A Clinical Risk Analysis of Postoperative Nausea and Vomiting After Colorectal Cancer Surgery

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Abstract

Objective Postoperative nausea and vomiting (PONV) is a frequent complication following colorectal surgery. The present study investigated the risk factors for PONV after colorectal cancer surgery.

Methods A retrospective study of 204 patients who underwent surgery for colorectal cancer was conducted. Univariate and multivariate analyses were performed to determine the clinicopathological factors associated with PONV.

Results The overall incidence of postoperative nausea (PON) and postoperative vomit (POV) was 26.5% (54/204), and 12.3% (25/204), respectively. The univariate analysis showed that female gender ($p < 0.001$), no current alcohol drinking habit ($p = 0.003$), and no stoma creation ($p = 0.023$) were associated with PON. Postoperative vomit was significantly correlated with female gender ($p = 0.009$), high body mass index ($p = 0.017$), and right-sided colon cancer ($p = 0.001$). The multivariate logistic regression analysis revealed that female gender (odds ratio [OR]: 4.225; 95% confidence interval [CI]: 2.170–8.226; $p < 0.001$) was an independent risk factor for PON. A high body mass index (OR: 1.148; 95%CI: 1.018–1.295; $p = 0.025$), and right-sided colon cancer (OR: 3.337; 95% CI: 1.287–8.652; $p = 0.013$) were independent risk factors for POV.

Conclusion Our findings suggest that female gender for PON and a high body mass index and right-sided colon cancer for POV are risk factors after colorectal cancer surgery. An assessment using these factors might be helpful for predicting PONV.

Keywords
- postoperative nausea and vomiting
- colorectal cancer

Introduction

Postoperative nausea and vomiting (PONV) is a common adverse effect of anesthesia and surgery and is also frequently seen after colorectal surgery in between 8 and 44% of the patients.[1–6] Postoperative nausea and vomiting is extremely distressing, as it exacerbates conditions such as general

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fatigue and/or postoperative wound pain in the already stressful early postoperative period. These outcomes were also reported to lead to a prolonged hospital stay and increased medical costs due to continuing symptoms and additional medication.[5,7–9]

Many types of surgical procedures performed under general anesthesia induce PONV. In particular, colorectal cancer surgery involves the gastrointestinal tract and induces not only PONV but also gastrointestinal-related complications, such as ileus, bowel obstruction, and anastomotic leakage.[10,11] Gastrointestinal symptoms following colorectal cancer surgery tend to be closely related to PONV, and the incidence and etiology of PONV in these cases may need to be considered separately from that in nongastrointestinal surgeries. However, while several risk factors for PONV following general surgery have been identified, few studies have discussed the risk factors for PONV associated with colorectal surgery.[5] A risk analysis in patients with colorectal cancer may help to determine the specific risk factors for PONV following colorectal cancer surgery.

Therefore, the present study investigated the risk factors for PONV in cases of colorectal cancer surgery.

Materials and Methods

Patients

A retrospective study of 204 consecutive patients who underwent colorectal surgery in a single institution at the Department of Surgery, Saga Medical Center Koseikan, between January 2018 and March 2020, was conducted. The medical records of all patients were reviewed in detail. The inclusion criterion was: primary tumor resection performed with open or laparoscopic surgery as elective surgery. The exclusion criteria were: nonresection of the primary tumor, emergency operation, and bowel obstruction at the time of operation. For the present study, the 204 total patients were divided into 2 groups based on the presence of postoperative nausea (PON) or postoperative vomiting (POV).

All patients and their families were informed about the surgical procedure and provided their written consent. Broad consent was obtained for the present study. The medical ethics committee of the Saga Medical Center Koseikan reviewed and approved the present study design (permission number: 21-03-01-05).

Approach

Colorectal cancer was confirmed preoperatively by colonoscopy and a pathological examination. The characteristics of the patients and the preoperative, operative, and postoperative parameters were analyzed. Data on the following variables were obtained: gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, smoking and drinking alcohol habit, medical history, bowel obstruction at the initial diagnosis, preoperative therapy, number of times the patient had undergone fasting preoperatively, blood test results, tumor location (right-sided: ascending to transverse colon, or left-sided: descending to the rectosigmoid colon and the rectum), TNM stage, tumor size, operative procedure, operative time, intraoperative bleeding, blood transfusion, additional operative procedure (resection of an additional organ due to another disease during the same operation), stoma creation, kind of anesthesia and analgesia, intraoperative fluid volume, urine volume during the operation, admission to the intensive care unit, starting day of drinking or eating solid food, day of first defecation, postoperative complications, and duration of postoperative hospital stay. Univariate and multivariate analyses were performed to determine the clinicopathological factors associated with PONV. Postoperative nausea and vomiting was defined as any nausea and/or vomiting occurred by postoperative day 2 in the present study.

Surgical Procedure and Patient Management

All patients underwent open or laparoscopic surgery with adequate lymphadenectomy. The decision to perform postoperative continuous epidural analgesia, continuous intravenous analgesia or no continuous analgesia was determined based on each the condition of each patient. The first choice for continuous analgesia was set as epidural analgesia. However, if patients were being medicated with antiplatelet agents for heart and/or brain disease, continuous intravenous analgesia or no continuous analgesia at all was prescribed. The epidural catheter was inserted at Th10-11, Th11-12, or Th12-L1 at the time of surgery. The discontinuation of continuous analgesia was determined by the doctor in charge, depending on the condition of the patient, such as whether or not they would be able to get out of bed and how much pain control they required after the operation. The epidural analgesia solution was composed of between 500 and 1000 µg fentanyl and 500 mg levobupivacaine with or without 5 mg droperidol mixed with normal saline to a total volume of 300 mL. The bolus dose was 3 ml at a basal infusion rate of between 2 and 4 ml/h and a lockout interval of 30 minutes. The intravenous analgesia solution was composed of 1000 µg fentanyl with or without 2.5 mg droperidol mixed with normal saline brought to a total volume of 50 ml. The bolus dose was 1 mL at a basal infusion rate of 1 ml/h, with a lockout interval of 10 minutes. The gastric tube was inserted at the introduction of the anesthesia and was removed in the operation room immediately after the operation. The pathological tumor stage was classified according to the seventh edition of the UICC-TNM classification. Prophylactic antiemetic medication, such as aprepitant, perphenazine, metoclopramide, dexamethasone, ondansetron, and ramosetron, was not used in any case.

Statistical Analyses

Continuous variables were expressed as the median and interquartile range (IQR), and categorical variables were expressed as numbers. In the univariate analysis, group comparisons used the Wilcoxon rank sum test for continuous variables and the Fisher exact test for binary variables. A multivariate analysis using stepwise multiple logistic regression was performed using the variables found to be significant ($p < 0.1$) by a univariate analysis. The data were expressed as odds ratios (ORs) with 95% confidence intervals

(CIs). A *p-value* < 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA).

Results

Among the 204 patients (116 male, 88 female) with colorectal cancer, 54 (26.5%) and 25 (12.3%) patients experienced PON and POV, respectively. No perioperative mortality was encountered.

►**Table 1** shows the results of the univariate analysis of the factors associated with PONV. The univariate analysis showed that female gender ($p < 0.001$), no current alcohol drinking habit ($p = 0.003$), and no stoma creation ($p = 0.023$) were associated with PON. Postoperative vomiting was significantly correlated with female gender ($p = 0.009$), a high BMI ($p = 0.017$), and right-sided colon cancer ($p = 0.001$). Regarding patient factors, the medical history of the patient, bowel obstruction at the initial diagnosis, and number of times the patient had undergone fasting preoperatively were not associated with PONV. Regarding the operative and postoperative factors, anesthesia factors showed no significant association with PONV. The multivariate logistic regression analysis revealed that female gender (OR: 4.225; 95%CI: 2.170–8.226; $p < 0.001$) was an independent risk factor for PON. Body mass index (OR: 1.148; 95%CI: 1.018–1.295; $p = 0.025$), and right-sided colon cancer (OR: 3.337; 95%CI: 1.287–8.652; $p = 0.013$) were independent risk factors for POV (►**Table 2**).

The postoperative course and complications were also examined. The starting day of drinking was significantly later in the group with POV than in the group without POV ($p = 0.006$). The day of first defecation and starting day of eating solid food were not correlated with the presence of either PON or POV. The postoperative stay was significantly shorter in the group with PON than in the group with POV ($p = 0.028$) (►**Table 3**).

Discussion

Postoperative nausea and vomiting, once it occurs, is not only uncomfortable for the patient but also causes problems that prevent the patient from leaving the bed early and resuming eating. In addition, vomiting may carry a risk of aspiration pneumonia and dehydration. In the present study, PON and POV occurred in 26.5% (54/204) and 12.3% (25/204) of the patients, respectively. These incidence rates seemed to be comparable to those observed in a previous report (between 8 and 44%).[1–6] However, further improvements are needed to achieve better surgical results and an improved quality of life for the patients. Although the issue of PONV is often discussed in anesthesiology, it is not still widely recognized by many surgeons, who do not seem to be aware of it.

The risk factors of PONV seemed to vary widely based on the patient-related, anesthesia-related, and intraoperative and postoperative factors.[8] Postoperative nausea and vomiting can be triggered by several perioperative stimuli, including opioids, volatile anesthetics, anxiety, adverse drug reactions, and motion.[8] Thus far, numerous evidenced risk factors of PONV have been shown in the guidelines for the management of PONV, such as female gender, history of PONV or motion sickness, nonsmoking, younger age, general versus regional anesthesia, use of volatile anesthetics and nitrous oxide, postoperative opioids, duration of anesthesia, and type of surgery (cholecystectomy, laparoscopic, gynecological).[12] However, these risk factors may vary depending on the type of surgery and on the background of the patient concerning the specific disease, like colorectal cancer. In addition, there may be other unique risk factors depending on the disease and type of surgery. Therefore, continual improvements and countermeasures against the risk factors of PONV may help reduce its incidence.

Our study demonstrated that female gender was an independent risk factor for PON in a multivariate analysis. In addition, female gender was a significant factor for POV in a univariate analysis and was close to significance in a multivariate analysis. Female gender was the strongest overall predictor and risk factor for PONV.[8,12,13] The mechanism underlying the relationship between female gender and an increased incidence of PONV is unknown at present.[13] However, it was confirmed that female gender was a risk factor for PONV even in the field of colorectal surgery. In general, younger age is also a strong risk factor for PONV.[8,12] Our study showed no correlation between age and the occurrence of PONV. This may be because the patients presenting with colorectal cancer often tend to be older than those presenting with otolaryngological or orthopedic diseases.

Our study demonstrated that a high BMI was an independent risk factor for POV. Although some previous reports have suggested that the incidence of PONV is increased in obese patients,[14,15] a recent systematic review did not find a relationship between BMI and the incidence of PONV. Intra-abdominal pressure in obese patients could be more dependant on a direct mass effect from the intra-abdominal adipose tissue than non-obese patients.[16] Regarding the postoperative period of the gastrointestinal tract, we speculated that increased visceral fat could lead to PONV from increased abdominal pressure and gastroesophageal reflux. Body mass index as a risk factor for PONV is also still controversial, so further studies are needed.

In our study, right-sided colon cancer was an independent risk factor for POV. This is a novel finding in the present study, and no previous report found a similar result. We speculated that it was because in cases of right-sided colon cancer, including the cecum of the transverse colon, the mesentery of the right-sided colon is isolated and dissected from the ventral side of the duodenum and/or from the pancreatic head. In addition, there are more opportunities to handle the stomach and the duodenum during dissection of the mesentery of the ascending and transverse colon, which may cause temporary upper gastrointestinal paralysis due to the mechanical stimulation, resulting in POV. Cienfuegos et al. and Masoomi et al. previously reported the clinicopathological differences between right- and left-sided colon cancer and found that postoperative ileus was significantly more frequent in cases of cancer in the right colon than in those in the

Table 1 Univariate analysis of the patients

	Nausea			Vomit		
	(-) $n = 150$	(+) $n = 54$	*p-value*	(-) $n = 179$	(+) $n = 25$	*p-value*
Patient factors						
Gender (male: female)	99:51	17:37	< **0.001**	108:71	8:17	**0.009**
Age (years old; median [IQR])	71 [63–78]	73 [66–81]	0.157	71 [65–78]	76 [68–82]	0.075
Body mass index (kg/m^2; median [IQR])	22.5 [20.2–25.0]	22.7 [19.0–26.6]	0.241	22.3 [19.8–25.1]	24.4 [20.0–27.2]	**0.017**
ASA-PS (PS0,1: PS2,3)	33:117	12:42	1.000	40:139	5:20	1.000
Currently smoking (yes:no)	43:107	9:45	0.102	48:131	4:21	0.330
Currently drinking alcohol (yes:no)	86:64	18:36	**0.003**	95:84	9:16	0.136
Patient history						
Cardiac disease (yes:no)	16:134	10:44	0.156	22:157	4:21	0.534
Pulmonary disease (yes:no)	3:147	2:52	0.610	4:175	1:24	0.483
Cerebrovascular disease (yes:no)	12:138	3:51	0.763	13:166	2:23	1.000
Hypertension (yes:no)	65:85	23:31	1.000	75:104	13:12	0.391
Diabetes mellitus (yes:no)	33:117	13:41	0.850	40:139	6:19	0.803
Dementia (yes:no)	4:146	3:51	0.384	5:174	2:23	0.206
Abdominal surgery (yes:no)	57:93	22:32	0.746	70:109	9:16	0.830
Bowel obstruction at the initial diagnosis (yes:no)	14:136	2:52	0.246	16:163	0:25	0.228
Preoperative therapy (yes:no)	9:141	0:54	0.116	9:170	0:25	0.604
Number of times the patient had undergone fasting preoperatively (times; median [IQR])	5[5-6]	5[5-7]	0.707	5[5-6]	5[5-7]	0.365
Blood test results						
Sodium (mmol/L; median [IQR])	141 [139–142]	141 [139–142]	0.554	141 [139–142]	141 [139–143]	0.445
Potassium (mmol/L; median [IQR])	4.2 [3.9–4.4]	4.1 [3.9–4.4]	0.293	4.2 [3.9–4.4]	4.1 [3.8–4.4]	0.198
Hemoglobin (g/dl; median [IQR])	12.8 [11.1–14.2]	13.0 [11.2–14.1]	0.574	12.8 [11.3–14.1]	13.2 [10.7–14.9]	0.534
Albumin (g/dl; median [IQR])	4.1 [3.6–4.3]	4.1 [3.8–4.3]	0.739	4.1 [3.6–4.3]	4.1 [3.8–4.4]	0.682
Tumor factor						
Tumor location (right:left)	50:100	25:29	0.101	58:121	17:8	**0.001**
T category (- T2: T3, T4)	47:103	20:34	0.500	57:122	10:15	0.496
N category (negative:positive)	85:65	34:20	0.520	103:76	16:9	0.666
M category (negative:positive)	135:15	50:4	0.786	162:17	23:2	1.000
Maximum tumor length (mm; median [IQR])	40 [25–55]	44 [26–53]	0.840	40 [28–55]	38 [16–56]	0.437

Table 1 (*Continued*)

	Nausea			Vomit		
	(-) $n = 150$	(+) $n = 54$	*p-value*	(-) $n = 179$	(+) $n = 25$	*p-value*
Operative factors						
Operative procedure (laparoscopic:open)	130:20	47:7	1.000	156:23	21:4	0.752
Operative time (minutes; median [IQR])	245 [204–303]	258 [222–306]	0.788	251 [205–303]	261 [207–309]	0.483
Intraoperative bleeding (ml; median [IQR])	27 [10–65]	20 [7–61]	0.404	25 [8–62]	20 [10–106]	0.762
Blood transfusion (yes:no)	18:132	8:46	0.636	20:159	6:19	0.102
Additional operative procedure (yes:no)	10: 140	5: 49	0.549	12:167	3:22	0.403
Stoma creation (yes:no)	14:136	0:54	**0.023**	14:165	0:25	0.225
Anesthesia factors						
Sevoflurane (yes:no)	48:102	13:41	0.303	54:125	7:18	1.000
Desflurane (yes:no)	100:50	40:14	0.393	122:57	18:7	0.820
Continuous intravenous anesthesia (yes:no)	147:3	53:1	1.000	175:4	25:0	1.000
Maximum intraoperative temperature (°C: median [IQR])	37.0 [36.4–37.4]	37.0 [36.6–37.2]	0.759	37.0 [36.4–37.4]	37.0 [36.8–37.2]	0.963
Infusion volume (ml:median [IQR])	2,510 [2,100–3,000]	2,690 [2,203–3,350]	0.506	2,550 [2,115–3,025]	2,540 [2,175–3,813]	0.793
Total dose of fentanyl/body weight (mg/kg:median [IQR])	4.82 [3.56–6.46]	4.40 [3.62–6.17]	0.447	4.86 [3.59–6.54]	4.13 [3.38–5.43]	0.082
Urine/body weight/ operation time (ml/kg/h:median [IQR])	2.86 [1.62–5.40]	3.48 [1.93–5.66]	0.222	3.00 [1.65–5.53]	3.63 [1.97–4.76]	0.668
Colloidal solution (ml:median [IQR])	500 [400–1000]	500 [400–1000]	0.762	500 [438–1,000]	500 [88–1,350]	0.833
Postoperative factor						
ICU admission (yes:no)	2:148	2:52	0.286	3:176	1:24	0.410
Continuous epidural analgesia (yes:no)	143:7	53:1	0.684	172:7	24:1	1.000
Continuous intravenous analgesia (yes:no)	6:144	0:54	0.344	6:173	0:25	1.000
Continuous usage of fentanyl as analgesia (yes:no)	148:2	53:1	1.000	177:2	24:1	0.326
Continuous usage of droperidol as analgesia (yes:no)	88:62	27:27	0.337	103:76	12:13	0.395

Abbreviations: ASA-PS, American Society of Anesthesiologist physical status; ICU, intensive care unit; IQR, interquartile range.
Numbers in bold represent statistical significance.

Table 2 Results of the multivariate analysis

Multivariate analysis				
Outcome	**Parameter**	**OR**	**(95% CI)**	***p-value***
Nausea	Female gender	4.225	(2.170–8.226)	**< 0.001**
Vomit	Female gender	2.540	(0.973–6.632)	0.057
	Body mass index	1.148	(1.018–1.295)	**0.025**
	Right-sided colorectal cancer	3.337	(1.287–8.652)	**0.013**

Abbreviations: CI, confidence interval; OR, odds ratio.
Numbers in bold represent statistical significance.

Table 3 Postoperative course and complications

	Nausea			Vomit		
	(-) $n = 150$	(+) $n = 54$	*p-value*	(-) $n = 179$	(+) $n = 25$	*p-value*
Starting day of drinking (POD0-1: ≥2)	149:1	53:1	0.058	178:1	22:3	**0.006**
Day of first defecation (POD0-4: ≥POD5)	146:4	49:5	0.057	173:6	22:3	0.083
Start day of eating solid food (POD; median [IQR])	3[3-4]	3[3-5]	0.329	3[3-5]	4[3-5]	0.249
Postoperative complication CD≥3 (yes:no)	9:141	3:51	1.000	11:168	1:24	1.000
Postoperative ileus CD≥3 (yes:no)	2:148	0:54	1.000	2:177	0:25	1.000
Postoperative stay (days; median [IQR])	10[9-12]	9[8-11]	**0.028**	10[9-12]	9[8-11]	0.131

Abbreviations: CD, Clavien-Dindo Number in bold represents statistical significance; IQR, interquartile range; POD, postoperative date.

left colon.[10,11] Therefore, it is possible that the occurrence and mechanism of PONV and postoperative ileus may be closely related. In our study, the occurrence of POV and PON did not correlate with the incidence of postoperative ileus. This phenomenon may be because we only had 2 cases (1%) of postoperative ileus. Therefore, it would be interesting to examine a larger number of patients in the future.

For the prevention of PONV, several prophylactic antiemetic medications, such as metoclopramide, aprepitant, ramosetron, granisetron, dexamethasone, droperidol, fosaprepitant, and ondansetron have been reported.[4,17–20] In our study, droperidol was used for either epidural analgesia or continuous intravenous analgesia since we expect to obtain an antiemetic effect. Continuous usage of droperidol as analgesia was not correlated with the incidence of PONV in the univariate analysis. This result might have been because the dosage of droperidol was small, so continuous usage was not associated with the occurrence of PONV. Prophylactic antiemetic medications have a large impact on patient care in high-risk populations. However, in a general surgical population at low to moderate risk of PONV, most patients will not benefit from routinely administered prophylactic antiemetic medications, since ~ 70% of the patients do not suffer from PONV.[20,21] In addition, multimodal prophylaxis therapy is recommended for patients with medium or high risk.[12] For postoperative procedures involving the gastrointestinal tract, such as colorectal cancer surgery, prophylactic administration of antiemetics may be considered, especially for high-risk cases. Therefore, it is important to identify patients with high-risk factors and to consider administering prophylaxis to these patients.

The postoperative course, such as the day on which patients started drinking and eating solid food, the day of first defecation, and the duration of postoperative stay, were also analyzed in the present study. Among them, only the starting day of drinking was significantly later in the group with POV than in the group without POV. This should be understandable, as patients who have vomited may have difficulty starting to drink. However, interestingly, PONV did not affect the day of first defecation, the starting day of eating solid food, or the occurrence of postoperative ileus (CD≥3). Regarding the postoperative stay, patients with PON tended to have a shorter postoperative stay than those without PON. We speculated that the reason for this was because the group without PON tended to have more patients with left-sided colorectal cancer than the group with PON (67 versus 53%) in our study. Therefore, left-sided colorectal cancer patients may remain hospitalized for a longer duration due to concerns about anastomotic leakage in rectal cancer patients. The occurrence of POV was not correlated with the postoperative stay. Together, these results suggest that PONV after colorectal cancer surgery seems to be only temporary in the early postoperative period and might be unlikely to influence the final outcome.

One limitation of the present retrospective study is that it was conducted at a single institution. Therefore, further studies will be needed in order to confirm the risk factors of PONV after colorectal cancer surgery.

Conclusion

In conclusion, our findings suggest that female gender is an independent risk factor for PON after colorectal cancer

surgery. In addition, a high BMI and right-sided colon cancer are independent risk factors for POV. Postoperative nausea and vomiting might be relatively unlikely to influence the postoperative course concerning the oral intake of solid food and postoperative stay. However, PONV is still extremely distressful for patients in the early postoperative period. Therefore, assessments using these factors might help prevent PONV.

Ethics Approval

The medical ethics committee of Saga Medical Center Koseikan reviewed and approved the present study design (permission number: 21-03-01-05).

Consent to Participate

All patients and their families were informed about the surgical procedure and provided their written consent. Broad consent for this study was obtained.

Consent for Publication

Broad consent was obtained for the present study.

Availability of Data and Material

The data sets generated during the present study are available from the corresponding author on reasonable request.

Author Contributions

Hiraki M., Koga M. and Miura D. designed the present study. Hiraki M., Tanaka T., Koga M., Miura D., Sato H., Mitsumizo S., and Kitahara K. treated the patients. Hiraki M. and Sadashima E. (specialist in statistics) analyzed the data. Hiraki M., Tanaka T., Koga M. and Miura D. interpreted the results and wrote the manuscript.

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None to declare.

Conflict of Interests

The authors have no conflict of interests to declare.

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