Risk Factors for Postoperative Ileus after Elective Colorectal Surgery

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Abstract

Purpose: The aim of this study was to determine whether various patient characteristics and perioperative clinical interventions might be correlated with the incidence of postoperative ileus (POI). **Methods:** We prospectively investigated 114 patients who were scheduled to undergo elective colorectal surgery. The associations of patient characteristics and clinical interventions with POI were examined statistically. We also included preoperative stress as a possible predictor of POI. **Results:** A total of 11 (9.7%) patients developed POI. Univariate analyses showed that an intraoperative remifentanyl dose of ≥ 4.0 mg was significantly associated with the occurrence of POI. Although a multivariate analysis showed that only an intraoperative remifentanyl dose of ≥ 4.0 mg was statistically correlated with the occurrence of POI ($p=0.0375$), the risk for POI increased significantly with the number of other predictive factors present: a male sex, and an intraoperative remifentanyl dose of ≥ 4.0 mg. A correlation between preoperative stress and the incidence of POI was not found. **Conclusions:** Our study suggests that an intraoperative remifentanyl dose of ≥ 4.0 mg is a risk factor for POI and that the risk increases when it coexists with a male sex. Further study is needed to clarify the correlations among a

male sex, intraoperative remifentanyl use, and the incidence of POI.

Key words: risk factor, postoperative ileus, postoperative complications, colorectal surgery

Introduction

Postoperative ileus (POI) is defined as lengthened bowel dysmotility occurring after surgery and lasting for more than 16 hours until the tolerance of an oral diet and the passage of flatus/stool¹⁾. With typical abdominal surgery, such as a gastrectomy or a colectomy, bowel recovery requires 72 hours or 3–5 hospital days^{2,3)}. If POI develops, the patient may suffer from nausea, vomiting, abdominal distention and pain, resulting in not only an increased risk of pulmonary complications and susceptibility to infection, but also an increased hospital stay and overall medical cost^{4,5)}.

In recent years, so-called Enhanced Recovery after Surgery (ERAS) protocols have been developed; these multimodal perioperative management strategies have flourished in the surgical arena, and the widespread use of minimally invasive surgical techniques, such as laparoscopic surgery, has further contributed to a reduction in the incidence of POI. Nevertheless, a certain proportion of patients continue to experience POI. For most elective surgeries, patients receive standardized medical services that provide them with nearly homogeneous procedures and care; however, some patients experience POI, while others do not. Early postoperative bowel obstruction (EPSBO), also known as prolonged POI,

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can lead to the development of adhesive small bowel obstruction, requiring multiple operations^{6,7)}. Despite this situation, few consistent risk factors for POI have been identified, and few studies have investigated specific preoperative patient characteristics that might be associated with an increased risk of POI.

The aim of the present study was to determine whether various patient characteristics and perioperative clinical interventions might be correlated with the incidence of postoperative ileus. We specifically focused on preoperative stress as a possible predictor of POI, since stress is known to be correlated with surgical outcome^{8,9)} and to affect both autonomic nervous activity and the immune state throughout the body, including the small and large intestine^{10,11)}.

Materials and Methods

Patients who were scheduled to undergo elective colorectal surgery during the 18-month period between January 2015 and June 2016 were evaluated for eligibility and registered in the study according to the following inclusion and exclusion criteria.

Inclusion criteria

- 1) Scheduled to undergo elective colorectal surgery.
- 2) Age of over 20 years at the time of consent.
- 3) Able to make medical decisions.

Exclusion criteria

- 1) Endometritis.
- 2) Peritonitis.
- 3) Scheduled to receive chemotherapy/ radiation therapy within two weeks prior to the operation or 1 month after the operation.
- 4) Hepatic disorder (aspartate transaminase [AST] ≥ 100 IU/L or alanine transaminase [ALT] ≥ 100 IU/L).
- 5) Renal disorder (serum creatinine ≥ 2 mg/dL or blood urea nitrogen [BUN] ≥ 25 mg/dL).
- 6) Colonic perforation.
- 7) Stoma.
- 8) Not expected to achieve a complete cure.
- 9) Pregnant or lactating.
- 10) Participation in a clinical trial within 16 weeks before the operation.
- 11) Judged to be ineligible for any reason other than those listed above.

Colorectal surgeries were defined as any colorec-

tal resection involving both large and small incisions of the peritoneum, including standard colonic resection and standard rectal resection using open, laparoscopic, or converted techniques. Standardization of care was assured by the fact that all the patients were treated by a single group of surgeons according to identical practice standards.

After providing written informed consent to participate in this study, all the patients underwent a stress evaluation at 5 PM on the day before their scheduled operation; their salivary amylase levels were measured using the Saliva Amylase Monitor¹²⁾, and their stress level was scored using the State-Trait Anxiety Inventory-Form JYZ (STAI)¹³⁾. Preoperative biochemical parameters that had been included in the hospital's electronic database were also inspected prior to registration to ensure eligibility. Patient characteristics, such as age at the time of surgery, sex, American Society of Anesthesiologists (ASA) grade, and body mass index (BMI), were included in the analysis. Operative variables included the type of procedure, anesthetic duration, operative duration, body temperature at the end of the procedure, and intraoperative narcotic administration. The presence of POI was considered a postoperative variable.

In this study, POI was defined as the absence of the passage of flatus for more than 72 hours and the intolerance of an oral diet from the 2nd to the 6th postoperative day; consequently, the presence or absence of POI was determined on the 7th postoperative day. In this study, paralytic ileus or functional bowel obstruction, but not mechanical bowel obstruction, was included as POI. The total opiate use was clearly recorded on the intraoperative and postoperative records, and the records revealed that remifentanyl was the only narcotic that was routinely and consistently used in all the patients as an analgesic agent intraoperatively. Other opioids were rarely used, and only in very small quantities.

This study was approved by the institutional review board at Shizuoka General Hospital (No. 15-01-60; January 27, 2015) and complied with the provisions of the Declaration of Helsinki. The approval was obtained prior to data collection and prior to accessing the electronic database for the Colorectal Unit at the hospital.

Table 1 Patient Characteristics

		N=114	
		n	ratio (%)
Sex	Male	67	58.8
	Female	47	41.2
Age	n	108	
	mean±SD	67 ± 11.9	
	median	67.5	
	range	25 – 91	
BMI	n	114	
	mean±SD	22.63 ± 3.01	
	median	22.33	
	range	16.69 – 33.95	
ASA	1	27	25.7
	2	67	63.8
	3	11	10.5
Procedure			
	lap-Sigmoidectomy	32	28.1
	lap-Ileocecal resection	26	22.8
	lap-Low anterior resection	23	20.2
	lap-Right hemicolectomy	13	11.4
	lap-Segmental resection	6	5.3
	lap-Transverse colectomy	5	4.4
	lap-Left hemicolectomy	5	4.4
	lap-Subtotal colectomy	2	1.8
	lap-Ileocolic resection	1	0.9
	lap-Anterior resection	1	0.9
Stress			
STAI score	1	3	2.8
	2	29	27.1
	3	48	44.9
	4	20	18.7
	5	7	6.5
Amylase	1	55	48.3
	2	10	8.8
	3	12	10.5
	4	37	32.5

lap-: Laparoscopic

Statistical analysis

Continuous variables were summarized as the mean, standard deviation (S.D.), median and ranges, whereas categorical variables were presented as frequencies and proportions. The cutoff values for each factor (age, BMI, duration of anesthesia, duration of surgery, dose of remifentanyl) were determined based on receiver operating characteristics (ROC) curve analyses. Categorized values for each stress measure (amylase level, STAI scores) were determined according to the test manufacturers' recommendations. Risk factors found to have a *p*-value of <0.06 in a univariate analysis were included in the multivariate analysis. The procedures for

colorectal resection were divided into three categories according to the site of resection: proximal to the intestine was categorized as procedures 1, distal to the intestine was categorized as procedures 2, and other parts of the colon were categorized as procedures 3. These categories were then included in the multivariate analysis to assess their effect on the POI. The results of the multivariate analysis were reported as odds ratios (ORs) with 95% confidence intervals (CIs) and *p*-values. The fit of the logistic models was assessed using the Hosmer-Lemeshow test⁽¹⁴⁾. The different patient categories were defined according to the number of risk factors identified in this study that were found to be present in each patient. The Cochran-Armitage trend test was used to evaluate the correlation between the number of risk factors and the occurrence of ileus.

All the statistical tests were two-sided, and *p*-values of <0.05 were considered statistically significant. All the statistical analyses were conducted using SAS software, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Of the 122 patients who satisfied the study criteria, 118 patients remained eligible; however, 4 patients with open procedures were excluded because patients undergoing open procedures are reportedly more susceptible to POI than patients undergoing laparoscopic procedures^(15,16). Consequently, the remaining 114 patients were included in the analysis. Sixty-seven patients (58.8%) were male, and 47 (41.2%) were female; the mean age was 67 years. All the surgeries were performed laparoscopically; common procedures included a sigmoidectomy (28.1%), ileocecal resection (22.8%), and low anterior resection (20.2%). All the procedures that were performed are summarized in **Table 1** and were categorized to clarify the patient characteristics of these categories in Supplemental **Table 1**.

A total of 11 (9.7%) patients developed POI. The univariate analyses showed that an intraoperative remifentanyl dose of ≥4.0 mg was significantly associated with the occurrence of POI, while a high preoperative stress level was not correlated with the occurrence of POI. Although the multivariate analysis showed that none of the independent variables was statistically correlated with the occurrence of

Supplemental Table 1 Patient Characteristics

		Procedures 1 (n=40)		Procedures 2 (n=61)		Procedures 3 (n=13)	
		n	ratio (%)	n	ratio (%)	n	ratio (%)
Sex	Male	18	45.0	43	70.5	6	46.2
	Female	22	55.0	18	29.5	7	53.9
Age	n	39		57		12	
	mean±SD	69.7 ± 13.3		65.7 ± 11.0		64.5 ± 11.1	
	median	72.0		66.0		64.5	
	range	25.0 – 87.0		34.0 – 91.0		50.0 – 86.0	
BMI	n	40		61		13	
	mean±SD	22.15 ± 2.61		22.97 ± 3.30		22.54 ± 2.77	
	median	21.61		22.60		22.80	
	range	17.45 – 27.47		16.69 – 33.95		18.05 – 28.40	
ASA	1	6	15.8	16	28.6	5	45.5
	2	25	65.8	37	66.1	5	45.5
	3	7	18.4	3	5.4	1	9.1
Stress STAI score	1	0	0.0	3	5.3	0	0.0
	2	7	18.4	18	31.6	4	33.3
	3	23	60.5	23	40.4	2	16.7
	4	5	13.2	10	17.5	5	41.7
	5	3	7.9	3	5.3	1	8.3
Amylase	1	18	45.0	28	45.9	9	69.2
	2	3	7.5	5	8.2	2	15.4
	3	4	10.0	8	13.1	0	0.0
	4	15	37.5	20	32.8	2	15.4

Procedures 1: lap-Ileocecal resection, lap-Right hemicolectomy, lap-Ileocolic resection

Procedures 2: lap-Sigmoidectomy, lap-Low anterior resection, lap-Left hemicolectomy, lap-Anterior resection

Procedures 3: lap-Segmental resection, lap-Transverse colectomy, lap-Subtotal colectomy

lap-: Laparoscopic

POI (**Table 2**), an intraoperative remifentanyl dose of ≥ 4.0 mg was significantly correlated with POI ($p=0.0375$) when analyzed after adjustments for an intraoperative remifentanyl dose of ≥ 4.0 mg, patient sex, and procedure category as independent variables (**Table 3**). The Hosmer-Lemeshow test showed a good fit for this model ($p=0.5893$). Furthermore, the Cochran-Armitage Trend Test for risk factors (male sex, intraoperative remifentanyl dose of more than 4.0 mg) showed that the incidence of POI increased significantly with the number of risk factors present ($p=0.006$), (**Table 4**).

Discussion

In the present study, we found that 9.7% of the patients in our series developed POI. Previous studies have reported incidences of POI varying from 4.5% to 32.4% for abdominal surgery¹⁷⁻¹⁹. One of the reasons for this wide range is the use of different definitions of POI. Among studies stating a specific definition of POI, incidences of between 12.7% and

19.6% have been reported for patients undergoing colorectal surgery²⁰⁻²³. The incidence of POI after laparoscopic surgery is reportedly lower than that after open surgery. Our results seem to agree with these previously reported findings. Considering the definition of POI used in this study and the careful patient selection with specific inclusion and exclusion criteria (i.e., no prior abdominal surgery and a comparatively healthy state) as well as the use of elective laparoscopic surgery for all the patients in our study, a POI incidence of 9.7% seems acceptable.

In our study, an intraoperative remifentanyl dose of more than 4.0 mg was found to be a risk factor for POI. Remifentanyl is a potent, short-acting synthetic opioid analgesic that has a rapid onset and a rapid recovery time²⁴. Remifentanyl was administered intravenously as a general anesthetic agent in our cases. Similar to other opioids, such as morphine²⁵, remifentanyl stimulates mu receptors in the gut; therefore, the routine use of remifentanyl for total intravenous anesthesia in this patient series may

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Table 2 Predictive factors associated with POI

Factors	N (n=114)	POI percentage (%) (n=11)	Univariate analysis		Multivariate analysis	
			OR 95% CI	p value	OR 95% CI	p value
Sex						
female	47	1(2.1)	1		1	
male	67	10(14.9)	8.069 (0.996, 65.359)	0.0504	6.044 (0.722, 50.613)	0.0971
Age (years)	108	11	1.027 (0.970, 1.088)	0.3544	-	-
67 <	48	3(6.3)	1		-	
67 ≥	60	8(13.3)	2.308 (0.577, 9.224)	0.2369	-	-
BMI	114	11	1.001 (0.814, 1.232)	0.9888	-	-
24.91 ≥	30	2(6.7)	1		-	
24.91 <	84	9(10.7)	1.680 (0.342, 8.259)	0.5231	-	-
ASA						
1	40	3(7.5)	1		-	
2	61	6(9.8)	1.345 (0.316, 5.720)	0.8692	-	-
3	13	2(15.4)	2.242 (0.332, 15.168)	0.4395	-	-
Stress						
STAI score	107	10	0.988 (0.919, 1.062)	0.7336	-	-
1+2	32	2(6.25)	1		-	
3	48	6(12.5)	2.143 (0.404, 11.355)	0.3219	-	-
4+5	27	2(7.4)	1.200 (0.158, 9.142)	0.8149	-	-
Amylase	114	11	0.996 (0.984, 1.008)	0.5356	-	-
1	55	6(10.9)	1		-	
2	10	2(20.0)	2.042 (0.349, 11.943)	0.238	-	-
3+4	49	3(6.1)	0.533 (0.126, 2.255)	0.1864	-	-
Anesthetic duration (minutes)	114	11	1.002 (0.993, 1.010)	0.7106	-	-
326.0 <	84	6(7.1)	1		-	
326.0 ≥	30	5(16.7)	2.600 (0.731, 9.253)	0.1401	-	-
Operation duration (minutes)	114	11	1.002 (0.993, 1.010)	0.7123	-	-
253.0 <	70	5(7.1)	1		-	
253.0 ≥	44	6(13.6)	2.053 (0.587, 7.182)	0.2605	-	-
Body temperature	108	10	1.173 (0.444, 3.102)	0.7473	-	-
Remifentanyl (mg)	114	11	1.014 (0.973, 1.058)	0.5064	-	-
4.0 <	70	3(4.29)	1		1	
4.0 ≥	43	8(18.60)	5.105 (1.273, 20.463)	0.0214	3.793 (0.916, 15.704)	0.0659

Table 3 Predictive factors associated with POI

Factors	N (n=114)	POI percentage (%) (n=11)	Univariate analysis		Multivariate analysis	
			OR 95% CI	p value	OR 95% CI	p value
Procedures						
1	40	3(7.5)	1		1	
2	61	6(9.8)	1.345 (0.316, 5.720)	0.8692	1.520 (0.315, 7.338)	0.622
3	13	2(15.4)	2.242 (0.332, 15.168)	0.4395	5.106 (0.650, 40.093)	0.1537
Sex						
Female	47	1(2.1)	1		1	
Male	67	10(14.9)	8.069 (0.996, 65.359)	0.0504	8.170 (0.892, 74.810)	0.063
Remifentanyl (mg)						
4.0 <	70	3(4.29)	1		1	
4.0 ≥	43	8(18.60)	5.105 (1.273, 20.463)	0.0214	5.142 (1.100, 24.049)	0.0375

Procedures 1: lap-Ileocecal resection, lap-Right hemicolectomy, lap-Ileocolic resection

Procedures 2: lap-Sigmoidectomy, lap-Low anterior resection, lap-Left hemicolectomy, lap-Anterior resection

Procedures 3: lap-Segmental resection, lap-Transverse colectomy, lap-Subtotal colectomy

Table 4 Number of risk factors associated with POI

Risk factors	N=114	POI	
		n	%
0	36	1	2.8
1	48	3	6.3
2	30	7	23.3
Cochran-Armitage Trend Test			p value
			0.006

Risk factor:

Male sex

Remifentanyl dose ≥ 4.0 mg

explain why the remifentanyl dose was associated with the POI. An association between opioid use for postoperative analgesia and POI has been reported in previous studies^{26,27}; however, few studies have reported that the intraoperative dose of opioids might contribute to the occurrence of POI. Our study suggests that remifentanyl has possible adverse effects related to POI, and its postoperative effects should be assessed for a longer follow-up period when the total dose exceeds 4.0 mg.

A male sex was not statistically correlated with POI in our study ($p=0.0971$). Using a definition of POI and eligibility criteria similar to ours, Millan reported an incidence of POI after colorectal surgery of a 15.9% and found that a male sex was a risk factor for POI²⁸. Among the various risk factors of POI, such as a poor patient condition and the presence of co-morbidities, including a prior operational history, an older age, a longer operation time,

a larger blood loss, and opiate use²⁹⁻³¹, a male sex has been reported relatively consistently as a risk factor for POI³². An association between a male sex and the risk of POI has been reported not only for abdominal surgeries, but also for plastic surgeries, such as joint arthroplasty and circumferential lumbar fusion^{33,34}. These reports suggest that a male sex is a common risk factor for POI and that POI can occur without direct manipulation of the intestine. The cause of POI is thought to be multifactorial, including surgical manipulation of the intestine and peritoneum, neural hypersensitivity, and inflammatory immune responses^{35,36}. Still, the cause remains unclear, and few studies have explored why men are more susceptible to POI than women or why remote surgical sites can affect bowel motility. The present study showed that the three procedure categories were not significantly correlated with the occurrence of POI. This phenomenon may be ex-

plained by the function of helper T cells during intestinal inflammation caused by surgical manipulations of the colon and rectum³⁷⁾.

We also found that the combination of a male sex and an intraoperative remifentanyl dose of more than 4.0 mg was more strongly correlated with the occurrence of POI than either individual risk factor alone. This phenomenon should also be investigated in future studies.

The primary objective of the present study was to clarify the correlation between preoperative stress and the occurrence of POI. Acute stress, including subjective emotional stress, is known to activate physiological stress systems. Numerous studies have also shown that physiological stress is correlated with psychological stress. Therefore, it seemed reasonable to hypothesize that a strong emotional experience of stress might affect postoperative outcome³⁸⁾, including the incidence of POI. To our surprise, we failed to identify such a correlation. To measure stress, we used the STAI, which is often used as a measure of psychological stress, and the salivary amylase level, which has been recently reported as a biological stress marker based on its correlation with stressful perception³⁹⁻⁴¹⁾. With the use of these measurements in mind, some explanations of the unexpected findings can be postulated. For example, current reviews have revealed that previous studies examining the association between physiological stress and psychological stress were mostly done on an experimental basis and were not based on clinical data^{42,43)}. Thus, some background factors might result in a disparity between clinical and experimental experiences of stress. Stress alleviation by mediating factors, such as personality traits and appraisal processes, might be another possible explanation⁴⁴⁾, since our subjects were all relatively healthy adult patients. In any case, preoperative stress might not have a notable effect on the incidence of POI among patients undergoing elective colorectal surgeries. Once we inferred this fact, we stopped our data sampling, resulting in a relatively small number of subjects; this was a limitation of our study. Further study is needed to clarify the correlation between a male sex, intraoperative remifentanyl use, and the incidence of POI.

Conflict of interest: None.

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