Postoperative analgesia using fentanyl plus celecoxib versus epidural anesthesia after laparoscopic colon resection

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ABSTRACT

Purpose Effective postoperative analgesia is essential to a patient's recovery after laparoscopic colon resection (LCR). We introduce a new analgesic protocol using fentanyl plus celecoxib following LCR.

Methods The subjects of this retrospective comparative study were 137 patients who underwent LCR, 63 of whom were treated with 72 h of epidural anesthesia (group E), and 74 of whom were treated with 24 h of fentanyl intravenous injection followed by 7 days of oral celecoxib (group FC). We evaluated the safety and efficacy of this new protocol.

Results The combination of fentanyl and celecoxib maintained a low postoperative pain score (<1.5, evaluated by the FACES Pain Scale) and reduced the need for rescue analgesic drugs for 7 days (groups E vs. FC: 5.39±3.77 vs. 2.79±2.92, $p<0.001$). The postoperative hospital stay was almost equal for the two groups (E vs. FC: 11.1±4.5 vs. 10.3±4.8 days, $p=0.315$). The operating room stay other than for surgery was significantly shorter for group FC (E vs. FC: 128.7±30.5 vs. 107.2±17.0 min, $p<0.001$). Neither group experienced complications, apart from one group FC patient, who suffered nausea and experienced vertigo.

Conclusions The new analgesic protocol using fentanyl plus celecoxib is an effective and time-saving strategy for LCR.

Introduction

Laparoscopic surgery for colorectal resection is beneficial for short-term postoperative outcomes in that wound pain is minimal, the risk of surgical-site infection is low, bowel movements are restored early, and postoperative hospitalization is relatively short [1]. Over the past decade, fast-track clinical pathways to further improve postoperative recovery have been introduced to laparoscopic colorectal surgery [2]. The Enhanced Recovery after Surgery (ERAS) protocol, which is a fast-track clinical pathway, is composed of various elements to improve perioperative management [3]. Although ERAS could decrease the complication rate and shorten the hospital stay [4, 5], it is difficult to perform all of the ERAS elements in a variety of clinical settings.

One of the most important elements for improving postoperative patients' recovery is achieving effective control of postoperative pain. Although minimally invasive surgery has been applied to colorectal surgery, it requires highly technical expertise and its surgical outcomes are still controversial [6–10]. Epidural anesthesia is an effective analgesic method used for various abdominal operations. The use of epidural anesthesia after laparoscopic colorectal surgery was first reported in 1995 [11]. Since then, epidural anesthesia has been implemented worldwide, not only for its analgesic effects, but also for its ability to enhance bowel movement recovery and prevent respiratory complications [12]. However, its

adverse effects include hypotension, urinary retention, respiratory depression, and motor blockade [13]. Moreover, some serious complications are associated with insertion of the epidural catheter, including dural puncture (resulting in severe headache), nerve damage, abscess formation, hematoma, and meningitis [14]. Epidural anesthesia is a high-risk procedure, especially for patients with a bleeding tendency. Based on these sequelae, the use of epidural analgesia following laparoscopic colorectal surgery has been questioned [2, 15, 16].

We believe that an effective, less-invasive method of postoperative analgesia is needed for laparoscopic colorectal surgery. Therefore, beginning in January 2014, we changed our protocol for postoperative analgesia from epidural anesthesia to a new analgesic protocol without epidural anesthesia. Celecoxib, a selective cyclooxygenase (COX)-2 inhibitor, has been commonly used as a potent analgesic agent in a variety of clinical settings [17–19]. It has also been reported that non-steroidal anti-inflammatory drugs (NSAIDs) exert synergistic analgesic effects when used concomitantly with opioids [20]. We previously reported the efficacy of our new analgesic protocol using celecoxib and fentanyl after laparoscopic gastrectomy [21]. However, to date, there are no reports on the analgesic effects of celecoxib after laparoscopic colorectal surgery. We conducted this retrospective comparative study to evaluate the efficacy and safety of our new analgesic protocol using celecoxib and fentanyl after laparoscopic colonic resection (LCR).

Patients and Methods

Patients

We studied the medical records of all consecutive patients who underwent elective LCR for primary colon cancers between June, 2008 and August, 2015. Excluded from this retrospective analysis were patients with colon cancers in pathologic stage IV, those with reduced port surgery, and those who required conversion to open surgery or underwent multiple organ resection. The extent of lymph node dissection and the cancer stage were classified according to the 2010 Japanese Society for Cancer of the Colon and Rectum guidelines [22].

From June 2008 to December 2013, patients who underwent LCR for colon cancer had their postoperative pain managed with epidural anesthesia (group E), whereas from January, 2014 to August, 2015, those who underwent the procedure had their postoperative pain managed with postoperative fentanyl and celecoxib (group FC). The institutional review board of Hokkaido University Hospital approved the study, which was conducted in accordance with the provisions of the Declaration of Helsinki.

Operative procedures

LCRs were either performed or supervised by one credentialed laparoscopic surgeon (S. H.) in our institution. A 2-cm umbilical skin incision was made and a 12-mm camera port was inserted at the start of the operation. The operative procedures were performed with five ports [two (including a camera port) and three with diameters of 12 and 5 mm, respectively] in a formulaic way. Dissection was done using a standard medial-to-lateral approach for left colon cancers and a standard retroperitoneal approach for right colon cancers. After dividing the vessels, the specimen was extracted through an umbilical incision in the abdominal wall. To extract specimens smoothly, the umbilical skin incision was extended to approximately 4–6 cm. For lower sigmoid colon cancers, the double stapling technique was used for the colorectal anastomosis, whereas a functional end-to-end anastomosis technique was used for colon cancers in other regions. Drainage tubes were not placed routinely.

Postoperative pain management and assessment

The patients were classified into two groups in accordance with the methodologic approach of the postoperative analgesia. The patients in group E received epidural analgesia before the induction of general anesthesia. Epidural catheters were inserted between Th10-11 and Th12-L1. The effect of the epidural blockade was tested with 2 mL of 1.5 % xylocaine before surgery. The operations were performed under the combination of general and epidural anesthesia, administering a continuous infusion

and intermitted boluses of 0.375 % ropivacaine (Anapeine® Injection; AstraZeneca, Osaka, Japan)]. Soon after surgery, the patients were given 0.2 % ropivacaine continuously at a rate of 4 mL/h via an epidural catheter. The catheter was removed after 72 h.

The operations in the group FC patients were performed under general anesthesia alone, without epidural anesthesia. Soon after surgery, intravenous fentanyl citrate (20 μg/h) (Fentanyl Injection; Janssen Pharmaceutical K.K., Tokyo, Japan) was started and continued for 24 h. Subsequently, on the morning of postoperative day (POD) 1, the patients were also given 200 mg celecoxib (Celecox®; Astellas Pharma, Tokyo, Japan) twice a day orally for 7 days.

To evaluate the degree of postoperative pain, we used the Wong–Baker FACES Pain Scale [23] because it could be applied easily to all patients, irrespective of age. Before surgery, each patient was given scoring sheets in which the six-point (0–5) pain scale was described. The nursing staff obtained the pain scores at rest from the patients three times a day after surgery. The highest score on the pain scale each day was used to assess the degree of postoperative pain.

Patients were allowed rescue analgesic drugs up to three times a day per drug, which included flurbiprofen axetil at a dose of 50 mg i.v. (Ropion®; Kaken Pharmaceutical, Tokyo, Japan), acetaminophen at a dose of 15 mg/kg i.v. (acelio® Intravenous Injection; Terumo Corporation, Tokyo, Japan), or pentazocine at a dose of 15 mg i.m. (Pentagin® Injection; Daiichi Sankyo, Tokyo, Japan). The

rescue analgesic requirements were evaluated according to the number of times these rescue analgesic drugs were used during the first 7 days after surgery.

Statistical analysis

Results are presented as means ± standard deviation. All statistical calculations were performed using a software package (StatView J-5.0; Abacus Concept, Berkeley, CA, USA). The patient variables were analyzed by Pearson's χ^2 test and Fisher's exact test. Data were compared between the groups using either a two-tailed Student's *t*-test or the Mann–Whitney U-test. A value of $p<0.05$ was considered to indicate significance for all data.

Results

Eligibility for analysis

During the study period, we performed 196 elective LCRs for primary colon cancer. However, 59 patients were excluded from the final analysis for the following reasons: colon cancer was diagnosed as pathologic stage IV in 24 patients, 31 patients underwent reduced port surgery, 1 patient required conversion to open surgery, and 3 patients underwent multiple organ resection. Accordingly, 137 patients were eligible for comparative analysis, with 63 in group E and 74 in group FC (Fig. 1).

Patients' characteristics

There were no significant differences between the groups (group E vs. group FC, respectively) in sex ratio (male/female 42/21 vs. 52/22, p=0.651), body mass index (23.8±4.2 vs. 22.8±2.9 kg/m^2, p=0.119), American Society of Anesthesiologists–physical status class I/II/III (10/47/6 vs. 14/52/8, p=0.851), or history of laparotomy (6 vs. 16, p=0.055). The patients were significantly younger in group E than in group FC (66.9±10.5 vs. 71.0±9.1 years, p=0.014), as shown in Table 1. The tumor characteristics were similar in the two groups, including maximum tumor diameter (35.5±19.5 vs. 36.9±19.9 mm, p=0.771), histologic types, and pathologic stages (Table 2).

Operative procedures

The operative procedures performed were similar in the two groups (E vs. FC). The ratio of D3 lymph node dissection (≤D2/D3; 33/30 vs. 20/54, p=0.002) and the number of dissected lymph nodes (13.6±9.0 vs. 19.5±11.8, p=0.001) were greater in group FC than in group E. The length of the umbilical skin incision was almost the same in both groups (5.89±1.68 vs. 5.78±1.30 cm, p=0.747). Despite the blood loss (39.8±95.5 vs. 12.6±30.3 g, p=0.022), which was greater in group E than in group FC, the operation time (178.6±46.9 vs. 166.1±43.5 min, p=0.111) was not significantly different between the groups.

However, the time the patients remained in the operating room for causes other than surgery (128.1±30.4 vs. 107.3±17.0 min, $p<0.001$) was significantly longer for group E than for group FC (Table 3).

Assessment of postoperative analgesia

The effects of postoperative analgesia were evaluated using the FACES Pain Scale and the need for rescue analgesic drugs between the day of surgery (POD 0) and POD 7. Fig. 2a shows the pain scale trends. The postoperative FACES Pain Scores were similar between PODs 0 and 7 except on POD 1: POD 0 (0.86±0.45 vs. 1.11±0.11, $p=0.079$), POD 1 (1.05±0.57 vs. 1.45±0.11, $p=0.008$), POD 3 (0.74±0.81 vs. 0.78±0.88, $p=0.775$), and POD 7 (0.21±0.41 vs. 0.18±0.61, $p=0.708$). Fig. 2b depicts the requirements for rescue analgesic drugs. The number of times analgesic drugs were used between PODs 0 and 5 was significantly lower in group FC than in group E. As a result, the overall number of times rescue analgesic drugs were used was significantly lower in group FC than in group E (5.40±3.77 vs. 2.79±2.92, $p<0.001$). One patient in group E was excluded from the evaluation of postoperative analgesia (Fig.2a, b) because he suffered pan-peritonitis on POD 1 and required open laparotomy.

Adverse effects and complications

No severe complications were associated with the postoperative analgesia in either group, including

hypotension, motor blockade, dizziness, respiratory depression, or postoperative ileus. A continuous infusion of fentanyl over 24 h was given to all but the one patient with slight vertigo and nausea. She recovered soon after discontinuing fentanyl without antiemetics. None of the patients had to discontinue celecoxib because of adverse effects during the drug-treatment course. Table 4 summarizes the results of perioperative hematologic examinations. There were no significant differences in postoperative white blood cell counts, hemoglobin levels, platelet counts, or levels of aspartate transaminase, alanine transaminase, blood urea nitrogen, or creatinine.

The incidence of postoperative complications was very low in both groups. Among the severe complications (Clavien–Dindo grades 3–5) was one case each of acute cholecystitis (1.6 %) and pan-peritonitis (1.6 %) in group E. The patient who suffered pan-peritonitis caused by small-intestinal injury required reoperation on POD 1. The starting dates for drinking (1.3±1.4 vs. 1.0±0.1 day, p=0.842), eating (4.1±2.0 vs. 4.8±1.9 day, p=0.060), and postoperative hospitalization (11.1±4.5 vs. 10.3±4.8 days, p=0.315) were similar in the two groups (Table 5).

Discussion

We demonstrated that the newly introduced analgesic protocol using fentanyl and celecoxib achieved potent analgesic effects following LCR. The combination of fentanyl and celecoxib maintained a low

postoperative pain score, the effect being almost comparable to that of epidural anesthesia, except on POD 1. Moreover, the need for rescue analgesic drugs was significantly lower in group FC than in group E. In a previous report, the mean maximum drug plasma concentration of celecoxib was reached about 2–4 h after a single 200-mg oral dose [24]. Because NSAIDs exert synergistic analgesic effects when used concomitantly with opioids [20], we considered that the continuous fentanyl infusion should be stopped when the blood concentration of celecoxib had reached the therapeutic dose. With our protocol, celecoxib administration is commenced on the morning of POD 1, and the continuous fentanyl infusion is ceased on the afternoon of POD 1.

Although the pain scores on POD 1 were significantly higher in group FC than in group E, the combination therapy substantially maintained the pain score at <1.5 and reduced the need for rescue analgesia. Although fentanyl monotherapy seems to have insufficient analgesic effect compared with epidural anesthesia, the concomitant administration of celecoxib seems to give pain relief equaling that of epidural anesthesia. It is imperative to suppress the strong pain that patients would suffer on POD 1; however, we recognize that the current protocol is still incomplete for suppressing the strong pain early after surgery. Thus, there is room for ameliorating the analgesic protocol. Acetaminophen is commonly used with NSAIDs or opioids [25-27]. Previous reports have demonstrated that acetaminophen had an opioid-sparing effect [26] and that scheduled-acetaminophen administration resulted in decreased opioid

use after cesarean delivery [27]. It seems likely that scheduled-acetaminophen administration combined with fentanyl and celecoxib on POD 1 can be a potent analgesic strategy following LCR.

It is also important to pay attention to the adverse effects of analgesic agents. It has been suggested that NSAIDs might increase the risk of gastrointestinal ulcers, renal toxicity, or anastomotic leakage [24, 28]. Although celecoxib, a selective COX-2 inhibitor, has renal toxicity equivalent to that of a non-selective COX inhibitor, it has less gastrointestinal toxicity [24]. In fact, none of the group FC patients in this study suffered gastrointestinal complications, such as anastomotic leakage or gastric ulcer, that delayed their recovery. Moreover, blood examinations revealed that the combination of fentanyl and celecoxib had no adverse hematologic effects. As a result, the timing of recommencement of drinking and eating and the postoperative hospital stay for group FC were almost equivalent to those for group E.

A previous study found that the perioperative administration of fentanyl increases the risk of nausea and vomiting in a dose-dependent manner [29]. Despite those adverse effects, fentanyl plays an important role in postoperative analgesic therapy because of its strong analgesic effect. In this study, only one patient suffered slight vertigo and nausea attributed to this adverse effect of fentanyl. Although she recovered soon after fentanyl was discontinued, preventing such adverse effects is important for any patients' recovery. There are some supportive strategies that could help avoid the adverse effects of fentanyl, such as preoperative flurbiprofen axetil administration [30] or perioperative continuous

intravenous lidocaine infusion [31].

Another important advantage of this new analgesic protocol without epidural anesthesia is that is time-saving and cost-effective. The time spent in the operating room for treatment other than surgery was significantly shorter in group FC than in group E. Schuster et al. demonstrated that the costs of the anesthesiologist and nurses for general surgery in an operating room were 1.02 and 0.75 euros per min, respectively (JP¥ 113.6 and 83.5 per min, respectively, based on 2011 data and exchange rates) [32]. The cost of postoperative analgesia in groups E and FC was estimated at JP¥ 5019 and JP¥ 2963 per patient, respectively, based on pharmaceutical prices calculated using the drug list of the Ministry of Health, Labour and Welfare of Japan. If we apply this calculation to our cases, the combination of fentanyl and celecoxib has the potential to reduce the personnel and medication costs by approximately JP¥ 4221 (21.4 min/operation) and JP¥ 2056 per patient, respectively. Hence, in terms of effective use of the operating room and cost reduction, replacing epidural anesthesia with our combination therapy of celecoxib and fentanyl after LCR should be reasonably considered.

The limitations of this study were first, that it was retrospective and the number of patients was small; and second, that there were several clinical differences between the groups, including age, extent of lymph node dissection, number of dissected lymph nodes, and blood loss. Group FC included more patients of advanced age who underwent D3 lymph node dissection. Although these conditions of group

FC seemed to be more invasive, the postoperative pain and hospitalization were almost comparable to those of group E. This suggests that the combination of celecoxib and fentanyl is a promising alternative for novel analgesic therapy following LCR.

In conclusion, our postoperative analgesic protocol using 24 h of fentanyl followed by 7 days of celecoxib was a safe, effective, and time-saving strategy following LCR. However, large-scale prospective randomized controlled trials are required to confirm its efficacy and safety.

Conflict of interest

We declare that there were no sponsors or funding sources for this study.

Author Disclosure Statement: T. Yoshida, S. Homma, S. Shibasaki, T. Shimokuni, H. Sakihama, N. Takahashi, H. Kawamura, and A. Taketomi report no conflicts of interest or financial ties.

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Figure legends:

Fig. 1 Between June, 2008 and August, 2015, a total of 196 elective laparoscopic colon resections were performed. In all, 59 patients were excluded from the study: 24, because they had colon cancers in pathologic stage IV; 31, who underwent reduced port surgery; 1, who required conversion to open surgery; and 3, who underwent multiple organ resection. From June, 2008 to December, 2013, 63 consecutive patients were given epidural anesthesia for postoperative pain (group E) and from January, 2014 to August, 2015, 74 consecutive patients were given fentanyl and celecoxib for postoperative pain (group FC)

Fig. 2 a Trends of pain scales. The postoperative FACES Pain Scores were similar from the day of surgery to POD 7, except on POD 1: POD 0 (0.86±0.45 vs. 1.11±0.11, p=0.079), POD 1 (1.05±0.57 vs. 1.45±0.11, p=0.008), POD 3 (0.74±0.81 vs. 0.78±0.88, p=0.775), and POD 7 (0.21±0.41 vs. 0.18±0.61, p=0.708). **b** The need for rescue analgesic drugs from the day of surgery to POD 7. The number of times

rescue analgesic drugs were given in group FC was significantly lower than in group E on PODs 0, 1, 2, 3, 4, and 5. The overall number of times rescue analgesic drugs were given was significantly lower in group FC than in group E (5.39±3.77 vs. 2.79±2.92, $p<0.001$). *$p<0.05$

Fig. 1

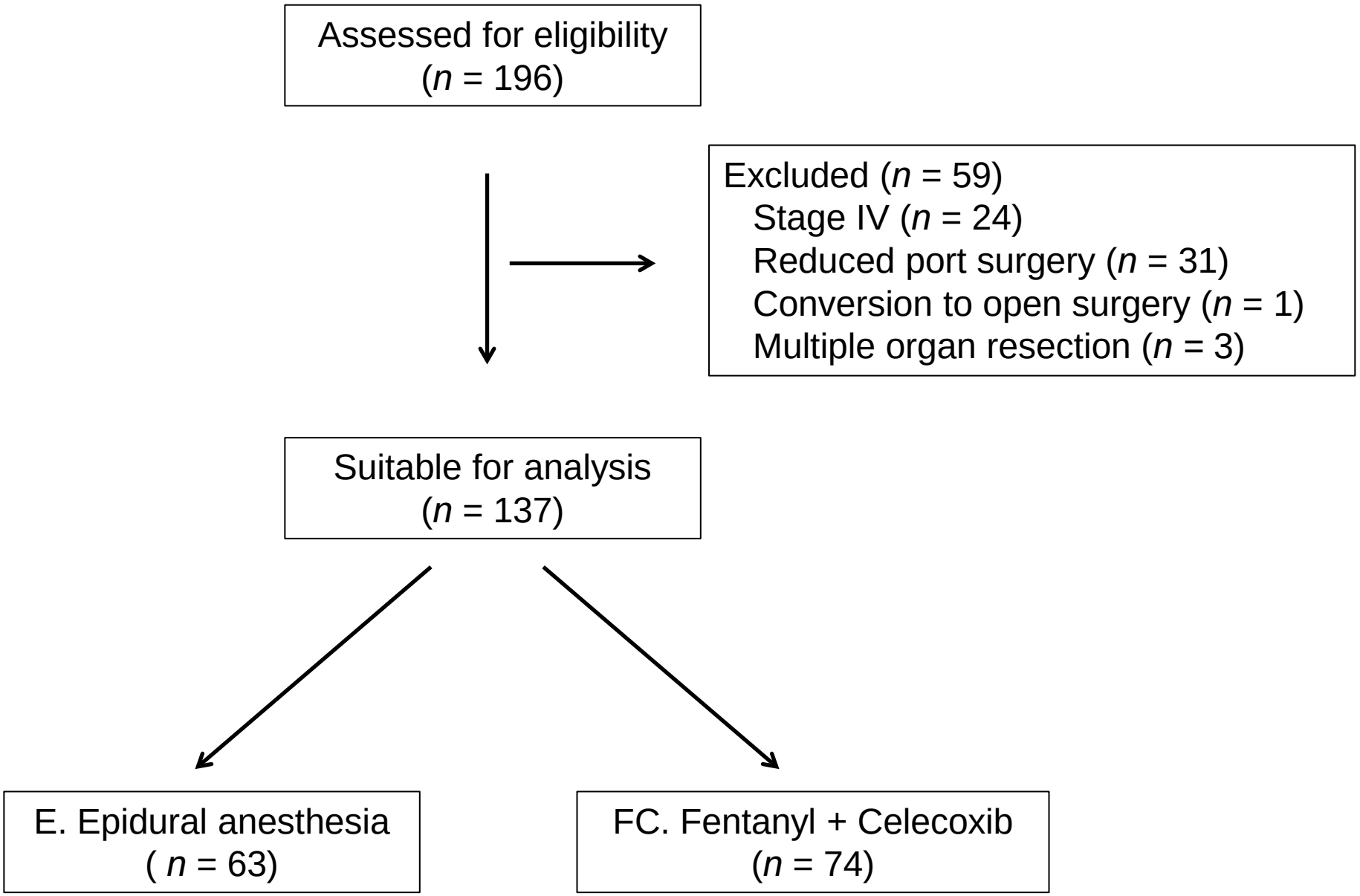
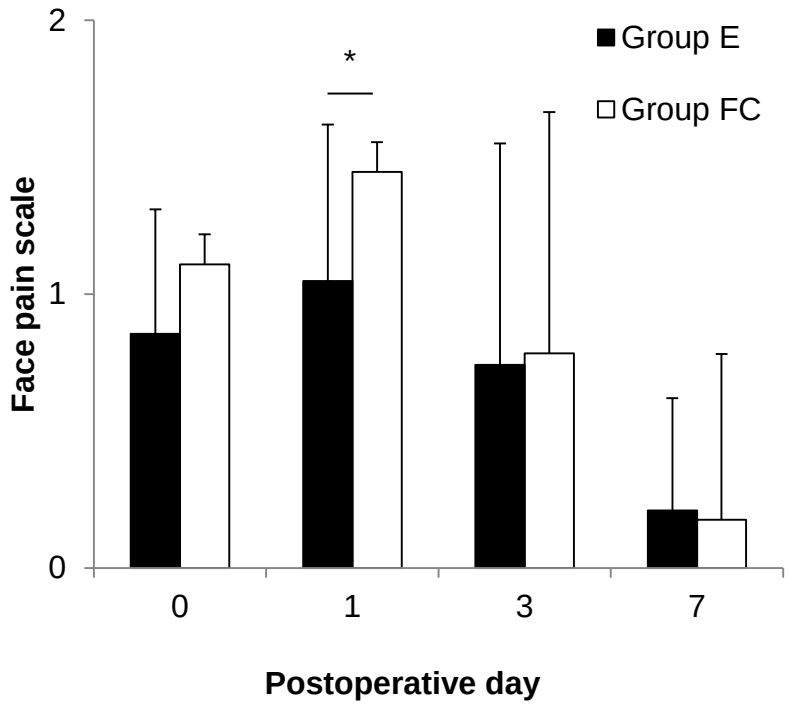

Assessed for eligibility
(*n* = 196)
Excluded (*n* = 59)
Stage IV (*n* = 24)
Reduced port surgery (*n* = 31)
Conversion to open surgery (*n* = 1)
Multiple organ resection (*n* = 3)
Suitable for analysis
(*n* = 137)
E. Epidural anesthesia
(*n* = 63)
FC. Fentanyl + Celecoxib
(*n* = 74)

Fig. 2

A


2
1
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Face pain scale
Group E
Group FC
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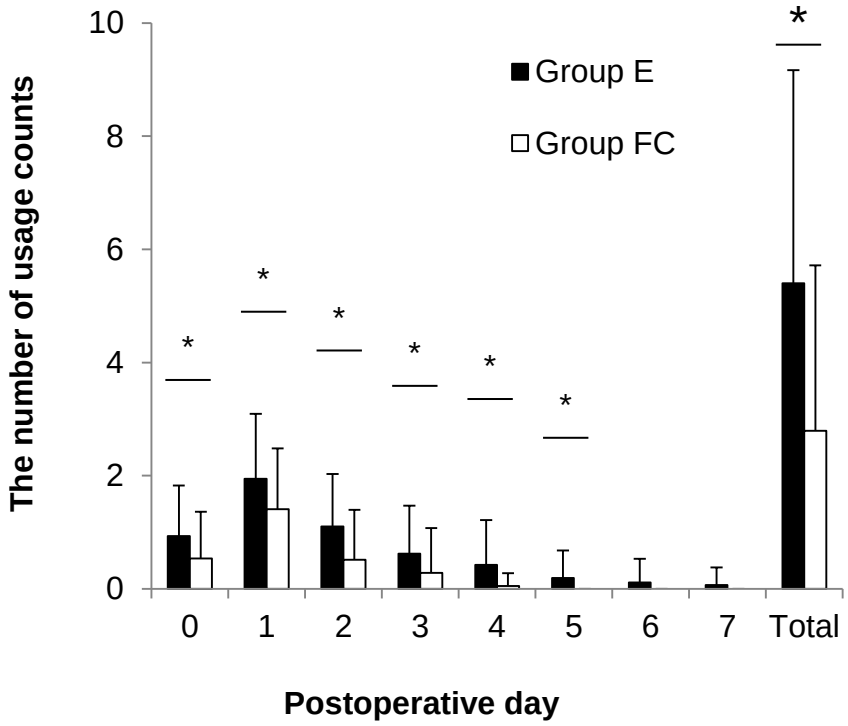
Postoperative day

B


10
8
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4
2
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The number of usage counts
Group E
Group FC
*
0
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5
6
7
Total
Postoperative day

Table 1. Patient characteristics

	E (*n* =63)	FC (*n* =74)	*p* value
Age (years)	66.9±10.5	71.0±9.1	0.014*
Male/femal (%)	42/21 (67/33)	52/22 (70/30)	0.651
BMI[a] (kg/m^2)	23.8±4.2	22.8±2.9	0.119
ASA–PS[b] I/II/III (%)	10/47/6 (15/75/10)	14/52/8 (19/70/11)	0.851
History of laparotomy (%)	6 (9.5)	16 (22)	0.055

Values are expressed as means ± standard deviations or percentage.
a. body mass index
b. American Society of Anesthesiologists–physical status
* $p<0.05$

Table 2. Tumor characteristics

Parameters	E (*n* =63)	FC (*n* =74)	*p* value
Maximum tumor diameter (mm)	35.5±19.5	36.9±19.9	0.771
Histologic type			
tub1/tub2/por1/por2/muc/pap/NEC[a]	18/37/1/1/2/4/0	30/36/0/0/6/1/1	0.174
(%)	(28/59/2/2/3/6/0)	(41/49/0/0/8/1/1)	
Pathologic "T" component			
Tis/1/2/3/4a/4b	8/14/13/25/3/0	2/17/8/39/7/1	0.085
(%)	(13/22/20/40/5/0)	(3/23/11/53/9/1)	
Pathologic "N" component			
0/1/2/3	45/15/3/0	47/24/2/1	0.484
(%)	(71/24/5/0)	(64/32/3/1)	
Pathologic stage			
0/I/II/IIIa/IIIb	8/21/15/16/3	2/17/28/24/3	0.068
(%)	(13/33/24/25/5)	(3/23/38/32/4)	

Values are expressed as mean ± standard deviation or percentage.
a. neuroendocrine carcinoma

Table 3. Operative outcomes

Outcome	E (*n* =63)		FC (*n* =74)		*p* value
Operative procedure	n	(%)	n	(%)	0.492
Ileocecal resection	9	(14)	19	(26)	
Right-hemi colectomy	17	(27)	14	(18)	
Transverse colectomy	4	(6)	5	(7)	
Left-hemi colectomy	9	(14)	5	(7)	
Sigmoidectomy	9	(14)	8	(11)	
High anterior resection	7	(11)	13	(17)	
Low anterior resection	6	(10)	8	(11)	
Hartmann operation	2	(3)	2	(3)	
Degree of lymph node dissection					
≤D2/D3 (%)	33/30 (52/48)		20/54 (27/73)		0.002*
Number of dissected lymph nodes	13.6±9.0		19.5±11.8		0.001*
Length of umbilical incision (cm)	5.89±1.68		5.78±1.30		0.747
Blood loss (g)	39.8±95.5		12.6±30.3		0.022*
Surgical time (min)	178.6±46.9		166.1±43.5		0.111
Time in an operating room other than for surgery (min)	128.1±30.4		107.3±17.0		<0.001*

Values are expressed as means ± standard deviations or percentage.
* $p < 0.05$

Table 4. Hematologic examination results

Measurement		E (n=63)[a]	FC (n=74)	p value
White blood cell (/mm^3)	Preoperation	6273±2192	6305±1715	0.925
	POD[b] 1	9165±2879	9433±2487	0.559
	POD 3	6419±1890	6210±1888	0.523
	POD 7	5958±2270	5870±1993	0.811
Hemoglobin (g/dL)	Preoperation	12.5±2.2	12.5±2.3	0.959
	POD 1	11.3±1.4	11.7±1.5	0.189
	POD 3	11.8±1.5	11.9±1.4	0.756
	POD 7	12.2±1.4	12.1±1.5	0.542
Platelet ($\times 10^4$/mm^3)	Preoperation	24.3±8.3	24.4±7.6	0.931
	POD 1	19.3±5.8	20.8±6.1	0.147
	POD 3	20.1±6.3	20.8±6.3	0.507
	POD 7	24.3±7.1	24.9±6.5	0.634
Aspartate transaminase (IU/L)	Preoperation	21.6±9.3	22.8±7.4	0.400
	POD 1	43.2±92.1	23.8±11.2	0.074
	POD 3	27.2±27.3	22.3±7.8	0.142
	POD 7	34.2±32.0	33.4±21.1	0.861
Alanine transaminase (IU/L)	Preoperation	18.2±9.6	19.3±11.7	0.551
	POD 1	29.8±54.0	21.7±19.8	0.236
	POD 3	26.1±44.1	18.2±11.8	0.141
	POD 7	36.2±41.5	31.5±23.8	0.410
Blood urea nitrogen (mg/dL)	Preoperation	15.1±5.0	14.7±4.5	0.652
	POD 1	11.3±5.2	12.6±4.7	0.107
	POD 3	8.0±3.8	8.4±3.6	0.554
	POD 7	12.3±5.2	10.8±5.0	0.094

Creatinine (mg/dL)	Preoperation	0.90±0.30	0.99±0.12	0.029*
	POD 1	0.84±0.14	0.88±0.33	0.534
	POD 3	0.79±0.41	0.91±0.30	0.060
	POD 7	0.94±0.31	0.99±0.26	0.297

Results are presented as means ± standard deviations.
a. one patient who required reoperation was excluded
b. postoperative days
* p <0.05

Table 5. Postoperative course of the study patients

Postoperative events	E (*n* =63)	FC (*n* =74)	*p* value
Adverse effects associated with anesthesia (%)	0 (0)	1 (1.4)	>0.999
Severe complications (Clavien–Dindo classification grade 3–5)			0.210
Acute cholecystitis (grade 3a)	1	0	
Panperitonitis (grade 3b)[a]	1	0	
(%)	(3.2)	(0)	
Commencement date for drinking (POD[b])[c]	1.3±1.4	1.0±0.1	0.842
eating (POD[b])[c]	4.1±2.0	4.8±1.9	0.060
Postoperative hospitalization (days)[c]	11.1±4.5	10.3±4.8	0.315

Results are presented as means ± standard deviations or percentage.
a. required reoperation
b. postoperative days