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Original article

Nausea and vomiting in a colorectal ERAS program: Impact on nutritional recovery and the length of hospital stay

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SUMMARY

Background & aims: Postoperative nausea and vomiting (PONV) and its impact on the hospital length of stay (LOS), have been extensively studied. However, most previous publications focused their studies on PONV during the first 24 h, and less is known about this complication during the ensuing days, its impact on nutritional recovery or its relation to other complications and the course of care.
Methods: An observational study involving 806 consecutive patients in a colorectal Enhanced Recovery After Surgery (ERAS) programme was performed. The primary objective was to analyse the incidence of early PONV on the day of surgery and the following 2 postoperative days (late PONV). Secondary objectives included evaluation of the influence of late PONV over the LOS and the nutritional recovery adjusted for confounding factors.
Results: PONV tended to increase over time (7% vs 7% and 10%, postop days 0, 1 and 2, respectively; $p < 0.05$). PONV on day 2 was associated in an adjusted analysis with poor oral intake, delayed solid food tolerance and an average increase in LOS of 2 nights. Risk factors for the presence of PONV on day 2 were the use of opioids on the same day, PONV on the day of the surgery and rectal procedures.
Conclusions: PONV continues to be frequent after the first 24 h in colorectal surgery despite high compliance to current anti emetic recommendations. PONV during day 2 negatively affects the nutritional postoperative recovery and independently prolongs the hospital stay. The findings of the current study highlight the adverse effects of opioids and the need of further discussion on how to best audit, prevent and treat late PONV in ERAS colorectal programmes.
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1. Introduction

The incidence of postoperative nausea and vomiting (PONV) has been reported to be as high as 30% [1] and has been related to unanticipated admission after ambulatory surgery [2] and up to a 2 days increase in hospital length of stay [3]. The current state of the art in enhanced recovery programmes for colorectal surgery advocate the use of predictive risk scores and antiemetic prophylaxis to reduce the frequency and impact of this complication [4,5]. However, guideline recommendations and predictive risk scores are focused only on the first 24 h postoperatively [6–8]. Therefore, we examined the incidence of PONV after colorectal procedures on the day of surgery, the ensuing first 2 postoperative days and its influence on the nutritional recovery and the LOS. The study was carried out in a controlled Enhanced Recovery After Surgery (ERAS) environment. ERAS is a multi-modal approach to recovery after major surgery that has been shown to have major impact on outcomes reducing length of stay and complications by 30–40% [9].

2. Methods

This single-centre study was conducted at a tertiary university hospital, credited by the Joint Commission International, and recognized as an ERAS® Centre of Excellence by the ERAS® Society. De-identified and standardised patient data were collected using

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the ERAS® Interactive Audit System for continuous auditing of the peri-operative process [10]. Data was prospectively collected by the ERAS lead nurse from the electronic medical charts and direct patient interview. Records were retrospectively reviewed for this research. Approval was granted from the hospital ethics committee to review the data for this observational study (Protocol #3758, Res 12/120). Consecutive patients ≥18 years of age, who underwent elective colorectal surgery, were included in the analysis. The study period included consecutive patients who underwent surgery between January 2015 and November 2018. Patients who underwent cytoreductive surgery/hyperthermic intraperitoneal chemotherapy (HIPEC) or remained ventilated after the procedure, were excluded from the analysis (Fig. 1). The primary objective was to analyse the incidence of PONV on the day of surgery and the following 2 days of hospital stay. Secondary objectives included studying the influence of late PONV on the course of the postoperative care with special attention to nutrition and LOS using multiple regression analysis adjusted for potentially confounding factors. Additional secondary objectives included an evaluation of compliance to recommended PONV prophylaxis, evaluation of risk factors for late PONV and evaluating the role of late PONV as a potential early sign of a serious complication.

2.1. Procedure

Patients were treated with the aim to follow the ERAS® Society colorectal guideline' [11]. All patients underwent general anaesthesia. Anaesthesia induction was performed using propofol in all cases. Anaesthesia maintenance involved total intravenous anaesthesia with propofol (TIVA) or sevoflurane according to usual practice of the attending anaesthesiologist. No specific recommendations were provided for the treatment of haemodynamic

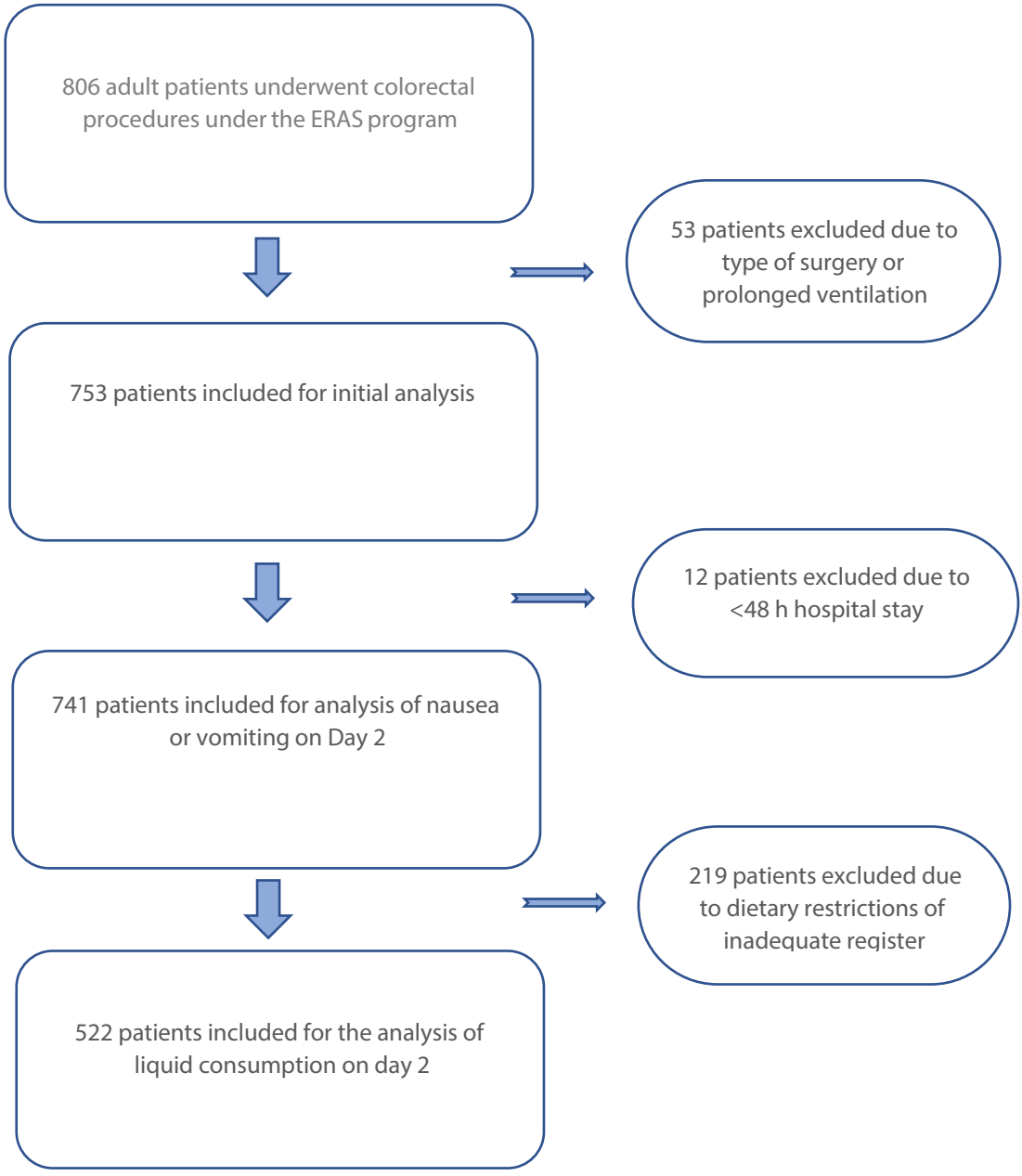

Fig. 1. Patient flow diagram.

abnormalities or for the use of neuromuscular blocking agents. Postoperative analgesia was provided by intravenous (IV) ketorolac 30 mg every 8 h and IV paracetamol 1 g every 6 h. Laparotomy procedures maintained continuous epidural analgesia (bupivacaine 0.125% + fentanyl 2.5 mcg/ml) during the first 48 h. Surgery was performed by four experienced colorectal surgeons. The type of surgery was categorized as colonic and small bowel procedures or as rectal procedure. The group categorized as colonic and small bowel procedures included: left hemicolectomy; ileocecal/right hemicolectomy; stoma procedure; total/subtotal colectomy, sigmoid resection and exploratory laparoscopic or laparotomy procedures. Rectal procedures included: anterior resection; abdominoperineal resection; proctocolectomy and Ileo-pouch anal anastomosis (IPAA). Surgical approach was categorized as minimally invasive when: laparoscopic; hand-assisted; surgery through existing stoma. Laparotomy and converted surgery where categorized as open surgery approach. Conversion was defined according to Chan et al. [12] as the need to perform a conventional laparotomy to accomplish the procedure; or premature abdominal incision for colorectal dissection or vascular control. Surgical duration was recorded in hours. Stimulation of gut motility consisted in chewing gum, laxatives or the combination of both therapies. Immediate drinking after surgery and normal oral diet on day 1 in patients with non-diverted colorectal anastomosis was encouraged in all patients. No patient received postoperative nutritional supplementation. Dietary tolerance was defined as tolerance to intake of two soft diet subsequent meals without nausea or vomiting. Fluid intake was measured daily.

Discharge criteria included tolerance to fluids and soft diet, adequate oral non-opioid analgesia, passage of flatus or stool and the patients' willingness to leave the hospital with adequate home support. First and second outpatient visits were scheduled for postoperative days 7 and 21, respectively. A 30-day telephone follow-up was performed.

2.2. Anti-emetic prophylaxis and treatment of PONV

PONV prophylaxis was recommended for all patients and consisted of intraoperative dexamethasone 8 mg IV and ondansetron 8 mg IV. After surgery, none of the patients continued to receive prophylactic antiemetics. Episodes of emesis (vomiting/retching), nausea and the administration of rescue antiemetic medication were recorded by site staff. Nausea was also assessed by direct questioning of the patients every day after wound closure until discharge. The severity of nausea was evaluated by the patients on a Visual Analogue Scale (VAS), with 0 representing no nausea and 10 the worst nausea imaginable. “Significant nausea” was defined as any score $\geq$4. Rescue antiemetic metoclopramide (10 mg IV) was administered to any patient experiencing “significant nausea”, retching, or vomiting.

2.3. Data handling

Data in presented in accordance with the Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOvER) recommendations [13]. Demographic variables included: date of surgery; age (years); sex; body mass index; American Society of Anaesthesiologists status; smoking status; and history of diabetes. Surgical day was defined as day 0 and the following postoperative days were numbered consecutively (day 1 and day 2). Postoperative morbidity was stratified according to the Dindo-Clavien classification of complications [14]; those graded 3b, 4, and 5 were considered to be “serious complications”. Serious postoperative complications included: surgical complications (i.e., wound infection, anastomotic leak, postoperative bleeding); and general complications (i.e., cardiovascular, deep venous thrombosis). Postoperative ileus was defined according to Chen et al. [15] ($\geq$2 episodes of vomiting > 200 ml occurred in the absence of a bowel movement). Resolution of postoperative ileus was defined as passage of material in a bowel movement in the absence of abdominal distension, nausea, or emesis. Compliance with guideline recommendations for antiemetic prophylaxis was recorded as a categorical dichotomous variable (i.e., Yes or No). Patients were considered to be receiving stimulation for gut motility when receiving chewing gum and/or laxatives. Daily liquid consumption was registered as ml of liquid over the patient's pre-operative weight in kg.

2.4. Statistical analysis

Continuous variables are described according to distribution. Non-parametric data are expressed as median and interquartile range. Categorical variables are expressed as percentages of the studied sample. The chi-squared test was used to compare the incidence on PONV between each postoperative day.

Multiple linear regression analysis was performed to examine the influence of PONV on day 2 over the LOS. Only patients with a hospital stay of >48 h were included in the analysis (Fig. 1). To avoid possible biases in causal inferences, the regression model was assumed to test the hypotheses of a causal effect of “PONV on day 2” (independent variable) over the “LOS” (dependent variable). Independent variables, other than PONV, were selected due to their possible influence on both LOS and PONV and were considered to be confounder variables. Highly correlated independent variables were removed or summarized into 1 category to avoid possible multicollinearity. Confounder variables included ASA status, type of surgery, surgical approach, duration of surgery, postoperative serious complication, postoperative ileus, total i.v. intraoperative fluids (ml/kg/h) and postoperative stimulation of gut motility. Type of surgery and surgical approach were treated as dummy variables due to their categorical and ordinal nature. Type of surgical approach was also categorized as minimally invasive and open surgery. Previous investigations have reported that nausea and vomiting may be studied as different events regarding their pathophysiology and risk factors (16). Therefore, because a significant association between PONV and LOS was documented, sub-analyses dividing PONV into two separate variables—nausea and vomiting—was performed. Risk factors for the occurrence of PONV on day 2 were also analysed. A multiple logistic regression was performed for traditionally described risk factors including age, sex, smoking status, TIVA or sevoflurane, history of PONV, and opioid use. Type of procedure, approach, and PONV on day 0 were also included. A multiple logistic regression was performed to analyse the role of late PONV on day 2 as an early sign of a serious postoperative complication that will be require reintervention. Variables analysed as potential confounding factors included, surgery duration, type of procedure, surgical approach, ASA status, intraoperative fluids and postoperative ileus. Analysis was performed using STATA version 13.0 (StataCorp LLC, College Station, TX, USA); $p < 0.05$ was considered to be statistically significant.

3. Results

During the period analysed, 806 patients underwent colorectal procedures guided by the ERAS® Society programme. Fifty-three patients were excluded from the analysis due to the type of surgical procedure (HIPEC/cytoreductive) or prolonged ventilation after surgery. A total of 753 patients were analysed. Patient flow diagram is presented in Fig. 1.

The median LOS was 4 days, and 748/753 (99%) patients received prophylactic antiemetics in the intraoperative.

Demographic, surgical characteristics and compliance to ERAS guideline are presented in Table 1 and Table 2.

During the day of surgery and the ensuing 2 postoperative days, 164/753 (22%) patients experienced at least 1 event of nausea and/or vomiting. PONV on day 2 continued to be a frequent complication showing a marginally significant upward trend when compared to day 0 and day 1 (7% on day 0 vs. 7% on day 1 and 10% on day 2, respectively; $p < 0.05$). Some patients had a transient early PONV episode, while an increasing number of patients continued or started to present late PONV on day 2 (Fig. 2).

Patients with PONV on day 2 presented a prolonged hospital stay when compared to the patients without this complication (4 (1) nights vs 7 (6) nights; $p < 0.0001$). When patients with late PONV on day 2 were separated into two groups (only late PONV vs. late PONV and serious complication or paralytic ileus) and compared to asymptomatic patients, a 2-nights prolonged hospital stay and a negative impact on nutritional recovery were still observed in the only late PONV group as compared with asymptomatic patients (Table 3).

In the multiple regression analysis adjusted for possible confounding variables, PONV on day 2 was found to significantly extend hospital stay by 2 nights ($p = 0.004$) (Table 4).

In a same way, in the multiple regression analysis evaluating the postoperative nutritional recovery, PONV on day 2 resulted in a 2 ml/kg reduction in oral liquid consumption and an averaged 2 nights delay in solid tolerance (Table 5 and Table 6).

In the multiple regression sub-analysis examining PONV on day 2 as 2 separate variables (i.e., nausea and vomiting), an average 4 nights increase in the LOS was associated with the presence of vomiting on day 2. Nausea alone presented a marginally significant association to a 1-night increase in the LOS (See Table 7).

When evaluating the role of late PONV as a potential early sign of a serious complication, we observed an unadjusted 3-fold increase risk for a later re-operation in patients presenting PONV on day 2 (13% in the PONV on day 2 group vs. 5% in other patients; OR 2.95 CI95% 1.4–6.3; $p = 0.008$). In a multiple logistic regression analysis, an adjusted 2.5-fold increase risk for reintervention in patients with PONV on day 2 was confirmed (Table 8). The sub-analysis dividing patients with PONV on day 2 into two different categories (late PONV and persistent PONV, Fig. 2) showed that 15% of patients starting with PONV on day 2 required a reintervention vs. 6% of patients that continued to have PONV from day 0 or 1 onto day 2 (persistent PONV group). Nonetheless, the odds risk for

Table 1
Patients characteristics (n = 753). Values are expressed as mean ± interquartile range or percentage from total study sample. Previous PONV= Postoperative nausea or vomiting in a previous anaesthesia; TIVA = Total intravenous anaesthesia with propofol; Minimally Invasive = Laparoscopic, Hand-assisted and approach through ostoma.

Demographics		Surgical Characteristics		
Age (years)	64 ± 11	Anaesthesia	78% TIVA	22% Sevofluorane
Female	52%	Previous PONV	12%	
BMI	25 ± 3	Intraoperative antiemetic prophylaxis	99.8%	
Preop nutritional assessment performed	75%			
Diabetes	8%	Length of Surgery	3 ± 1	Hours of Surgery
Smoker	15%	Surgery	19%	Open Surgery Approach
ASA	5% ASA 1	Opioid Use day 1	81%	Minimally Invasive
	70% ASA 2	Opioid Use Day 2	18%	Rectal Procedures
	23% ASA 3		82%	Colonic and Small Bowel Procedures
	2% ASA 4		25%	
			19%	

Table 2
Compliance with ERAS guideline's recommendations.

Compliance group	Hospital compliance measure	Compliance	Non-compliance	Missing
Total		**66,0%**	**26,0%**	**8,0%**
PreAdmission	Preadmission patient education	96,3%	3,2%	0,4%
PreOp	No Oral bowel preparation done unless applicable	54,6%	44,4%	1,0%
PreOp	Preoperative oral carbohydrate treatment	91,9%	7,3%	0,8%
PreOp	Preoperative long-acting sedative medication	95,2%	4,4%	0,4%
PreOp	Thrombosis prophylaxis	92,7%	7,3%	0,0%
PreOp	Antibiotic prophylaxis before incision	99,6%	0,4%	0,0%
PreOp	PONV prophylaxis administered	100,0%	0,0%	0,0%
IntraOp	Intraoperative epidural used if applicable	97,2%	2,8%	0,0%
IntraOp	Minimally invasive surgical approach	81,0%	19,0%	0,0%
IntraOp	No long-acting systemic opioids given	99,2%	0,4%	0,4%
IntraOp	Upper-body forced-air heating cover used	96,2%	0,3%	3,5%
IntraOp	No NG tube used postoperatively	88,9%	11,1%	0,0%
IntraOp	No resection-site drainage unless applicable	32,7%	66,7%	0,6%
PostOp	Time to termination of urinary drainage (nights)	59,6%	35,2%	5,2%
PostOp	Stimulation of gut motility	69,5%	29,3%	1,2%
PostOp	Postoperative epidural used if applicable	96,3%	3,7%	0,0%
PostOp	Balanced fluids day 0	77,9%	22,1%	0,0%
PostOp	Weight change on POD 1	53,4%	1,6%	45,0%
PostOp	Duration of IV fluid infusion (nights):	11,2%	88,5%	0,3%
PostOp	Energy Intake On day of surgery, postoperatively	0,1%	96,2%	3,7%
PostOp	Energy Intake on Postoperative Day 1	0,1%	95,3%	4,6%
PostOp	Mobilisation at all on day of surgery	63,6%	31,9%	4,5%
PostOp	Mobilisation on postoperative day 1	9,7%	23,3%	67,0%
PostOp	Mobilisation on postoperative day 2	2,0%	24,4%	73,6%
PostOp	30 day follow up performed	73,8%	24,8%	1,4%

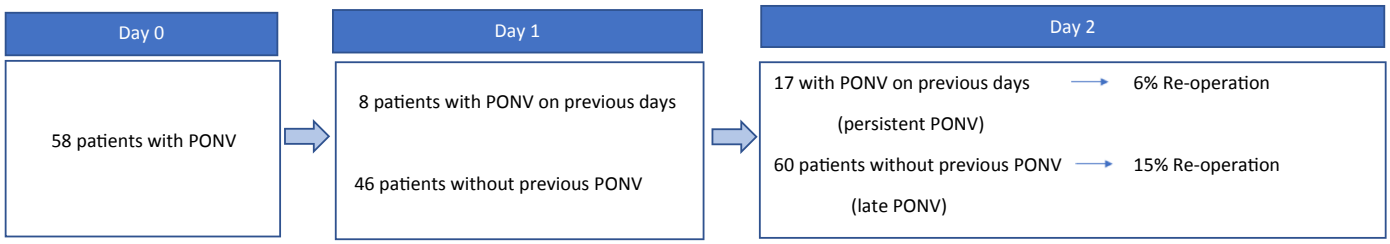

Fig. 2. Evolution of patients with PONV.

Table 3
Data is expressed as median (interquartile range). LOS = Length of stay measures in nights; PONV = postoperative nausea and/or vomiting; Severe complication or Ileus was considered present when occurring during the 30 day follow up. Difference between the groups was analysed with a Kruskal–Wallis Test with post-hoc analysis. A $p < 0.05$ was considered significant.

	LOS	Intraoperative I.V. fluids in ml/kg/h of surgery	Total I.V. fluids on day 0 ml/kg	Oral fluid consumption in ml on day 0	Oral fluid consumption in ml on day 1	Oral fluid Consumption ml day 2	Days to passage of first flatus	Days to solid food tolerance
Asymptomatic for PONV on day 2 without serious postop complication or ileus (n = 596)	4 (2)	7 (6)	33 (19)	0 (20)	100 (375)	500 (500)	2 (1)	3 (2)
Patients with PONV on day 2 without serious postop complication or ileus (n = 67)	6[b] (4)	7 (5)	31 (24)	0 (20)	200 (300)	0[a] (325)	2 (2)	4[a] (4)
Patients with severe complication and/or ileus (n = 78)	14[b] (10)	7 (6)	38[b] (37)	0 (10)	0[b] (250)	0[a] (100)	3[b] (4)	9[b] (7)

[a] Different from Asymptomatic.
[b] Different from all groups.

Table 4
Adjusted results of the multiple linear regression analysis showing factors that influence the length of hospital stay (nights in hospital). PONV = Post-operative nausea or vomiting. CI = Confidence interval (n = 741). A $p < 0.05$ was considered significant. R2 for multivariate analysis = 0.46.

Independent Variables	Univariate β	P value	Multivariate β	CI 95%	P value
PONV on Day 2	+3 (nights)	<0.0001	+2 (nights)	0.5 to 3	0.006
Severe Post-op Complication	+17 (nights)	<0.0001	+15 (nights)	13 to 16	<0.0001
Open surgery approach	+5 (nights)	<0.0001	+2 (nights)	1 to 3	<0.0001
Post-operative Ileus	+6 (nights)	<0.0001	+3 (nights)	1 to 4	<0.0001
Intraoperative i.v. fluids ml/kg/h	+0.1 (nights)	0.02	+0.1 (nights)	0.08 to 0.20	0.001
Length of surgery in hours	+1 (night)	0.0001	+1 (night)	0.6 to 1.5	<0.0001
ASA ≥ 3	+1 (night)	0.005	+1 (night)	0.3 to 2	0.01
Stimulation of gut motility	−4 (nights)	<0.001	−2 (nights)	−2 to −0.8	<0.001
Rectal Procedure	+2 (nights)	0.0001	0.14 (nights)	−0.8 to 1.1	0.7

Table 5
Adjusted multiple linear regression analysis showing the influence of independent variables on the daily oral liquid consumption on postoperative day 2 (ml consumed in one day/patient weight in kg). PONV = Post-operative nausea or vomiting, CI = Confidence interval. NA = Not applicable for multivariate analysis due to non-significant univariate correlation. *p value for univariate correlation. A $p \leq 0.05$ was considered significant. R2 for multivariate analysis = 0.22.

Independent Variables	Univariate β	P value	Multivariate β	CI 95%	P value
PONV on Day 2	−3 (ml/kg)	<0.0001	−2.1 (ml/kg)	−3.22 to −0.98	0.0002
Severe Post-op Complication	−4 (ml/kg)	<0.0001	−1.57 (ml/kg)	−3 to −0.6	0.04
Open surgery approach	−3 (ml/kg)	<0.0001	−1.88 (ml/kg)	−2.9 to −0.9	0.0003
Post-operative Ileus	−4 (ml/kg)	<0.0001	−2.3 (ml/kg)	−3.7 to −0.9	0.001
Stimulation of gut motility	+3 (ml/kg)	<0.0001	+2 (ml/kg)	+1.18 to +2.80	<0.0001
Length of surgery in hours	−0.8 (ml/kg)	<0.0001	−0.4 (ml/kg)	−0.7 to −0.06	0.009
ASA ≥ 3	−1 (ml/kg)	0.01	−0.9 (ml/kg)	−1.7 to −0.01	0.05
Rectal Procedure	−1 (ml/kg)	0.007	−0.6 (ml/kg)	−1 to 1	0.96
Intraoperative i.v. fluids ml/kg/h	−0,3 (ml/kg)	0.75	NA	NA	NA

reintervention in patients with late PONV on day 2 vs. persistent PONV on day 2 was not statistically significant (OR 3, CI95% 0.33 to 24; $p = 0.4$).

Risk factors for PONV on day 2 included the use of opioids on day 2 but not the use of opioids on day 0. However, PONV on day 0 was associated with a 3-fold increased odds ratio of presenting PONV also in day 2. Rectal procedures compared with colonic and small bowel interventions presented a 2-fold increased odds ratio for delayed PONV on day 2. Several of the classical risk factors associated with early PONV such as gender, smoking, history of motion sickness, or type of anaesthesia (TIVA vs sevoflurane), were not associated with PONV on day 2 (Table 9).

Table 6
Adjusted multiple linear regression analysis showing the influence of independent variables affecting the time necessary for patients to tolerate solid food intake. PONV=Post-operative nausea or vomiting, CI= Confidence interval. NA= Not applicable for multivariate analysis due to non-significant univariate correlation (n = 714). A $p \leq 0.05$ was considered significant. R2 for multivariate analysis = 0.20.

Independent Variables	Univariate β	P value	Multivariate β	CI 95%	P value
PONV on Day 2	+3 (nights)	<0.0001	+2 (nights)	0.7 to 3	0.001
Severe Post-op Complication	+9 (nights)	<0.0001	+7 (nights)	5 to 9	<0.0001
Post-operative Ileus	+5 (nights)	<0.0001	+4 (nights)	2 to 5	<0.0001
Duration of surgery (hours)	+0.71 (nights)	<0.0001	+0.38 (nights)	0.1 to 0.7	0.005
Intraoperative i.v. fluids ml/kg/h	+0.06 (nights)	0.06	+0.07 (nights)	0.01 to 0.13	0.01
Open Surgery	+2 (nights)	<0.0001	+1 (night)	0.13 to 2	0.02
Stimulation of gut motility	−2 (nights)	<0.0001	−1 (night)	−1.43 to 0.03	0.06
Rectal Procedure	+1 (night)	0.02	+1 (night)	−0.6 to 1.3	0.47
ASA ≥ 3	+0.14 (nights)	0.7	NA	NA	NA

Table 7
Multiple regression analysis showing the effect of various factors on the length of hospital stay when considering Nausea and Vomiting on Day 2 as two separate events. CI = Confidence interval. NA = Not applicable for multivariate analysis due to non-significant univariate correlation (n = 741). A $p < 0.05$ was considered significant. R2 for multivariate analysis = 0.45.

Independent Variables	Univariate β	P value	Multivariate β	CI 95%	P value
Vomiting on Day 2	+6 (nights)	0.0001	+4 (nights)	1 to 6	0.001
Nausea on Day 2	+2 (nights)	0.004	+1 (night)	−0.1 to 2	0.07
Severe Post-op Complication	+16 (nights)	<0.0001	+14 (nights)	13 to 16	<0.0001
Open surgery approach	+5 (nights)	<0.0001	+3 (nights)	2 to 4	<0.001
Post-operative Ileus	+6 (nights)	<0.0001	+3 (nights)	1 to 4	0.0001
Intraoperative i.v. fluids ml/kg/h	+0.09 (nights)	0.002	+0.14 (nights)	0.08 to 0.2	<0.0001
Duration of surgery (hours)	+1.4 (nights)	<0.0001	+1 (night)	0.7 to 1.2	<0.0001
ASA ≥ 3	+1 (nights)	0.01	+0.6 (nights)	0.07 to 1.2	0.02
Rectal Procedure	+0.7 (nights)	0.001	0.14	−0.8 to 1.2	0.75

Table 8
Multiple logistic regression results for risk factors and their association with a later serious postoperative complication requiring a re-intervention. CI = Confidence interval.

Independent Variables	Odds Ratio	CI 95%	P value
PONV on Day 2	2.5	1.1 to 5.5	0.02
Length of surgery in hours	1.3	1.05 to 1.6	0.02
Rectal Procedure	1	0.5 to 2.2	0.9
Open surgery approach	1.7	0.76 to 3.5	0.2
ASA ≥3	1.4	0.7 to 3	0.3
Intraoperative i.v. fluids (ml/kg/h)	1	0.94 to 1	0.88
Post-operative Ileus	2.33	0.9 to 6	0.06

Table 9
Multiple logistic regression results for risk factors and their association with nausea or vomiting on Day 2. CI= Confidence interval, TIVA = total intravenous anaesthesia.

Independent Variables	Odds Ratio	CI 95%	P value
PONV on Day 0	3	1.5 to 6	0.002
Opioid use on Day 2	2.5	1.4 to 4.7	0.002
Rectal Procedure	1.8	1.03 to 3.2	0.03
Opioid use on Day 1	0.6	0.3 to 1.11	0.1
Open Surgery Approach	1.19	0.65 to 2.14	0.56
Female	1.17	0.7 to 2	0.55
Sevofluorane	0.9	0.5 to 1.5	0.6
Smoker	1.09	0.54 to 2.2	0.79
History of PONV or motion sickness	1	0.44 to 2	0.9
Age	1	0.97 to 1.01	0.5

4. Discussion

PONV is traditionally studied as an immediate and anaesthesia-related postoperative complication. This study confirmed that although PONV may present immediately after surgery, it progressively develops for at least 2 days following a colorectal procedure, despite the use of prophylaxis and ERAS implementation. Additionally, the presence of PONV at day 2 negatively affected the postoperative nutritional recovery and prolonged the hospital stay.

PONV occurring at day 2 can be an early sign of serious complications. However, when these patients were excluded from the analysis (Table 2) and the confounding variables (including clinical, surgical, and postoperative features, Table 3) were adjusted, PONV on day 2 continued to present an average increase of 2 nights in the LOS. These results suggest that a significant proportion of patients are at risk of prolonged hospital stays due to delayed or persistent PONV; this finding opens a discussion on how best to capture and manage this complication.

Unsurprisingly, a significant reduction of liquid consumption on day 2 was independently attributed to the presence of late PONV in an adjusted analysis (Table 5). Similarly, solid food tolerance was delayed on an average of 2 nights due to the onset of late PONV (Table 6). These findings suggest that the prolonged hospital stay observed in patients with late PONV may be attributed to the negative impact over the nutritional postoperative recovery.

Researchers investigating ambulatory surgery have described the increased risk of post-discharge nausea or vomiting in patients that presented with immediate PONV at the postoperative recovery unit [17]. Their findings correlate with our study, which suggests that an adequate approach to early PONV may help reduce the incidence of PONV in the ensuing days. Furthermore, it appears that antiemetic prophylaxis and ERAS implementation had a beneficial effect on early PONV since there were only 7% of patients with this problem. This is lower than the figures reported in previous literature [1]. Nevertheless, despite nearly all the patients in this study receiving prophylaxis, there were still patients that experienced early PONV. It remains unclear if changes in the choices of prophylactic medications or anaesthetic techniques can achieve better results.

Furthermore, PONV in the later stages may be a more prominent problem in ERAS, due to the finding that the frequency of PONV increased with time. Additionally, it is in this stage of patient care

that patients go from a standardised and prophylactic antiemetic intervention to an heterogenous strategy that may vary significantly from centre to centre. Persistent PONV after the first 24 h was also observed in a recently published retrospective study in a colorectal ERAS programme [18]. Similar to the current findings, the use of morphine was also associated with late PONV [18]. The impact of opioids on the gastrointestinal tract and with PONV are well documented [19]. These side effects of opioids also stand out when ERAS principles are employed. In the current study, 19% of the patients required opioid analgesia during day 2 and the use of opioids was associated to increased PONV. These findings highlight that the development of opioid sparring or opioid free analgesia protocol is essential to address the problem of postpreparative gastrointestinal dysfunction.

However, some patient will inexorably require rescue pain medication with opioids. For this group, the use of long-acting 5-HT3 antagonists has been associated with promising results in patients receiving postoperative opioid analgesia or those who experienced delayed chemotherapy-induced nausea and vomiting [20]. Specifically, palonosetron proved to be effective in controlling PONV during the first 72 h after gynaecological and laparoscopic surgery in recent clinical trials [21]. Similarly, prolonging the antiemetic prophylaxis administered during day 0 onto day 1 and 2 may reduce the incidence of late PONV. Both the use of extended antiemetic prophylaxis or long-acting 5-HT_3 antagonists in colorectal patients should be adequately addressed in future studies.

As discussed above, late PONV may present as the only postoperative complication; however, it may also indicate a more serious postoperative complication. Segregating these two separate entities is of paramount importance in clinical practice. It is possible that PONV on day 2 in patients that were asymptomatic in the previous days can be an early warning of a more severe complication, especially if they are not receiving opioid analgesia (see Fig. 2). Although this was not statistically supported in this study; it represents an important question to be addressed in future studies with larger sample sizes.

It has been commonly assumed that postoperative nausea and vomiting can be studied as grades of the same phenomenon and therefore bundled as one outcome in the analysis. However, the interchangeable use of the terms “nausea” and “vomiting” can lead to confusion [16]. Contributing to a standardised and clearer study of PONV, Tramèr et al. proposed that nausea and vomiting should be reported and analysed separately [22]. Consistent with this and as expected, the current results demonstrated that vomiting has a stronger correlation with prolonged LOS than nausea alone. Nevertheless, we believe that neither should be neglected because both may affect the outcome and the capacity or willingness of the patient and health care provider to accept hospital discharge after colorectal surgery.

The current study had limitations that should be considered when interpreting the results. First, the single-centre design requires external validation to corroborate our findings; also, it cannot be immediately extrapolated to patients undergoing other types of surgeries. Additionally, although antiemetic prophylaxis was used in almost all patients on day 0; in our centre, no prophylactic anti-emetic is typically indicated after day 0, and nausea is only treated with metoclopramide when it appears. Hence, this management may not be aggressive enough, which may result in difficulties in managing PONV. Nonetheless, the percentage of patients presenting with PONV on day 0, and during the rest of the hospital stay is similar to the numbers reported in previous publications [17]. Patients included in the ERAS® programme were under strict follow-up, and compliance to guidelines was continuously audited. This may influence daily practice and limit the generalizability of the results observed to a population undergoing surgery with more traditional perioperative care. Moreover, mobilization registers after day 0 were poor, and postoperative opioid use was not registered quantitatively but as a categorical variable. Finally, the use of a multimodal approach to PONV prophylaxis according to the estimated risk may have modified the incidence of PONV in the current study. However, an alternative strategy employed in many practices is to administer antiemetic prophylaxis to all patients. This approach is gaining popularity among anaesthetists given that the cost and side-effect profiles of commonly used antiemetic drugs are small [23]. In a recent trial the use of a simplified protocol (female patients receiving triple prophylaxis (dexamethasone and ondansetron plus either a target-controlled infusion with propofol or droperidol) and male patients receiving double prophylaxis, dexamethasone, and ondansetron) was examined. The authors found a reduced incidence of PONV and better compliance to antiemetic prophylaxis [24]. In the current study, 78% of the patients underwent a general anaesthesia using total intravenous anaesthesia with propofol and received also dexamethasone and ondansetron during the intraoperative. Of the remaining 22%, only 10 patients presented ≥ 2 risk factors. The influence of these variables over the results cannot be assessed by this study.

In summary, although traditionally studied as an anaesthesia-related postoperative complication, this study demonstrated that despite a relatively low incidence on day 0, PONV continues to be a frequent complication after the first 24 h of surgery, even when employing ERAS principles. This may impact the postoperative recovery because PONV during day 2 negatively affects the nutrition and independently prolongs the hospital stay. These findings highlight the need for further studies on how best to audit, prevent, and treat late PONV in ERAS colorectal programmes.

Details of authors contributions

Conception and design: all authors.
Analysis SML, ST, OL and AA.
Interpretation of data: all authors.
Critical revision of the article for important intellectual content: all authors.

Declaration of interests

None to declare.

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