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Association between intraoperative end-tidal carbon dioxide and postoperative nausea and vomiting in gynecologic laparoscopic surgery

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Gynecologic laparoscopic surgery has a high incidence of postoperative nausea and vomiting (PONV). Studies suggest that low intraoperative end-tidal carbon dioxide (EtCO₂) is associated with an increased incidence of PONV, but the results have not been consistent among studies. This study investigated the association between intraoperative EtCO₂ and PONV in patients undergoing gynecologic laparoscopic surgeries under general anesthesia. This retrospective cohort study involved patients who underwent gynecologic laparoscopic surgeries under general anesthesia at Kyoto University Hospital. We defined low EtCO₂ as a mean EtCO₂ of < 35 mmHg. Multivariable modified Poisson regression analysis examined the association between low EtCO₂ and PONV during postoperative two days and the postoperative length of hospital stay (PLOS). Of the 739 patients, 120 (16%) had low EtCO₂, and 430 (58%) developed PONV during postoperative two days. There was no substantial association between low EtCO₂ and increased incidence of PONV (adjusted risk ratio: 0.96; 95% confidence interval [CI] 0.80–1.14; *p* = 0.658). Furthermore, there was no substantial association between low EtCO₂ and prolonged PLOS (adjusted difference in PLOS: 0.13; 95% CI – 1.00 to 1.28; *p* = 0.816). Intraoperative low EtCO₂, specifically a mean intraoperative EtCO₂ below 35 mmHg, was not substantially associated with either increased incidence of PONV or prolonged PLOS.

The incidence of postoperative nausea and vomiting (PONV) remains high despite considerable improvements in treatment over the past few decades. PONV is nausea or vomiting in the first 24–48 h after surgery¹. Well-established risk factors for PONV include female gender, history of PONV or motion sickness, nonsmoking, and postoperative opioid use². The risk of PONV is up to 80% in high-risk patients with all four risk factors³. The incidence of PONV is particularly high among patients undergoing gynecologic laparoscopic surgery⁴. PONV is associated with decreased patient satisfaction⁵, increased postoperative complications⁶, and longer postoperative length of hospital stay (PLOS)⁷.

Hypocapnia may be associated with decreased systemic vasodilation⁸ and may cause tissue ischemia⁹, intestinal ischemia¹⁰, and cerebral ischemia^{11,12}. Animal studies have reported that serotonin levels in the brain, a highly emetogenic substance, increase with intestinal^{13,14} and cerebral ischemia¹⁵. Based on the hypothesis associating hypocapnia with increased serotonin levels due to intestinal and cerebral ischemia, studies associate intraoperative hypocapnia with increased incidence of PONV^{16,17}. However, the relationship between hypocapnia and PONV remains unclear because some studies had conflicting results^{18,19}.

Therefore, we examined the association between intraoperative end-tidal carbon dioxide (EtCO₂) and the incidence of PONV in patients undergoing gynecologic laparoscopic surgery. We adjusted for important confounding factors and assessed the effects of the duration and severity of low EtCO₂ exposure.

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Methods

Ethics. The Certified Review Board of Kyoto University, Kyoto, Japan (Chairperson Prof. Shinji Kosugi) approved the protocol for this study (approval no.: R1272-3, January 23, 2020). Additionally, the informed consent requirement was waived due to this study's retrospective nature.

Study design, setting, and population. In this single-center retrospective cohort study, we used data from the Kyoto University Hospital IMPROVE Anaesthesia Care and Outcomes (Kyoto-IMPACT) database. The Kyoto-IMPACT database aims to clarify the relationship between intraoperative respiratory and cardiovascular parameters and postoperative outcomes. We consecutively selected patients who underwent surgery under the care of anesthesiologists at Kyoto University Hospital (1121 beds). We have published several studies using the Kyoto-IMPACT database^{20,21}. We included adult female patients aged 18 years or older who underwent gynecologic laparoscopic surgery (i.e., adnexal surgery and/or hysterectomy) at Kyoto University Hospital between January 2012 and December 2017. The gynecologic laparoscopic surgery population was selected because the predicted incidence rate of PONV in this population is 30–40%, assumed to be a medium risk of PONV⁴. The exclusion criteria were as follows: (1) patients with postoperative intensive care unit admission; (2) those who underwent multiple surgeries within one week during the study period; (3) those who received epidural anesthesia; (4) those with missing smoking data, and (5) those with missing intraoperative EtCO₂ data.

Data collection. We collected data from the anesthesia information management and electronic medical record systems and constructed the Kyoto-IMPACT database. EtCO₂ was continuously measured using a side-stream gas analyzer (GF-220R Multigas/Flow Unit, Nihon Kohden*, Japan) that was automatically uploaded to the anesthesia information management system every 1960s. Intraoperative EtCO₂ was the mean EtCO₂ level from skin incision to skin closure. We removed EtCO₂ levels lower than 20 mmHg as artifacts (EtCO₂ during aspiration or position change). The definitions of variables, including the minimum and maximum EtCO₂ levels, can be found in Supplementary Data Table S1. We collected data on PONV by reviewing all clinical data contained in the electronic medical records. Ward nurses assessed the presence of nausea and vomiting at least twice daily. We defined PONV as one or more episodes of nausea or vomiting during the first 2 days after surgery and vomiting as one or more episodes of vomiting during the same period.

Exposure. To determine how EtCO₂ affects PONV, we defined exposure by calculating the dose, time, and cumulative effects of EtCO₂. First, we evaluated the dose effects of EtCO₂ using the mean EtCO₂. Next, we divided the patients into two groups based on the cutoff EtCO₂ level of 35 mmHg proposed by Way and Hill²². We defined low EtCO₂ as a mean EtCO₂ lower than 35 mmHg and normal EtCO₂ as a mean EtCO₂ greater than or equal to 35 mmHg. We classified the patients in either of these groups and used them as the primary exposure for further analysis. Additionally, we categorized the mean EtCO₂ levels into quartiles (i.e., < 35, 35–37, 37–40, and ≥ 40 mmHg) because the relationship between EtCO₂ and PONV might not be linear. To assess the effects of the duration and severity of low EtCO₂ exposure, we determined the time effect based on the minutes when the EtCO₂ level was below 35 mmHg and measured the cumulative effect as the area with EtCO₂ levels below the threshold of 35 mmHg for each patient. Furthermore, we categorized the minutes and area under the threshold of an EtCO₂ level of 35 mmHg into quartiles; the lowest quartile was the reference category.

Outcomes. The primary outcome in this study was PONV, defined as PONV for two days postoperatively. The secondary outcomes were nausea for two days postoperatively, vomiting for two days postoperatively, PONV for 3–7 days postoperatively, and PLOS. We defined PLOS as the duration of hospital stay after surgery for patients who survived until discharge.

Statistical analysis. We analyzed the relationship between intraoperative EtCO₂ and PONV before data collection. We used the Mann–Whitney test for group comparisons, and continuous variables were expressed as the median and interquartile range (IQR), and categorical variables were expressed as counts and percentages (%).

First, we performed modified Poisson regression analysis with robust variance to calculate the risk ratio for low EtCO₂ (mean EtCO₂ of less than 35 mmHg) and PONV, with the reference category of normal EtCO₂ (mean EtCO₂ ≥ 35 mmHg)²³. Additionally, we calculated the risk ratios of the mean EtCO₂ level in the first quartile (mean EtCO₂ of less than 35 mmHg), third quartile (mean EtCO₂ of 37–40 mmHg), and fourth quartile (mean EtCO₂ of more than or equal to 40 mmHg). The second quartile (mean EtCO₂ of 35–37 mmHg) was the reference category because it was considered normocapnia. Furthermore, we examined the time and cumulative effects of EtCO₂ by evaluating how each quartile affected PONV, with the first quartile (with minutes under an EtCO₂ of 35 mmHg and the area below the threshold of 35 mmHg) being the reference category. We created a model using the covariates previously used to demonstrate the relationship between intraoperative EtCO₂ and PONV. The model included age, smoking history, surgery duration, body mass index (BMI), total intravenous anesthesia (TIVA), mean arterial pressure (MAP), intraoperative fentanyl use, postoperative fentanyl dose for intravenous patient-controlled analgesia (IVPCA), the use of prophylactic antiemetics, the addition of droperidol to postoperative IVPCA, American Society of Anesthesiologists Physical Status (ASAPS), malignancy, and emergency surgery. Additionally, a modified Poisson regression model investigated whether the dose, time, or cumulative effect of EtCO₂ affects postoperative nausea two days, vomiting two days, and PONV 3–7 days postoperatively, adjusting for the aforementioned models. To further evaluate the relationship between EtCO₂ and PLOS, we performed a linear regression analysis adjusting for the possible covariates in the aforementioned models.

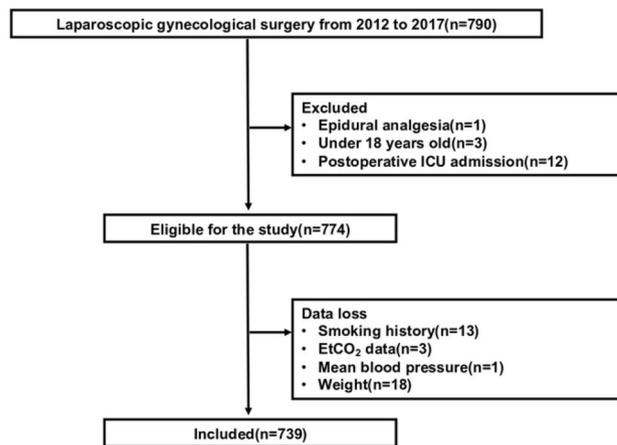


Figure 1. Flowchart of this study. We consecutively included patients aged 18 years or older who underwent laparoscopic gynecologic surgery under general anesthesia at Kyoto University Hospital from 2012 to 2017. Subsequently, cases that met the eligibility criteria were selected and analyzed as complete cases.

The relationship between intraoperative EtCO₂ and PONV may depend on patient and surgical characteristics. Therefore, we performed a subgroup analysis to assess this potential heterogeneity. We used the modified Poisson regression model for the following subgroups: (1) age (≥ 50 / < 50 years), (2) malignancy (yes/no), (3) smoking history (ever smoked/never smoked), (4) duration of surgery (≥ 4 / < 4 h), (5) TIVA (yes/no), (6) the use of intraoperative prophylactic antiemetics (yes/no), (7) postoperative fentanyl dose for IVPCA (≥ 20 / < 20 $\mu\text{g}/\text{h}$) and (8) addition of droperidol in IVPCA (yes/no). We calculated the crude risk ratio of PONV in each subgroup and examined the interaction between subgroups and the mean of intraoperative EtCO₂.

To maximize statistical power, all eligible patients enrolled in the Kyoto-IMPACT database since 2012, when postoperative nausea and vomiting began to be recorded in their current form, were included in the analysis. To determine the study power, we estimated that approximately 120 laparoscopic gynecologic surgeries were performed annually at Kyoto University Hospital, with 720 surgeries performed over six years. The risk ratio was 1.53, the incidence of PONV was 40%⁴, and the proportion of low EtCO₂ was 50%²⁴, giving an estimated power of 80%. The rate of missing data was 0.04%, so we conducted a complete case analysis. All statistical tests were two-tailed. We used Stata/SE 15.1 (StataCorp LLC, College Station, Texas, USA) to conduct all statistical analyses.

Ethics approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Certified Review Board of Kyoto University, Kyoto, Japan (Chairperson Prof. Shinji Kosugi) approved the protocol for this study (approval no.: R1272-3, January 23, 2020). Additionally, the informed consent requirement was waived due to this study's retrospective nature.

Results

Baseline patient characteristics. Of the 790 patients who underwent laparoscopic gynecologic surgery between 2008 and 2017, 774 met our inclusion criteria, and we included 739 in the complete case analysis (Fig. 1). Low EtCO₂ (defined as the mean EtCO₂ level of less than 35 mmHg) occurred in 120 patients (16%), whereas PONV occurred in 430 patients (58%). Table 1 shows the overall baseline characteristics of the study participants. The median EtCO₂ values were 37 mmHg (IQR, 35–40 mmHg) overall, 33 mmHg (IQR, 32–34 mmHg) in patients with low EtCO₂, and 38 mmHg (IQR, 36–40 mmHg) in patients with normal EtCO₂.

Association between low EtCO₂ and PONV. Table 2 shows the study's main results. PONV occurred in 67 (55.83%) of the 120 patients in the low EtCO₂ group, whereas 363 (58.64%) of the 619 patients were in the normal EtCO₂ group. We could not find a substantial association between low EtCO₂ and PONV (crude risk ratio, 0.95; 95% confidence interval [CI] 0.80–1.13; $p = 0.577$) (adjusted risk ratio, 0.96; 95% CI 0.80–1.14; $p = 0.658$). For further analysis, we divided EtCO₂ into quartiles. The second quartile (mean EtCO₂ 35–37 mmHg) was the reference, and the definition of low EtCO₂ was the lowest quartile of mean EtCO₂ (mean EtCO₂ of less than 35 mmHg). The second (mean EtCO₂ of 35–37 mmHg), third (mean EtCO₂ 37–40 mmHg), and fourth (mean EtCO₂ ≥ 40 mmHg) quartiles of mean EtCO₂ values were not substantially associated with increased incidence of PONV, with low EtCO₂ (first quartile [mean EtCO₂ of less than 35 mmHg]) as the reference category.

For the time effects of EtCO₂, compared with short-term exposure (first quartile of exposure time to EtCO₂ of less than 35 mmHg, 0–11 min), long-term exposure to EtCO₂ levels of less than 35 mmHg (fourth quartile of exposure time to EtCO₂ of less than 35 mmHg, 67–613 min) was not substantially associated with increased incidence of PONV (crude risk ratio, 1.09; 95% CI 0.91–1.30; $p = 0.323$) (adjusted risk ratio, 1.03; 95% CI 0.87–1.22; $p = 0.700$).

Characteristics	All patients (n = 739)	Low EtCO ₂ (n = 120)	Normal EtCO ₂ (n = 619)
Age (years)	45 (36–56)	47 (34–58)	44 (36–55)
ASA-PS			
I	402 (54.55%)	60 (50.42%)	342 (55.34%)
II	322 (43.69%)	58 (48.74%)	264 (42.72%)
III	13 (1.76%)	1 (0.84%)	12 (1.94%)
BMI	21.28 (19.35–23.62)	21.73 (19.38–24.45)	21.16 (19.35–23.52)
Malignant	205 (27.74%)	25 (20.83%)	180 (29.08%)
Never smoker	567 (76.73%)	87 (72.50%)	480 (77.54)
Emergency surgery	42 (5.70%)	6 (5.04%)	36 (5.83%)
Duration of surgery (min)	186 (125–270)	156 (110–233)	195 (129–276)
Blood loss (ml)	10 (0–100)	0 (0–75)	17 (0–100)
Transfusion volume (ml)	0 (0)	0 (0)	0 (0)
Infusion volume (ml)	1400 (1000–2040)	1265 (920–1920)	1450 (1000–2060)
TIVA	135 (18.27%)	25 (20.83%)	110 (17.77%)
Mean MAP (mmHg)	73 (68–80)	73 (68–81)	73 (68–80)
Intraoperative antiemetics use	284 (38.43%)	37 (30.83%)	247 (39.90%)
Addition of droperidol in IVPCA	321 (43.44%)	38 (31.67%)	283 (45.72%)
Total intraoperative fentanyl dose (µg)	200 (150–250)	200 (100–250)	200 (150–250)
Postoperative fentanyl dose in IVPCA (µg/h)	20 (0–25)	20 (0–25)	20 (0–25)
Mean EtCO ₂	37 (35–40)	33 (32–34)	38 (36–40)
Minimum EtCO ₂	31 (29–33)	28 (26–30)	32 (30–34)
Maximum EtCO ₂	42 (40–46)	37 (36–39)	43 (41–47)

Table 1. Patient characteristics (n = 739). Values are given as median (interquartile range) or count (%). *ASAPS* American Society of Anesthesiologists Physical Status, *BMI* body mass index, *TIVA* total intravenous anesthesia, *MAP* mean arterial pressure, *IVPCA* intravenous patient-controlled analgesia, *EtCO₂* end-tidal carbon dioxide.

	N	POD2-PONV	Crude risk ratio (95% CI)	P-value	Adjusted risk ratio (95% CI)	P-value
Mean EtCO₂						
Normal EtCO ₂	619	363 (58.64%)	1	–	1	–
Low EtCO ₂	120	67 (55.83%)	0.95 (0.80–1.13)	0.577	0.96 (0.80–1.14)	0.658
Mean EtCO₂						
< 35 mmHg	120	67 (55.83%)	1.01 (0.82–1.24)	0.906	1.04 (0.85–1.28)	0.650
35–37 mmHg	171	101 (59.06%)	1.07 (0.89–1.27)	0.451	1.09 (0.92–1.30)	0.284
37–40 mmHg	254	155 (61.02%)	1.10 (0.94–1.29)	0.217	1.15 (0.98–1.34)	0.079
≥ 40 mmHg	194	107 (55.15%)	1	–	1	–
Minutes below EtCO₂ 35 mmHg						
Quartile value 1 (0–11 min)	185	102 (55.14%)	1	–	1	–
Quartile value 2 (12–25 min)	187	106 (56.68%)	1.02 (0.85–1.23)	0.764	1.04 (0.87–1.24)	0.653
Quartile value 3 (26–66 min)	181	110 (60.77%)	1.10 (0.92–1.31)	0.276	1.10 (0.93–1.30)	0.222
Quartile value 4 (67–613 min)	186	112 (60.22%)	1.09 (0.91–1.30)	0.323	1.03 (0.87–1.22)	0.700
Area under the threshold of EtCO₂ 35 mmHg						
Quartile value 1 (0–7)	183	98 (53.55%)	1	–	1	–
Quartile value 2 (8–36)	182	104 (57.14%)	1.03 (0.86–1.23)	0.744	1.01 (0.85–1.21)	0.825
Quartile value 3 (37–107)	186	113 (60.75%)	1.08 (0.91–1.29)	0.358	1.10 (0.93–1.30)	0.232
Quartile value 4 (108–2213)	188	115 (61.17%)	1.08 (0.91–1.29)	0.346	1.03 (0.87–1.23)	0.654

Table 2. Multivariable analysis of the relationship between EtCO₂ and POD2-PONV. *EtCO₂* end-tidal carbon dioxide, *POD 2* postoperative day 2, *PONV* postoperative nausea and vomiting, *CI* confidence interval.

Finally, for the cumulative effects of EtCO₂, the fourth quartile of the area under the EtCO₂ threshold of 35 mmHg (108–2213) was not substantially associated with increased incidence of PONV compared with the first quartile (0–7) (crude risk ratio, 1.08; 95% CI 0.91–1.29; $p = 0.346$) (adjusted risk ratio, 1.03; 95% CI 0.87–1.23; $p = 0.654$).

	Number of events (%)	Crude risk ratio (95% CI)	P-value	Adjusted risk ratio (95% CI)	P-value
POD2: postoperative nausea					
Normal EtCO ₂	346/619 (55.90%)	1	–	1	–
Low EtCO ₂	66/120 (55.00%)	0.98 (0.82–1.17)	0.857	0.99 (0.82–1.18)	0.916
POD2: postoperative vomiting					
Normal EtCO ₂	184/619 (29.73%)	1	–	1	–
Low EtCO ₂	37/120 (30.83%)	1.03 (0.77–1.39)	0.807	1.17 (0.88–1.55)	0.264
POD 3–7: PONV					
Normal EtCO ₂	383/619 (61.87%)	1	–	1	–
Low EtCO ₂	70/120 (58.33%)	0.94 (0.80–1.11)	0.480	0.95 (0.81–1.12)	0.583

Table 3. Multivariable analysis of the relationship between EtCO₂ and secondary outcomes. EtCO₂ end-tidal carbon dioxide, POD 2 postoperative day 2, POD 3–7 postoperative days 3 to 7, PONV postoperative nausea and vomiting, CI confidence interval.

	Median (IQR)	P value	Crude difference in PLOS (95% CI)	P-value	Adjusted difference in PLOS (95% CI)	P-value
Length of stay(day)						
Normal EtCO ₂	6 (5–8)	0.782	1	–	1	–
Low EtCO ₂	6 (5–7)		–0.15 (–1.29 to 0.97)	0.783	0.13 (–1.00 to 1.28)	0.816

Table 4. Multivariable analysis of the relationship between EtCO₂ and PLOS. EtCO₂ end-tidal carbon dioxide, PLOS postoperative length of stay, IQR interquartile range, CI confidence interval.

Association between low EtCO₂ and nausea and vomiting 2 days postoperatively and PONV 3–7 day postoperatively. The adjusted risk ratio for the low EtCO₂ group (mean EtCO₂ of less than 35 mmHg) did not indicate an association between low EtCO₂ and nausea and vomiting two days postoperatively or PONV 3–7 days postoperatively (Table 3), with normal EtCO₂ being the reference category.

Association between low EtCO₂ and PLOS. The median PLOS was 6 days (IQR, 5–8 days) (Table 4). The median PLOS in patients with low EtCO₂ was not different from that in patients with normal EtCO₂ (6 days [IQR, 5–8 days] vs. 6 days [IQR, 5–7 days]; $p=0.782$). Linear regression analysis showed that low EtCO₂ was not likely to be associated with PLOS (crude adjusted difference in PLOS, –0.15; 95% CI –1.29 to 0.97; $p=0.783$) (adjusted difference in PLOS, –0.13; 95% CI –1.00 to 1.28; $p=0.816$).

Subgroup analysis. Subgroup analyses included age (≥ 50 / < 50 years), malignancy, smoking history, duration of surgery (≥ 4 h/ < 4 h), TIVA, the use of intraoperative prophylactic antiemetics, postoperative fentanyl dose for IVPCA (≥ 20 μ g/h/ < 20 μ g/h) and addition of droperidol in IVPCA. There was no interaction between these variables and PONV (Table 5).

Discussion

In this retrospective cohort study, mean of intraoperative EtCO₂ was not substantially associated with increased incidence of PONV and prolonged PLOS in patients undergoing gynecologic laparoscopic surgery. Furthermore, we examined the effects of the duration and severity of low EtCO₂ exposure using the time and cumulative effects of EtCO₂ but found no clear association.

Two small studies have studied whether there is an association between low EtCO₂ and PONV^{17,18}, but the results have been inconsistent. A randomized controlled trial (RCT) involving 75 patients who underwent percutaneous nephrolithotripsy reported that the hypercapnia management group had less PONV¹⁷. However, a prospective observational study involving 90 pediatric patients who underwent inguinal surgery has reported that elevated levels of EtCO₂ were an independent predictor of PONV¹⁸. As the aforementioned studies have different types of surgery and patient backgrounds, their results might not be directly applicable to patients undergoing gynecologic laparoscopic surgery.

Furthermore, three studies on patients who had undergone gynecologic surgery have shown inconsistent results. An RCT involving 387 patients who underwent gynecologic laparoscopic surgery reported mild hypercapnia management did not reduce PONV¹⁹. That study did not evaluate the effects of low EtCO₂ (mean EtCO₂ level of less than 35 mmHg). Alternatively, a retrospective cohort study involving 146 patients undergoing open gynecologic surgery has reported that the minimum EtCO₂ level of ≤ 31 mmHg lasting longer than 10 min was associated with an increased incidence of PONV¹⁶. Still, that study only evaluated the effects of extremely low EtCO₂ levels (mean EtCO₂ of ≤ 31 mmHg). It did not evaluate the dose and time effects of low EtCO₂ below the commonly defined EtCO₂ level of 35 mmHg. Furthermore, an RCT involving 60 patients undergoing gynecologic laparoscopic surgery reported that low EtCO₂ management reduced the incidence of nausea, PONV score, and the use of rescue antiemetics²⁵; these results differed from the two aforementioned studies. Management to keep

	N	POD2-PONV	Crude risk ratio (95% CI) of low EtCO ₂	P-value	P for interaction
Overall	739	430 (58.19%)	0.95 (0.80–1.13)	0.577	
Age (year)					0.837
< 50	454	246 (54.19%)	0.96 (0.76–1.20)	0.725	
≥ 50	285	184 (64.56%)	0.91 (0.70–1.18)	0.486	
Malignancy					0.594
Yes	205	135 (65.85%)	0.90 (0.64–1.26)	0.540	
No	534	295 (55.24%)	0.98 (0.80–1.20)	0.913	
Smoking history					0.640
Ever	172	92 (53.49%)	1.02 (0.72–1.45)	0.892	
Never	567	338 (59.61%)	0.93 (0.76–1.14)	0.511	
Duration of surgery (h)					0.491
≥ 4	238	148 (62.18%)	0.87 (0.61–1.23)	0.442	
< 4	501	282 (56.29%)	0.99 (0.51–1.21)	0.959	
TIVA					0.274
Yes	604	369 (61.09%)	0.91 (0.76–1.10)	0.376	
No	135	61 (45.19%)	1.19 (0.77–1.83)	0.428	
Intraoperative antiemetics					0.990
Yes	284	168 (59.15%)	0.95 (0.70–1.28)	0.757	
No	455	262 (57.58%)	0.95 (0.77–1.17)	0.666	
Postoperative fentanyl dose in IVPCA (µg/h)					0.921
< 20	246	121 (49.19%)	0.99 (0.73–1.35)	< 20	
≥ 20	493	309 (62.68%)	0.98 (0.80–1.21)	≥ 20	
Addition of droperidol in IVPCA					0.502
Yes	321	175 (54.52%)	1.01 (0.75–1.37)	Yes	321
No	418	255 (61.00%)	0.90 (0.73–1.11)	No	418

Table 5. Subgroup analyses stratified by patient and operative variable. *POD 2* postoperative day 2, *PONV* postoperative nausea and vomiting, *CI* confidence interval, *TIVA* total intravenous anesthesia, *IVPCA* intravenous patient-controlled analgesia.

EtCO₂ at a low level may avoid PONV by inhibiting cerebral vasodilation, preventing increased intracranial pressure caused by the pneumoperitoneum and Trendelenburg position, which would not affect the ischemia-sensitive vestibular system. However, this study may have an internal validity problem in which it was not blinded. Furthermore, it had a generalizability problem because it excluded patients with severe systemic diseases, ASAPS-III patients, those with a history of PONV motion sickness, and smokers.

Considering that the results of previous studies are inconsistent, the evidence on the association between intraoperative low EtCO₂ and PONV remains limited. Therefore, we conducted this study, which involved the largest cohort from real-world data, which provided a sufficient sample size, resulting in a statistical power of 80% to detect a risk ratio of 1.53. Furthermore, adjusting for important confounders, such as blood pressure, age, and intraoperative fentanyl use, and assessing the dose–effect of low EtCO₂ (mean EtCO₂ of less than 35 mmHg) and the effects of the duration and severity of low EtCO₂ exposure, we could not demonstrate an association between low EtCO₂ and PONV. Even extremely low EtCO₂, defined as EtCO₂ of less than 31 mmHg sustained for more than 10 min¹⁶, failed to show an association with PONV (Supplemental Data Table S2).

This study has several strengths. First, it investigated the association between the effects of EtCO₂ and PONV and PLOS, the dose effects of EtCO₂ (mean level of less than 35 mmHg) and the effects of the duration (time effects, long-term exposure to EtCO₂ of less than 35 mmHg) and severity (cumulative effects, area under the threshold of EtCO₂ of less than 35 mmHg). Among the three previous studies that examined the association between intraoperative low EtCO₂ and PONV, which only evaluated the dose effects^{17–19}, only one study evaluated the association between the time effects of low EtCO₂ and PONV¹⁶. Second, this study adjusted for potential confounding factors that were not adjusted in previous studies, such as blood pressure, age, and intraoperative fentanyl use, using a modified Poisson regression model. Third, this was a large study with sufficient sample size. All previous studies had small sample sizes, so the number of confounding factors that can be adjusted is limited.

This study has several limitations. First, we extracted information on the presence of nausea and vomiting from the records of assessments performed by the ward nurses at least twice a day, so PONV occurring at other times may have been overlooked. However, we thought that moderate to severe PONV reported voluntarily by patients or required treatment was fully measured. Second, we did not consider the PaCO₂–EtCO₂ gap to calibrate EtCO₂ levels using PaCO₂ levels. Thus, we underestimated the effects of low EtCO₂ and overestimated the effects of hypercapnia. However, since PaCO₂ is usually 2–5 mmHg higher than EtCO₂ in healthy populations, this was considered a limited effect. Last, there may be unknown and unmeasured confounding factors, such as potential reasons for anesthesiologists to target a specific EtCO₂ level, missing data on intraoperative ventilation parameters, and PONV risk factors among patient factors is, history of PONV and motion sickness.

Conclusion

Intraoperative low EtCO₂ (mean EtCO₂ level less than 35 mmHg) was not substantially associated with either increased incidence of PONV or prolonged PLOS in patients undergoing gynecologic laparoscopic surgery.

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Competing interests

The authors declare no competing interests.

Additional information

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