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Title

The association of intraoperative endtidal carbon dioxide with the risk of postoperative nausea and vomiting

Brief title

The association of intraoperative EtCO₂ with the risk of PONV

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Abstract

Purpose: Patients undergoing gynecological surgery are considered to be a high-risk cohort for postoperative nausea and vomiting (PONV). The purpose of this study was to assess the association of intraoperative end-tidal carbon dioxide (EtCO₂) with risk of PONV in patients underwent gynecological open surgery.

Methods: In this single-center retrospective observational study, we included patients aged 20-60 years who underwent elective gynecological open surgery. We obtained data for the incidence of PONV within 24 hours after operation. We collected EtCO₂ every minute during the operation, and determined the lowest value of EtCO₂. We compared the lowest EtCO₂ between patients with and without PONV. Multivariate logistic regression analysis was performed to assess the independent association of EtCO₂ with the risk of PONV.

Results: A total of 146 patients were included in the current study. There were 81 patients with PONV within 24 hours after the operation. The median lowest value of EtCO₂ in patients with PONV was significantly lower than that in patients without PONV (31 vs 33 mmHg, $p=0.02$). In the multivariate logistic regression model, we found that lowest EtCO₂ ≤ 31 mmHg was independently associated with increase in the risk of PONV (adjusted odds ratio=3.37, $p=0.02$).

Conclusion: In this retrospective observational study, low intraoperative EtCO₂ was shown to be independently associated with increased risk of PONV. However, this results may be skewed by un-collected information including

previous PONV, motion sickness or other unknown bias, future study should be conducted to refute or confirm our findings.

(243 words)

Introduction

Postoperative nausea and vomiting (PONV) is common after general anesthesia [1]. PONV lowers patients' satisfaction [2] and is associated with a higher risk of postoperative complications [3]. It is also related to an increase in medical expenses due to extension of the hospitalization period [1, 3]. The establishment of a method for anesthetic management that can prevent PONV is therefore desirable.

Although the mechanisms underlying the development of PONV are still unclear, ischemia in the intestinal tract and brain has been reported to cause the release of dopamine and serotonin [4, 5] and result in stimulation of the medullary vomiting center [6]. Therefore, such ischemia has been proposed as one of the significant factors for PONV. Hypocapnia is known to be associated with decreased cardiac output and increased systematic vascular resistance [7, 8], which may lower blood flow in the brain and intestinal tract [9, 10]. Thus, intraoperative hypocapnia may increase the risk of PONV. However, there has been little evidence regarding the relationship between intraoperative hypocapnia and the risk of PONV.

Accordingly, we examined the relationship between intraoperative end-tidal carbon dioxide (EtCO₂) and the risk of PONV in gynecological open surgery.

Methods

Study design

This study was a single-center retrospective observational study. The Kobe University Hospital Ethics Committee approved this investigation (Approved on 31th/October/2016, No.160142). The committee waived the need for informed consent for studies involving the use of a database.

Participants

Inclusion criteria for this study were female patients who underwent elective gynecological open surgery in the period between January 2014 and June 2016, in whom general anesthesia without epidural anesthesia was performed, and who were 20 to 60 years of age. We excluded patients without reliable information and patients who had not been extubated in the operating room after surgery.

Patients' characteristics

We obtained information from anesthetic records on patients' characteristics including age, body weight, height, body mass index (BMI), smoking habit, American Society of Anesthesiologists physical status (ASA-PS), operation procedure, operation time, anesthesia time, amount of intraoperative bleeding, amount of intravenous fluid infusion, intraoperative urine output, maintenance anesthetic agents (propofol or inhalation anesthesia), intraoperative use of non-steroid anti-inflammatory drugs (NSAIDs; including flurbiprofen and diclofenac), dexamethasone, metoclopramide and droperidol,

total dose of intraoperative fentanyl and the use of transverse abdominis plane block. We also obtained information from medical records on dose of intravenous fentanyl was administered postoperatively.

Standard anesthesia

No premedication was given to any of the patients. Attending anesthesiologists considered Apfel score to make individual anesthetic plan [1, 11]. Unfortunately, the information of Apfel score was not recorded formally. Anesthesia was induced with propofol at 1 to 2 mg/kg, rocuronium at 0.6 mg/kg, and remifentanyl at 0.25 to 0.5 $\mu\text{g/kg/min}$ to facilitate tracheal intubation. Anesthesia was maintained using desflurane, sevoflurane or propofol with fentanyl and remifentanyl. The ventilation strategy was based on the decision of attending anesthesiologists, which is commonly including target tidal volume of approximately 8 mL/kg of predicted body weight, plateau airway pressures not exceeding 30 cmH₂O and 5 cmH₂O of PEEP level. Metoclopramide at 20mg was administered during the operation according to the attending anesthesiologist. For postoperative pain management, the attending physician used a transverse abdominis plane block and/or continuous infusion of fentanyl. Administration of NSAIDs or acetaminophen was also used for postoperative analgesia. All patients received 20 mg of metoclopramide once after the operation as a routine practice.

Primary outcome

The primary outcome was the incidence of PONV that occurred within

24 hours after the operation. We defined nausea as an unpleasant feeling of the urge to vomit, and we defined vomiting as expulsion of stomach contents through the mouth. The attending anesthesiologist and the responsible nurse assessed PONV at least every 8 hours for 24 hours after the operation, and data for the incidence of PONV were electronically stored. We used these data for this study.

Intraoperative end-tidal carbon dioxide level

EtCO₂ was continuously measured intraoperatively using a sidestream infrared capnometer (E-sCAiOVE-00; GE Healthcare; Helsinki, Finland), and data for EtCO₂ level every minute were electronically stored. We electrically retrieved data for level of EtCO₂ in all of the participants in this study, and we determined the lowest EtCO₂ under mechanical ventilation during the operation.

Statistical analysis

The results are shown as median with interquartile range (IQR) or n (%). Patients were divided into two groups: patients with PONV and those without PONV and compared these two groups using the Mann-Whitney U test or chi-square test as appropriate. The association of the lowest EtCO₂ with simultaneously measured minute ventilation volume (minute-vol) (ml/kg) was assessed using Pearson's correlation coefficient.

To assess the association between low EtCO₂ and incidence of PONV, we compared the lowest EtCO₂ in patients with PONV and those without PONV. If the lowest EtCO₂ level during the operation had a significant association with

the incidence of PONV, we planned to perform receiver operating characteristic (ROC) curve analysis to assess the cutoff level of the lowest EtCO₂ for predicting the incidence of PONV. To assess the association of duration of hypocapnia, we compared the durations in which EtCO₂ was below the cutoff level (minutes) patients with PONV and those without PONV. Since the relationship between lowest EtCO₂ and risk of PONV may not be linear, we also plan to separate patients using the lower limit of in the normal range (35 mmHg) and cutoff level, and we compared the incidences of PONV in the subgroups for sensitive analysis. To assess the independent association of EtCO₂ below the cutoff level with the incidence of PONV, multivariate logistic regression analysis was performed with adjustment for known predictors of the incidence of PONV such as smoking habit, maintenance anesthetic agents (propofol vs inhalational anesthetic), duration of anesthesia, the use of transverse abdominis plane block and postoperative use of fentanyl.

Among patients with EtCO₂ below the cutoff level, we obtained the duration with EtCO₂ below the cutoff level and calculated its median value. Then, we have divided patients with EtCO₂ below the cutoff level into two groups according to the median value of the duration ("long duration" and "short duration" of hypocapnia). Then, we further developed multivariate model to assess the association of short and long duration with EtCO₂ below the cutoff level.

Data were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12]. We used R [13] to perform statistical analysis. A P value <0.05 was defined as a

statistically significant difference.

Results

Study flow

During the study period, 409 female patients underwent elective gynecological open surgery. In those patients, there were 275 patients in whom general anesthesia without epidural anesthesia was performed. Among them, 163 patients were between 20 and 60 years of age. We excluded 4 patients who had not been extubated in the operating room after surgery and we excluded 13 patients due to lack of reliable information. Finally, we included 146 patients in this study. There were 81 patients (55.5%) with PONV within 24 hours after the operation.

Comparison the characteristics of patients with and without PONV

Table 1 shows a comparison of the characteristics of patients with PONV and those without PONV. There was no significant difference between the two groups in age, weight, height, BMI, smoking habit, ASA-PS, type of operation, operation time, anesthetic time, amount of intraoperative bleeding, amount of intravenous fluid, intraoperative urine output, maintenance anesthetics, intraoperative use of NSAIDs, dexamethasone, metoclopramide and droperidol, the dose of droperidol, total amount of fentanyl used during anesthesia and postoperative use of intravenous fentanyl. The patients with PONV were less likely to be used transverse abdominis plane block in compared with those without PONV ($p=0.02$).

Intraoperative lowest EtCO₂ and its association with incidence of PONV

The median lowest value of EtCO₂ was 32 (IQR: 30-34) mmHg in all of the patients. There was a significant correlation between lowest EtCO₂ and minute-vol ($r=-0.32$, $p<0.01$); the higher minute-vol, the lower EtCO₂.

The median lowest value of EtCO₂ in patients with PONV was 31 (IQR: 30-34) mmHg, which was significantly lower than the median lowest value of 33 (IQR: 31-35) mmHg in patients without PONV ($p=0.02$). ROC curve analysis showed an area under the curve of the lowest EtCO₂ of 0.61 with the best cutoff value of 32 mmHg in patients with PONV (Figure 1). Therefore, we used ≤ 31 mmHg (less than 32 mmHg) as cut off point for our study according to the predefined analysis plan.

In patients with PONV, the proportion of patients with EtCO₂ ≤ 31 mmHg was 50.6% (41/81), which was significantly higher than those of 30.8% (20/65) in patients without PONV ($p=0.015$). According to the pre-defined categorization, we divided the patients into three groups according to the lowest EtCO₂: 31 mmHg or less, 32 to 34 mmHg, and 35 mmHg or more. The incidences of PONV in those three groups were 67%, 51%, and 40%, respectively, and the differences were significant ($p=0.04$) (Figure 2).

In the multivariate logistic regression model, we found that lowest EtCO₂ ≤ 31 mmHg was independently associated with increase in the risk of PONV compared with lowest EtCO₂ ≥ 35 mmHg (32-34 mmHg: adjusted odds ratio=1.79 (95%CI: 0.68-4.74), $p=0.24$, ≤ 31 mmHg: adjusted odds ratio=3.37 (95%CI:1.26-9.02), $p=0.02$) (Supplemental table).

In supplemental figure, we have reported the scatter bar graph to show the number of patients in each of lowest EtCO₂ and the cumulative minutes of

EtCO₂ ≤31 mmHg. In 61 patients with EtCO₂ ≤31 mmHg, the median duration with EtCO₂ ≤31 mmHg was 10 minutes. Accordingly, we further divided patients with EtCO₂ ≤31 mmHg to “short duration” (<10 minutes) and “long duration” (10≥ minutes) with hypocapnia. The median duration with EtCO₂ ≤31 mmHg was 2 minutes (IQR: 1, 4) in short duration cohort and 31 minutes (IQR: 16, 51) in long duration cohort. In table 2, we found that long duration (10≥ minutes) with EtCO₂ ≤31 mmHg was independently associated with increase in the risk of PONV, but not with short duration (<10 minutes) (“short duration with ≤31 mmHg”: adjusted odds ratio=2.95, 95% CI: 0.88-9.89, p=0.08, “long duration with ≤31 mmHg”: adjusted odds ratio=3.71, 95% CI: 1.21-11.3, p=0.02).

Discussion

Key findings

In patients who underwent elective gynecological open surgery, we found that the low intraoperative EtCO₂ level was associated with increased risk of PONV. Even after adjustment with possible confounders, lowest intraoperative EtCO₂ ≤31 mmHg was independently associated with increased risk of PONV in compared with those ≥35 mmHg. In our sensitive analysis, we also found that the longer duration with duration with EtCO₂ ≤31 mmHg had more robust association with the risk of PONV rather than those of short duration.

Although this study was a hypothesis-generating retrospective study, there is little information on the impact of intraoperative EtCO₂ on the risk of PONV. Thus, the current findings might be relevant, and further discussion is required.

Comparison with previous studies

There have been two studies in which the effect of intraoperative EtCO₂ on risk of PONV was assessed. In a randomized double-blind clinical trial by Saghaei et al, 78 patients who were scheduled to undergo percutaneous nephrolithotomy were assigned to three groups with different targets of EtCO₂: 31-33 mmHg (hypocapnia group), 37-39 mmHg (normocapnia group) and 43-45 mmHg (hypercapnia group). The incidence of vomiting in the hypocapnia group was 38.5%, which was significantly higher than the incidence 8.3% in the hypercapnia group (p=0.025) [14]. In another randomized double-blind clinical

trial by Son et al, 400 patients who were scheduled to undergo laparoscopic gynecological surgery were also assigned to three groups with different targets of PaCO₂: 36-40 mmHg, 41-45 mmHg and 46-50 mmHg. In that trial, PaCO₂ was measured indirectly by corrected EtCO₂ (EtCO₂ plus the difference between PaCO₂ and EtCO₂) during surgery. The incidence of nausea during a period of 24 hours after the operation was not significantly different among the three groups (54%, 48%, and 50%, respectively, p=0.59) [15].

To considering above prior studies, we should note that there is still limited information for the association of intraoperative hypocapnia (ex ≤ 31 or 31-34mmHg) with the risk of PONV in gynecological surgery cohort. In this regards, our study might be relevant to generate the hypothesis that the preventing intraoperative hypocapnia had a potential to lower the risk of PONV.

Interpretation

In our cohort, attending anesthesiologists considered Apfel score to plan their anesthetic management [1, 11]. Accordingly, in patient with higher risk of PONV, attending physicians were more likely to use the regional block, to reduce the dose of opioids and to use prophylactic antiemetic following to the recommendations of the guideline for preventing PONV [1]. This fact may interact the association of known risk factors with the risk of PONV. Indeed, in our multivariate model, adjusted odds ratio of smoking habit, the use of propofol and droperidol was <1.0 , but not reach the statistical significance, although prior studies were reported to be associated with decrease the risk of PONV [16]. To considering the above fact, our patients may appear to be the cohort using

guideline for PONV, which may be current common cohort, not the past cohort studied more than decade ago. We should note that the manipulation of EtCO₂ or PaCO₂ had never consider in the guideline. Therefore, the control of EtCO₂ was done according to each attending anesthesiologist. Such a circumstances may give us a chance to observe the native association with the risk of PONV.

Although it is a limited retrospective study in nature, our study show the possible association with intraoperative hypocapnia and the risk of PONV in gynecological surgery cohort. The finding is the same line of the randomized controlled trials by Saghaei et al in patients with percutaneous nephrolithotomy, which suggested that intraoperative hypocapnia might have the potential to increase the risk of PONV.

There are several possible explanation for the significant association between hypocapnia and the risk of PONV. Hypocapnia is known to be associated with decreased cardiac output and between increased systematic vascular resistance [7, 8], which may induce ischemia in the brain and intestinal tract [9, 10]. The onset of brain ischemia, particularly in the striatum and hippocampus, causes the release of monoamine neurotransmitters such as dopamine and serotonin [4]. Ischemia and subsequent reperfusion in the intestinal tract have also been reported to cause serotonin release [5]. Increased dopamine and serotonin would activate the area postrema located in the chemoreceptor trigger zone (CTZ) [6, 17], which may cause PONV through the stimulation of the medullary vomiting center [6]. Additionally, the terminal of the afferent vagus nerve distributed in the gastrointestinal tract has receptors for

serotonin, and connect to the nucleus tractus solitarius and the area postrema [18]. Thus, their stimulation by serotonin may increase the risk of PONV.

However, we should note that there might be another unknown mechanism for the association between lowest EtCO₂ and the risk of PONV seen in our cohort.

Limitations

This study has some limitations. This was an observational study in nature, and thus our findings showed an association but not a causality link. It should be noted that patients at high risk of PONV may have received different anesthesia than that for patients at low risk of PONV, which may have affected the results profoundly. Furthermore, our practice to administrate metoclopramide to all patients may also have affected our results. In this regards, our small single-center study may be with weak generalizability. Finally, it is important to note that we did not have any information on risk factors for PONV including motion sickness and prior history of PONV.

Since the guidelines to prevent the PONV has been available, the choice of maintenance anesthetics and the use of prophylactic antiemetic was according to the known risk assessment as like using Apfel score or Koivuranta's score [11, 19]. Nonetheless, the incidence of PONV is still high. Therefore, developing new approach for PONV might be necessary. The avoiding the lower range of EtCO₂ is cost-less and easy to perform even in poor resource site, and might be reasonable regarding with the physiological point of view, however, never mentioned in the guideline. In our cohort, the lowest

EtCO₂ was eventually low, which make a possibility to assess the native association of EtCO₂ with the risk of PONV. Although this study had significant limitations raised above, it may have a value to be a preliminary hypothesis generating study to establish the management of intraoperative mechanical ventilation in order to prevent PONV in patients undergone gynecological surgery. Our findings should be confirmed or refuted by future prospective or interventional studies.

Conclusion

In this retrospective observational study conducted in patients who underwent gynecological open surgery, intraoperative lowest EtCO₂ ≤ 31 mmHg was independently associated with the risk of PONV. As this results may be skewed by un-collected information including previous PONV, motion sickness or other unknown bias, future study should be conducted to refute or confirm our findings.

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Reference

1. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramer MR, Society for Ambulatory A. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118:85-113.
2. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. *Br J Anaesth*. 2000;84:6-10.
3. Kenny GN. Risk factors for postoperative nausea and vomiting. *Anaesthesia*. 1994;49 Suppl:6-10.
4. Sarna GS, Obrenovitch TP, Matsumoto T, Symon L, Curzon G. Effect of transient cerebral ischaemia and cardiac arrest on brain extracellular dopamine and serotonin as determined by in vivo dialysis in the rat. *J Neurochem*. 1990;55:937-40.
5. Teramoto Y, Urano T, Nagai N, Takada Y, Ikeda K, Takada A. Plasma levels of 5-HT and 5-HIAA increased after intestinal ischemia/reperfusion in rats. *Jpn J Physiol*. 1998;48:333-9.
6. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology*. 1992;77:162-84.
7. Theye RA, Milde JH, Michenfelder JD. Effect of hypocapnia on cardiac output during anesthesia. *Anesthesiology*. 1966;27:778-82.
8. Hermes A, Kontos HPMJ, David W. Richardson, and John L. Patterson JR. Circulatory responses to hypocapnia in the anesthetized dog. *Am J Physiol*.

1965;208(1):139-43.

9. Guzman JA, Kruse JA. Splanchnic hemodynamics and gut mucosal-arterial PCO₂ gradient during systemic hypocapnia. *J Appl Physiol* (1985). 1999;87:1102-6.

10. Laffey JG, Kavanagh BP. Hypocapnia. *N Engl J Med*. 2002;347:43-53.

11. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 1999;91:693-700.

12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet*. 2007;370:1453-7.

13. Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant*. 2013;48:452-8.

14. Saghaei M, Matin G, Golparvar M. Effects of intra-operative end-tidal carbon dioxide levels on the rates of post-operative complications in adults undergoing general anesthesia for percutaneous nephrolithotomy: A clinical trial. *Adv Biomed Res*. 2014;3:84.

15. Son JS, Oh JY, Ko S. Effects of hypercapnia on postoperative nausea and vomiting after laparoscopic surgery: a double-blind randomized controlled study. *Surg Endosc*. 2017;31:4576-82.

16. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, Danner K, Jokela R, Pocock SJ, Trenkler S, Kredel M, Biedler A, Sessler DI, Roewer N, Investigators I. A factorial trial of six interventions for the prevention

of postoperative nausea and vomiting. *N Engl J Med*. 2004;350:2441-51.

17. Borison HL. Area postrema: chemoreceptor circumventricular organ of the medulla oblongata. *Prog Neurobiol*. 1989;32:351-90.

18. Bunce KT, Tyers MB. The role of 5-HT in postoperative nausea and vomiting. *Br J Anaesth*. 1992;69:60S-2S.

19. Koivuranta M, Laara E, Snare L, Alahuhta S. A survey of postoperative nausea and vomiting. *Anaesthesia*. 1997;52:443-9.

Table 1. The comparison of the characteristics of patients with PONV and those without PONV

		Patients with PONV (n=81)	Patients without PONV (n=65)	P value
Age (years)		45 [41, 53]	47 [42, 54]	0.64
Body weight (kg)		58.0 [50.8, 67.7]	58.0 [52.1, 68.4]	0.79
Height (cm)		158.8 [153.9, 161.6]	157.5 [154.8, 162.1]	0.93
BMI		22.7 [20.4, 27.2]	23.5 [20.2, 26.4]	0.82
Smoking habit		16 (19.8%)	15 (23.1%)	0.69
ASA-PS	1	35 (43.2%)	24 (36.9%)	0.07
	2	44 (54.3%)	33 (50.8%)	
	3	2 (2.5%)	8 (12.3%)	
Operative procedure	Hysterectomy	50 (61.7%)	45 (69.2%)	0.67
	Ovarian	23 (28.4%)	13 (20.0%)	
	Uterine	3 (3.7%)	2 (3.1%)	
	myomectomy	5 (6.2%)	5 (7.7%)	
	Others	5 (6.2%)	5 (7.7%)	
Operation time (minutes)		215 [152, 320]	200 [142, 315]	0.71
Anesthesia time (minutes)		264 [208, 366]	269 [202, 390]	1.00
Amount of intraoperative bleeding (ml)		440 [230, 855]	305 [180, 890]	0.26
Amount of intraoperative intravenous infusion (ml)		2300 [1800, 3360]	2320 [1600, 3550]	0.86
Intraoperative urine output (ml)		165 [100, 420]	230 [135, 435]	0.41
Propofol anesthesia		42 (51.9%)	39 (60.0%)	0.40
Intraoperative use of NSAIDs		47 (58.0%)	30 (46.2%)	0.18

Intraoperative use of dexamethasone	1 (1.2%)	2 (3.1%)	0.59
Intraoperative use of metoclopramide	5 (6.2%)	1 (1.5%)	0.23
Intraoperative use of droperidol	40 (49.4%)	35 (53.8%)	0.62
The dose of droperidol (mg)	1.25 [1.25, 1.25]	1.25 [1.25, 1.25]	0.13
Intraoperative fentanyl administration (µg/kg)	9.2 [5.4, 11.8]	8.6 [5.8, 12.0]	1.00
Use of transverse abdominis plane block	31 (38.3%)	37 (56.9%)	0.02
Postoperative fentanyl administration (µg/hr)	30 [25, 50]	35 [25, 50]	0.19

Data are presented as medians [25%, 75% interquartile range] or n (%).

PONV: postoperative nausea and vomiting, BMI: body mass index, ASA-PS:

American Society of Anesthesiologist-physical status, NSAIDs: non-steroid anti-inflammatory drugs.

Table 2; Multivariate regression analysis for the risk of PONV

Variables	Adjusted odds ratio (95%CI)	p-value
Smoking habit	0.86 (0.35, 2.12)	0.74
Propofol (vs. inhalation anesthetics)	0.94 (0.44, 2.01)	0.88
Anesthesia time (minutes)	1.00 (1.00, 1.00)	0.36
Use of droperidol	0.85 (0.41, 1.80)	0.68
Postoperative dose of fentanyl ($\mu\text{g}/\text{hour}$)	1.03 (0.98, 1.08)	0.22
Use of transverse abdominis plane block	0.49 (0.23, 1.06)	0.069
Intraoperative lowest EtCO ₂ 32-34 mmHg (vs. $\geq 35\text{mmHg}$)	1.77 (0.67, 4.69)	0.25
The duration with EtCO ₂ $\leq 31\text{mmHg}$ was <10 minutes (short duration) (vs. $\geq 35\text{mmHg}$)	2.95 (0.88, 9.89)	0.08
The duration with EtCO ₂ $\leq 31\text{mmHg}$ was ≥ 10 minutes (long duration) (vs. $\geq 35\text{mmHg}$)	3.71 (1.21, 11.3)	0.02

CI: confidence interval, PONV: postoperative nausea and vomiting.

Figure legends

Figure 1. Receiver operator characteristic (ROC) curve to evaluate the association of lowest EtCO₂ for the risk of PONV

ROC curve analysis showed an area under the curve of the lowest EtCO₂ of 0.61 with the best cutoff value of 32 mmHg in patients with PONV.

Figure 2. Incidence of PONV according to the lowest EtCO₂

The patients were divided into three groups according to lowest EtCO₂ during the operation: 31 mmHg or less, 32 to 34 mmHg, and 35 mmHg or more. The numbers of patients in the three groups were 61, 55, and 30, respectively. The incidences of PONV in the three groups were 67%, 51%, and 40%, respectively, and the differences were significant ($p=0.04$).

PONV: postoperative nausea and vomiting, EtCO₂: endtidal carbon dioxide.

Supplemental table; Multivariate regression analysis for the risk of PONV according to the lowest EtCO₂.

Supplemental figure; the scatter bar graph for the number of patients in each of lowest EtCO₂ and the cumulative minutes of EtCO₂ ≤31 mmHg.

This graph shows the number of patients in each of lowest EtCO₂ and the cumulative minutes of EtCO₂ ≤31 mmHg in patients without PONV (A) and with PONV (B). The Block bar is for the patients with lowest EtCO₂ ≤31 mmHg and gray bar is for those EtCO₂ >31 mmHg.

Figure1

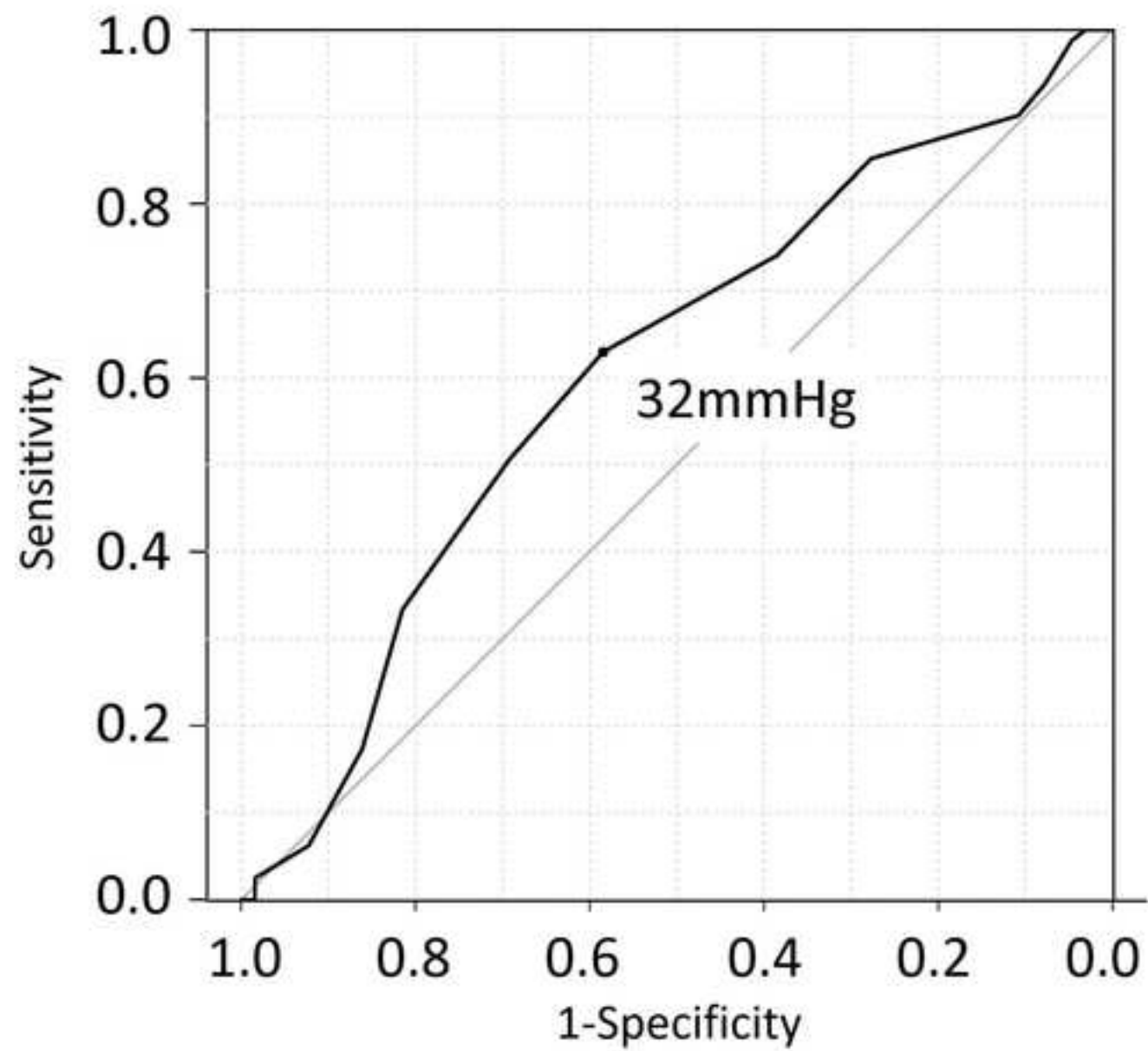
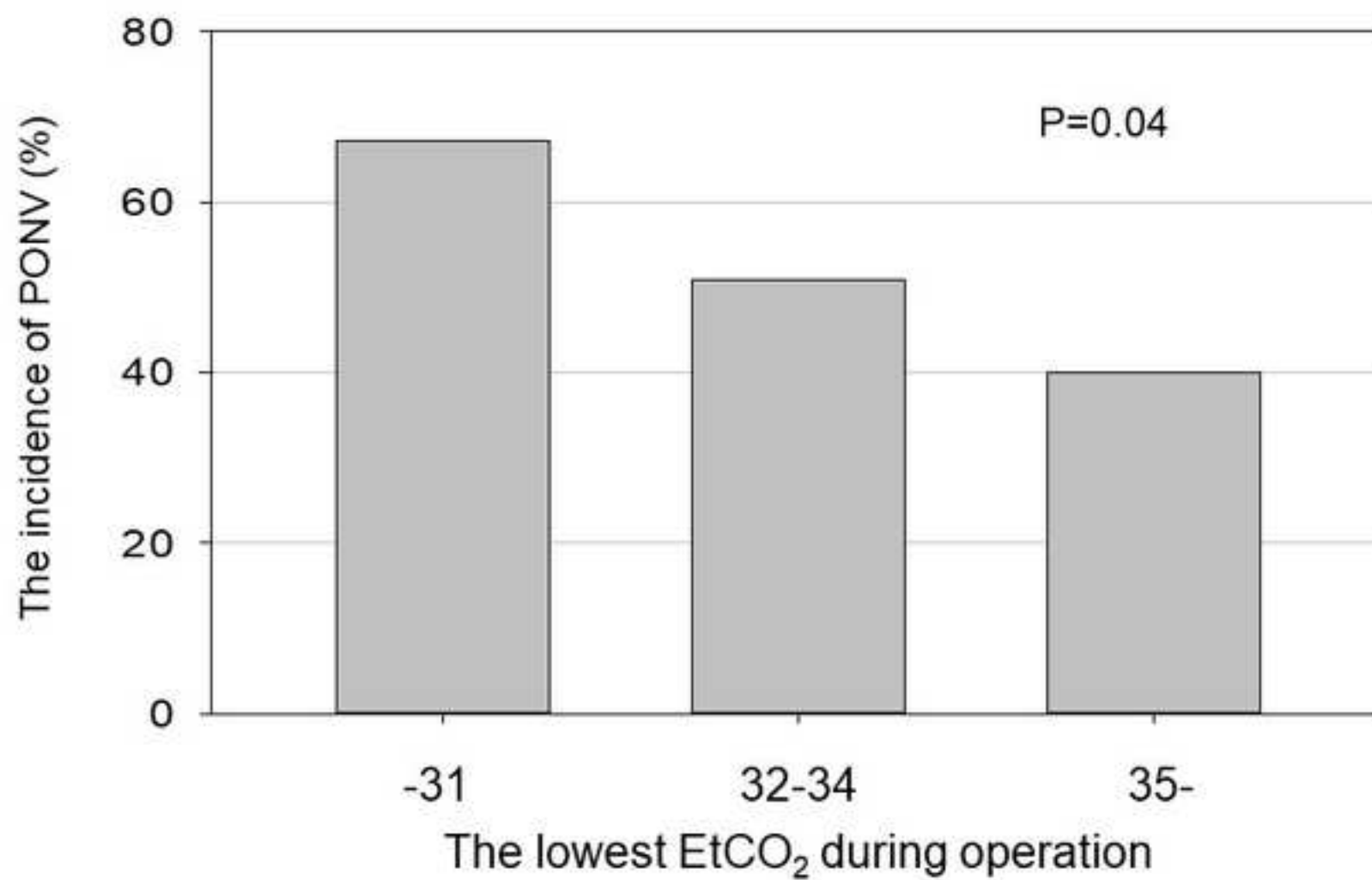


Figure2



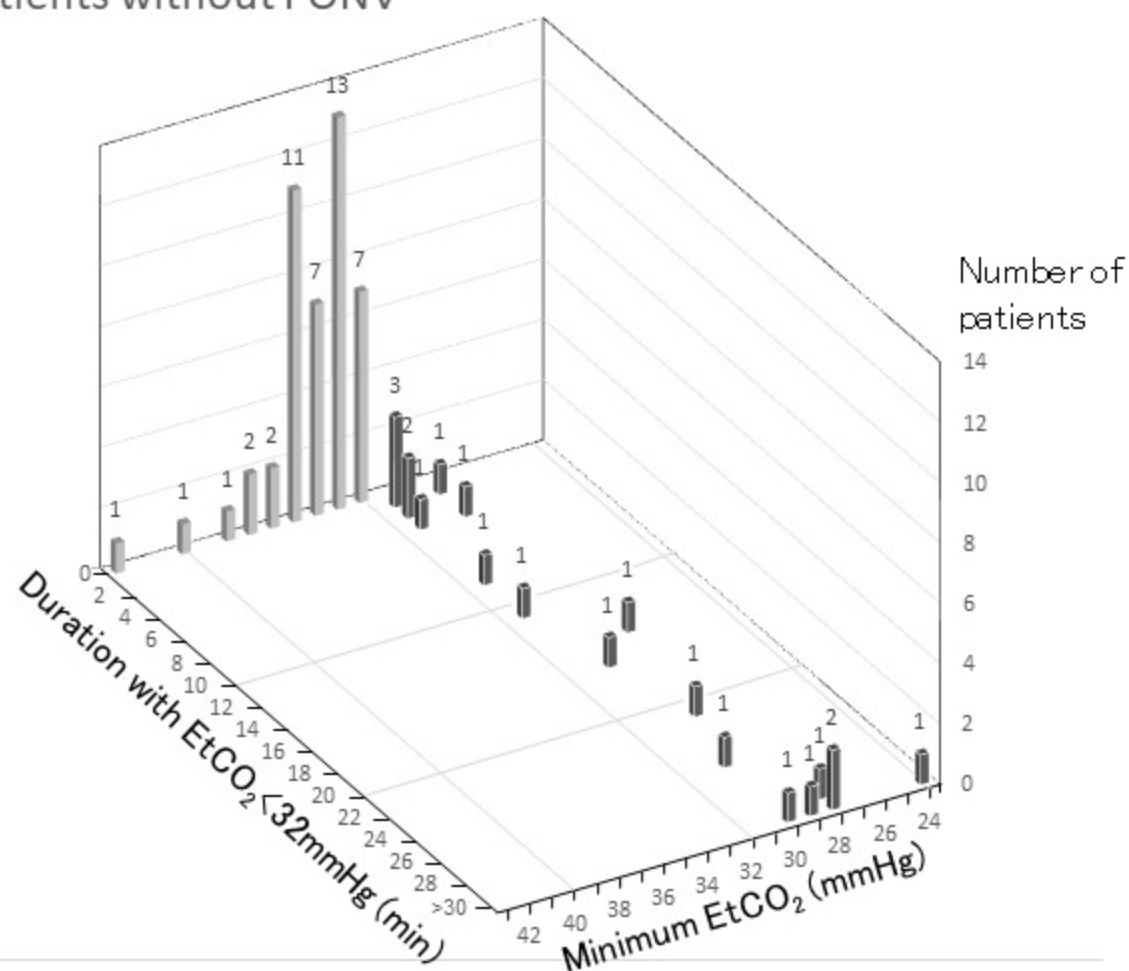
Supplemental Table; Multivariate regression analysis for the risk of PONV according to the lowest EtCO₂.

Variables	Adjusted odds ratio (95%CI)	p-value
Smoking habit	0.89 (0.37, 2.15)	0.79
Propofol (vs. inhalation anesthetics)	0.92 (0.44, 1.93)	0.82
Anesthesia time (minutes)	1.00 (1.00, 1.00)	0.34
Use of droperidol	0.85 (0.40, 1.78)	0.66
Postoperative dose of fentanyl (µg/hour)	1.03 (0.98, 1.08)	0.23
Use of transverse abdominis plane block	0.49 (0.23, 1.03)	0.06
Intraoperative lowest EtCO ₂ 32-34 mmHg (vs. ≥35mmHg)	1.79 (0.68, 4.74)	0.24
Intraoperative lowest EtCO ₂ ≤31mmHg (vs. ≥35mmHg)	3.37 (1.26, 9.02)	0.02

CI: confidence interval, PONV: postoperative nausea and vomiting.

Supplemental file 1

A) Patients without PONV



B) Patients with PONV

