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Original Article

Association between the Remifentanil Dose during Anesthesia and Postoperative pain

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Remifentanil is an ultra-short-acting opioid that sometimes causes opioid-induced hyperalgesia, which has led to controversy regarding the association between intraoperative remifentanil administration and postoperative pain. This study aimed to assess the effects of the intraoperative remifentanil dose on postoperative pain. Patients undergoing esophageal, gastric/hepatobiliary, or intestinal/colon surgery and using postoperative patient-controlled epidural analgesia were analyzed. The patients were divided into two groups based on the average intraoperative remifentanil dose (high-dose remifentanil [HR] group: ≥0.1 μg/kg/min; low-dose remifentanil [LR] group: <0.1 μg/kg/min). In all, 406 patients met the inclusion criteria. A significant difference in the average dose of remifentanil was seen between the groups during the anesthesia period (0.14±0.05 vs. 0.07±0.02 μg/kg/min). However, no significant difference was seen in pre- or intraoperative patient characteristics. Numerical rating scale (NRS) scores on postoperative day 1 were similar between the groups (HR: 1.7±2.0; LR: 1.7±2.0; $p=0.74$). The incidence of poor pain control (NRS >3/10) was also similar between the groups (HR: 14%; LR: 16%; $p=0.57$). Older age (>60 years) and type of surgery (esophageal surgery) were associated with worse postoperative NRS scores. No significant association was seen between the intraoperative remifentanil dose and postoperative NRS scores following thoracoabdominal surgery with postoperative epidural pain management.

Key words: high-dose remifentanil, postoperative numerical rating scale, type of surgery, epidural block

Opioids are frequently used as therapy for moderate to severe chronic and acute pain and are commonly used in general anesthesia [1]. Opioid-induced hyperalgesia (OIH) has been shown to occur in the perioperative period. OIH following analgesia with opioids may continue for a long time after withdrawal [2]. The concept of OIH has been known for more than 100 years [3]. Both clinical and experimental studies have shown that remifentanil has the potential to increase pain sensitivity and the intensity associated with the stimulation of pain receptors or sensory nerves [4,5]. Several studies have identified increased opioid requirements and deteriorating pain scores in patients exposed to high intraoperative opioid doses [6-10]. Nonetheless, clinical trials have shown that administering large doses of opioids during surgery may increase postoperative pain. However, the true incidence and mechanisms of OIH remain controversial.

Remifentanil is a potent μ-opioid receptor agonist that has been consistently associated with the development of remifentanil-induced hyperalgesia, a paradoxical phenomenon whereby patients receiving opioids for intraoperative pain control may develop increased post-

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operative sensitivity to pain stimuli and may thus require higher opioid consumption [11]. However, proper anesthesia management has the potential to reduce surgery-induced pain [12]. An improved understanding of OIH in the clinical setting is therefore needed to minimize harm and reduce the opioid dosage.

Given the difficulty of demonstrating OIH in clinical trials owing to the lack of good models [1], we decided to use the numerical rating scale (NRS) to evaluate pain on postoperative day 1 (POD1) in this study. The primary hypothesis of the present study was that the use of low-dose remifentanil during anesthesia might reduce postoperative pain scores.

Material and Methods

Data source, study design and setting, and participants. We conducted a retrospective observational study at Okayama University Hospital. All patient data were de-identified at the hospital, and the anonymous data were collected to create a database. The ethics committee of our institution (Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital) approved the study design and waived the requirement for informed consent because all data were anonymous (approval No. 2009-012). Patient informed consent was not deemed necessary by the Institutional Review Board. All methods were carried out in accordance with relevant guidelines and regulations. We obtained our data from the medical and anesthesia electronic records at Okayama University Hospital, an institutional data repository that includes robust perioperative data and clinical details about all patients. We included patients who underwent gastrointestinal surgery and postoperatively received patient-controlled epidural analgesia (PCEA) between January 1, 2015 and December 31, 2017. We excluded patients aged younger than 20 years and older than 70 years.

We also collected patient demographics, including age, gender, body mass index (BMI), and type of surgery (esophageal, gastric/hepatobiliary, or intestinal/colon), as well as data regarding preoperative comorbidities (American Society of Anesthesiologists physical status 1/2/3), smoking, alcohol consumption, hypertension, diabetes mellitus (DM), and hyperlipidemia from the database. From the anesthesia records, the remifentanil dose including the total dose during anesthesia, surgery time, type of anesthesia (inhalational or total intravenous anesthesia (TIVA)), and fentanyl dose were recorded. The patients were then divided into two groups based on the intraoperative average remifentanil dose (high-dose remifentanil [HR] group: ≥ 0.1 μg/kg/min; low-dose remifentanil [LR] group: < 0.1 μg/kg/min). We chose a dose of 0.1 μg/kg/min as the cut-off value for group stratification in this study, since this is the standard dose in our clinical anesthesia practice in patients to whom we administer epidural analgesia intraoperatively. We also investigated a cut-off dose of 0.15 μg/kg/min for group stratification in our population and found that NRS scores on POD1 were not significantly different compared to those obtained when the smaller cut-off dose was used. Hence, we selected a remifentanil dose of 0.1 μg/kg/min dose as the cut-off value for group stratification.

We collected data including the NRS scores (ranging from 0 representing no pain to 10 representing the worst possible pain) at rest on POD1 and the postoperative length of hospital stay (LOS) from the postoperative rounds database.

Outcomes. Our primary outcome was the NRS score on POD1. NRS scores were assessed by the anesthesiologist while on postoperative rounds on POD1 and then entered into the database. We defined patients with NRS > 3 as the worse NRS group and those with NRS ≤ 3 as the better NRS group according to the palliative pain guideline [13]. We focused on the relationship between the intraoperative remifentanil dose and postoperative NRS scores. We also analyzed the NRS scores on POD1 according to surgery type and compared them between the HR and LR groups.

Anesthesia management. We selected general anesthesia (TIVA) or inhalational anesthesia [desflurane or sevoflurane] for all cases. All patients were monitored using electrocardiography, noninvasive blood pressure measurement, and peripheral arterial oxygen saturation measurement. Some severely affected patients underwent invasive arterial blood pressure monitoring. Anesthesia induction was conducted using propofol (1-2 mg/kg) and remifentanil (0.2-0.4 μg/kg/min). Tracheal intubation was facilitated with rocuronium (1-1.5 mg/kg). We controlled the remifentanil dose based on the patients' vital signs (heart rate and blood pressure) and bispectral index under inhalational anesthesia or TIVA in order maintain a mean arterial

pressure above 55-60 mmHg and a heart rate between 40 and 100 beats/min in all cases. Our policy was to maintain intraoperative remifentanil infusion at the lowest possible dose based on the anesthesiologist's determination.

All patients, except for those who underwent esophageal surgery, were extubated in the operating room and were then taken to the recovery room for observation of their vital signs during the first hour after surgery. After the patient's condition was confirmed to be stable, the patient was discharged to the general ward. Esophageal surgery cases were extubated in the ICU on the morning of POD1.

PCEA. The indications for an epidural block were the absence of bleeding or coagulation issues, the anesthesiologist's preference, and the patient's approval. In patients who received PCEA, an epidural catheter was inserted at Th8 to Th10 before the induction of general anesthesia. Ropivacaine 0.2% was given to patients as soon as the epidural catheter was inserted at a baseline of 4 ml/h until the end of surgery. Postoperatively, a 3-ml bolus of ropivacaine 0.2% was allowed three times every hour with a 15-min lockout time. This analgesia protocol was discontinued by nurses or surgeons when it was judged to be unnecessary. Postoperative pain management was conducted by surgeons based on the above pain protocol. A multimodal analgesia technique, including other analgesics, was adapted to each patient.

Statistical analysis. We used Fisher's exact test or the chi-squared test to analyze categorical data and a *t*-test to compare numerical data. Thereafter, 95% confidence intervals (CIs) were used to identify significant predictors of pain control and were expressed in line plots. A linear regression model was used in the subgroup analysis, which assessed the relation between pain control and the type of surgery. Thereafter, a multivariate logistic regression model yielding odds ratios and 95% CIs was used to identify significant predictors of higher NRS scores.

The threshold for significance was set at $p < 0.05$. JMP software (version JMP Pro 14; SAS, Cary, NC, USA), the STATA statistical software package (version Stata/SE 16.1; StataCorp, College Station, TX, USA), and IBM SPSS Statistics 25.0 (IBM Corporation, Armonk, NY, USA) were used for all analyses.

Results

We identified 598 patients who had undergone thoracoabdominal surgery during the study period. After excluding 88 patients who had not received remifentanil ($n = 29$), had missing information ($n = 16$), or had undergone more than one operation ($n = 43$), the remaining 510 patients were included in the study. Among them, 406 patients who received epidural analgesia postoperatively were finally included in the analysis.

The average remifentanil doses during the anesthesia period were 0.14 ± 0.05 for the HR group (N = 180) and 0.07 ± 0.02 μg/kg/min for the LR group (N = 226) (Fig. 1). Table 1 shows the preoperative demographic characteristics of the HR and LR groups. No significant differences were found in any baseline characteristics between the two groups (age: HR, 57 ± 12 years vs. LR, 59 ± 10 years; $p = 0.1$; female gender: HR, 36% vs. LR, 36%; $p = 0.95$; BMI: HR, 22 ± 4 kg/m^2 vs. LR, 22 ± 3 kg/m^2; $p = 0.99$). In addition, no significant differences were seen between the two groups in terms of comorbidities such as smoking ($p = 0.31$), alcohol consumption ($p = 0.99$), hypertension ($p = 0.92$), DM ($p = 0.25$), and hyperlipidemia ($p = 0.67$). The rates of the different types of surgery were similar between the two groups (HR: esophageal 24%, gastric/hepatobiliary 27%, intestinal/colon 49% vs. LR: esophageal 20%, gastric/hepatobiliary 29%, intestinal/colon 51%; $p = 0.6$). The rate at which laparoscopic surgery was performed was

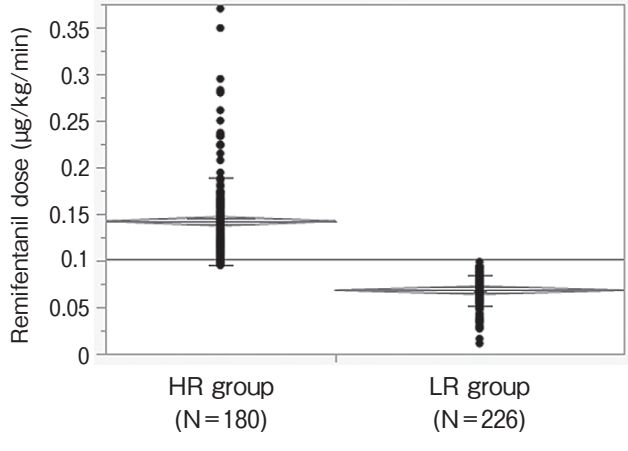

Fig. 1 Comparison of intraoperative average remifentanil dose between the two groups. The average remifentanil doses in the high-dose remifentanil (HR) and low-dose remifentanil (LR) groups were 0.14 ± 0.05 and 0.07 ± 0.02 μg/kg/min, respectively ($p < 0.001$).

Table 1 Demographic characteristics

	HR (N = 180)	LR (N = 226)	*P* value
Age (years)	57 ± 12	59 ± 10	0.1
Gender (female), N (%)	64 (36%)	81 (36%)	0.95
BMI	22 ± 4	22 ± 3	0.99
ASA 1/2/3	65/97/18	77/128/21	0.43
Smoking, N (%)	111 (62%)	128 (57%)	0.31
Alcohol, N (%)	113 (63%)	142 (63%)	0.99
Hypertension, N (%)	25 (22%)	32 (22%)	0.92
Diabetes mellitus, N (%)	24 (21%)	22 (15%)	0.25
Hyperlipidemia, N (%)	7 (6%)	7 (5%)	0.67
Surgery type			0.60
Esophageal, N (%)	44 (24%)	46 (20%)	
Gastric/hepatobiliary, N (%)	48 (27%)	66 (29%)	
Intestinal, N (%)	88 (49%)	114 (51%)	
Laparoscopic, N (%)	81 (45%)	99 (44%)	0.81

Values are presented as means ± standard deviations or number (%). HR, high-dose remifentanil group; LR, low-dose remifentanil group; BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2 Anesthetic and surgical characteristics

	HR (N = 180)	LR (N = 226)	*P* value
TIVA, N (%)	57 (32%)	63 (28%)	0.42
Surgery time (min)	327 ± 202	310 ± 181	0.4
Fentanyl (μg)	350 ± 260	300 ± 370	0.15
Crystalloid (ml)	2,400 ± 1,300	2,400 ± 1,100	0.82
Colloid (ml)	460 ± 560	460 ± 480	0.95
Bleeding (ml)	210 ± 301	300 ± 1,152	0.29
Transfusion, N (%)	8 (4.4%)	11 (4.9%)	0.84
NRS > 3, N (%)	25 (14%)	36 (16%)	0.57
LOS (days)	22 ± 19	21 ± 19	0.45

Values are presented as means ± standard deviations or number (%). NRS, numerical rating scale; TIVA, total intravenous anesthesia; LOS, length of hospital stay.

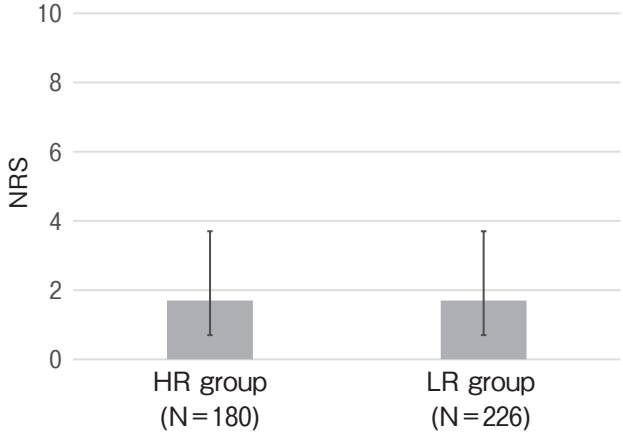

Fig. 2 Analyses of postoperative numerical rating scale (NRS) scores at rest on postoperative day 1 (POD1). NRS scores were similar between the two groups (high-dose remifentanil [HR] group: 1.7 ± 2.0 vs. low-dose remifentanil [LR] group: 1.7 ± 2.0, $p = 0.74$).

also similar (HR: 45% vs. LR: 44%; $p = 0.81$).

Table 2 shows the intraoperative factors for both groups. The intraoperative anesthesia method used was similar (TIVA: HR: 32% vs. LR: 26%; $p = 0.42$), as were the surgical time (HR: 327 ± 202 min vs. LR: 310 ± 181 min; $p = 0.4$) and intraoperative fentanyl use (HR: 350 ± 260 μg vs. LR: 300 ± 370 μg; $p = 0.15$). No significant differences were seen between the two groups with regard to fluid or transfusion management or bleeding (Table 2). The NRS scores at rest on POD1 were similar between the two groups (HR: 1.7 ± 2.0 vs. LR: 1.7 ± 2.0; $p = 0.74$) (Fig. 2). The frequency of worse pain control (NRS > 3/10) was also similar between the groups (HR: 14% vs. LR: 16%; $p = 0.57$), as was the LOS (HR: 22 ± 19 days vs. LR: 21 ± 19 days; $p = 0.45$).

The results of multivariate logistic regression analysis for worse NRS score (> 3/10) are shown in Table 3. Only esophageal surgery and older age (> 60 years) were associated with worse postoperative NRS scores. The intraoperative remifentanil dose and preoperative patient characteristics were not associated with higher postoperative NRS scores.

The analysis according to the type of surgery showed that esophageal surgery was associated with a higher intraoperative remifentanil dose and higher postoperative NRS score compared with the other types of surgery (gastric or colon surgery) (Table 4) (Fig. 3),

Table 3 Results of multivariate analysis of NRS scores >3/10 on POD1

	OR	95%CI	*P* value
Age >60 years	1.580	1.036–2.408	0.033
Gender, female	1.461	0.943–2.263	0.090
ASA ≥2	0.821	0.533–1.265	0.372
Average dose of remifentanil, high	0.837	0.556–1.261	0.395
Type of surgery, esophageal	2.227	1.387–3.716	0.001

POD1, Postoperative day 1; OR, Odds Ratio; CI, confidence interval; ASA, American Society of Anesthesiologists.

Table 4 Comparison of NRS scores by type of surgery

	HR (N=180)	LR (N=226)	*P* value
Esophageal surgery (N=90)	HR (N=44)	LR (N=46)	
NRS	1.5±2.4	1±1.6	0.23
NRS >3, N(%)	6 (14%)	3 (6.5%)	0.26
Gastric/hepatobiliary surgery (N=114)	HR (N=48)	LR (N=66)	
NRS	1.6±1.8	1.5±1.9	0.8
NRS >3, N(%)	6 (13%)	8 (12%)	0.95
Intestine/Colon surgery (N=202)	HR (N=88)	LR (N=114)	
NRS	1.9±1.9	2±2.2	0.73
NRS >3, N(%)	13 (15%)	26 (23%)	0.2

Values are presented as means ± standard deviations or number (%). HR, high-dose remifentanil group; LR, low-dose remifentanil group; NRS, numerical rating scale.

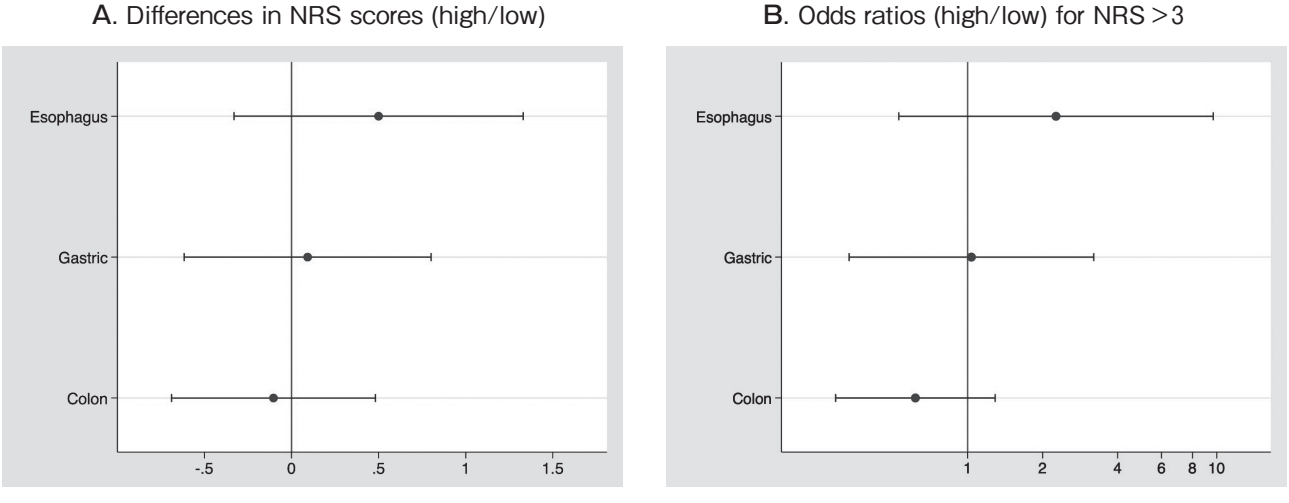

Fig. 3 Correlation between remifentanil dose and postoperative NRS score according to type of surgery. **A** shows differences in NRS scores (high/low) according to the type of surgery. Significantly higher remifentanil doses were used during esophageal surgery as compared to the other surgeries; **B** shows the odds ratios (high/low) for NRS scores >3 (worse pain control) according to the type of surgery. Esophageal surgery was associated with a higher intraoperative remifentanil dose and higher postoperative NRS scores compared with the other types of surgery (gastric or colon surgery).

although the difference was not statistically significant.

Discussion

In this study, no significant relationship was found between intraoperative remifentanil use and postoperative NRS scores in patients receiving epidural pain management following thoracoabdominal surgery. Older age (>60 years) was associated with higher NRS scores on POD1 irrespective of the intraoperative remifentanil dose. The intraoperative remifentanil dose tended to be higher and the NRS scores at POD1 tended to be worse in esophageal surgery compared with colon and gastric surgery.

There is no clear definition for what is considered a high dose of remifentanil. A large infusion dose of remifentanil (over 0.2 μg/kg/min) is known to lead to greater postoperative pain because of OIH [6-10]. In our institute, we try to reduce the remifentanil dose by using an epidural block, which is somewhat controversial. The disadvantages of an intraoperative epidural block include the risk of hypotension requiring volume resuscitation and the use of inotropes. However, the merits of this procedure include a decrease in anesthetic drug requirements, as the analgesic effects of the epidural block make it possible to avoid deep anesthesia. In fact, in this study, we were able to decrease the intraoperative remifentanil dose without any hemodynamic imbalance.

Zhang *et al.* [14] showed that the intraoperative use of a high dose of remifentanil (1.2 μg/kg/min) decreased the postoperative visual analog scores and morphine use on POD1 compared with a regular dose of remifentanil (0.2 μg/kg/min) after thyroidectomy. Their infusion rate was quite high compared with ours. Additionally, we co-administered local anesthetics via the epidural catheter and did not need to use a high dose of remifentanil. A recent clinical trial reported controversial results after the intraoperative administration of high-dose remifentanil. Treskatsch *et al.* [15] reported no significant differences in postoperative pain intensity or morphine consumption between an intraoperative high-dose remifentanil (0.2 μg/kg/min) group and an intraoperative low-dose remifentanil group (<0.1 μg/kg/min) who underwent abdominal surgery, in findings similar to our results. Koo *et al.* [16] also reported that high-dose remifentanil had no effect on postoperative pain intensity or opioid consumption compared with a threefold lower dose of remifentanil (2666.8 ± 858.4 vs. 872.0 ± 233.3 μg, respectively; $p < 0.001$) in hepatobiliary surgery. To our knowledge, no other clinical studies have reported any influence of the administration of high-dose remifentanil (≥0.1 μg/kg/min) on clinical outcomes related to pain parameters.

Compared with gastric and colon surgery, esophageal surgery involves not only thoracic and abdominal resection, but also cervical resection. Thus, a higher remifentanil dose is required during esophageal surgery, because the epidural block does not suppress nociceptive pain in the cervical region.

We were able to control nociceptive pain input by using an epidural block following both laparoscopic and open surgical procedures. In all cases, we achieved good postoperative pain control (NRS ≤3, >80%) by using epidural patient-controlled analgesia. Although we could not collect complete information regarding other types of postoperative analgesics, our surgical teams designed the protocol for postoperative pain management. Thus, we believe that similar management was conducted on POD1 in both groups.

In a systematic review, Yang *et al.* [17] reported associations between poor postoperative pain control and the following nine preoperative risk factors among 53,362 patients undergoing surgery: younger age, female gender, smoking, history of depressive symptoms, higher BMI, history of anxiety symptoms, sleep difficulties, the presence of preoperative pain, and the use of preoperative analgesics. In the present study, the risk factors for poor postoperative pain management were older age and type of surgery (esophageal surgery); these were similar to the risk factors found in previous reports.

This study had several limitations. First, given the retrospective nature of the research, we were unable to control the administration of analgesia postoperatively, which could have affected the NRS scores, our primary outcome measure. Pain management is difficult to judge because it can be affected not only by the remifentanil dose, but also by many other factors; however, in this study, we could not collect complete information, such as the use of postoperative analgesics (NSAIDs/acetaminophen/opioids, PCEA dose usage), in detail. Second, we only focused on NRS scores on POD1, whereas postoperative analgesics are usually given to patients for at least 3 days after surgery and are

discontinued by the nursing staff. We believe that future studies should focus on the time course of NRS scores over a period of 2-3 days after surgery. Third, we used epidural analgesia in all patients. Although the attending anesthesiologists checked the accuracy of the epidural block, it was not confirmed by contrast injection studies. Fourth, we only focused on NRS scores at rest, not during movement. Fifth, our group stratification based on a remifentanil dose of 0.1 μg/kg/min was subjective and did not have an objective basis.

In conclusion, in this study, no significant relationship was found between intraoperative remifentanil dose and postoperative NRS scores in patients undergoing epidural pain management following thoracoabdominal surgery. Older age (> 60 years) and esophageal surgery, but not intraoperative remifentanil dose, were associated with higher postoperative NRS scores. In esophageal surgery, there was a tendency to administer higher intraoperative remifentanil doses and for patients to report higher NRS scores on POD1 compared with colon and gastric surgery.

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