relevant factors. After matching was completed, univariate analyses verified that the two groups were similar in all variables except for antiemetics.

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