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ORIGINAL ARTICLE

Perioperative fluid management influences complication rates and length of hospital stay in the enhanced recovery after surgery (ERAS) protocol for patients with colorectal cancer

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Abstract

Purpose To evaluate the efficacy and safety of the enhanced recovery after surgery (ERAS) protocol and quantify the impact of each ERAS item on postoperative outcomes.

Methods We used a generalized linear model to compare 289 colorectal cancer patients treated with the ERAS protocol between June, 2015 and April, 2021, with 99 colorectal cancer patients treated with the conventional colorectal surgery pathway between April, 2014 and June, 2015.

Results The median length of hospital stay (LOHS) was significantly shorter in the ERAS group, at 9 days (range 3–104 days) vs. 14 days (range 4–44 days) ($p < 0.001$), but the complication rates (Clavien–Dindo grade 2 or more) were similar (16.6% vs. 22.2%; $p = 0.227$). However, in the ERAS group, the higher the compliance with ERAS items, the lower the complication rate and LOHS (both $p < 0.001$). Multiple regression analysis demonstrated that "Discontinuation of continuous intravenous infusion on POD1" and "Avoidance of fluid overload" were significantly associated with the LOHS ($p < 0.001$ and $p = 0.008$).

Conclusion The ERAS protocol is safe and effective for elective colorectal cancer surgery, and compliance with the ERAS protocol contributes to shorter LOHS and fewer complications. Items related to perioperative fluid management had a crucial impact on these outcomes.

Keywords Colorectal cancer · Compliance rate · Complication rate · Enhanced recovery after surgery · Length of hospital stay

Introduction

The enhanced recovery after surgery (ERAS) protocol is a comprehensive treatment plan that incorporates a set of techniques proven to maintain physiological function and promote the recovery of postoperative patients. Previous studies have shown that the ERAS protocol facilitates a smooth transition to discharge without increasing postoperative complication rates [1]. ERAS compliance is related to complication rates and length of hospital stay (LOHS) [1–6], but the relevance and contribution of each item on the ERAS is unclear. It is understood that as many items as possible promote postoperative recovery, but which ERAS items play a more important role has not been elucidated. Thus, a detailed analysis of the independent contributions of ERAS items to postoperative outcomes is necessary. In this study, we evaluated the efficacy and safety of the ERAS protocol, as well as the impact of compliance with each ERAS item, on postoperative outcomes, especially complication rates and LOHS.

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Methods

Patient eligibility

We compared the results of 289 colorectal cancers treated with the ERAS protocol between June, 2015 and April, 2021, with those of 99 colorectal cancers treated with the conventional colorectal surgery pathway between April, 2014 and June, 2015.

Items in perioperative routines from the ERAS protocol

Table 1 lists the items from the ERAS that were applied in perioperative routines. Postoperative nausea and vomiting (PONV) measures were originally based on the four major risk factors proposed by Apfel et al. [7]: female gender, history of motion sickness and PONV, non-smoker, and postoperative opioid use. We implemented PONV countermeasures based on the "Consensus guidelines for the management of postoperative nausea and vomiting" [8], which evolved from that proposal. ERAS protocol deviations were defined as an inability to recommence oral food intake on postoperative day (POD) 1,

Table 1 Items from the perioperative routine applied in the enhanced recovery after surgery (ERAS) protocol

ERAS item		Explanation
(1)	Preadmission education	Sharing educational brochure and explanation by clinical nurse specialist
(2)	PONV measures	Countermeasures against PONV based on "Consensus guidelines for the management of postoperative nausea and vomiting"
(3)	No preoperative MBP	Giving magnesium citrate for left-sided, but not right-sided, colon and rectal surgery
(4)	Taking Elental on the day of surgery	Giving an isotonic Elental drink, 260 mOsm (dissolving 50 g of Elental powder in 500 ml water), at 6 am on the day of surgery
(5)	Using perioperative epidural, TAP block, or intravenous anesthesia	Use of a thoracic epidural placed preoperatively for open surgery, with the continuous epidural infusion of fentanyl and levobupivacaine unless contraindicated. Alternatively, a TAP block plus intravenous fentanyl PCA can be performed for laparoscopic surgery
(6)	Intraoperative antibiotics	Giving flomoxef sodium unless contraindicated
(7)	Avoidance of fluid overload (intraoperative fluid < 2000 ml)	To optimize fluid volume, 3 ml/kg/h of intraoperative crystalloid and colloid fluid (usually intraoperative fluid < 2000 ml) is the standard volume administered
(8)	No drain	No drain except for low anterior resection, for any specific reason
(9)	Removal of NG tube on intratracheal exubation	–
(10)	Sitting position on the day of surgery	Maintaining the patient in a sitting position soon after complete waking after surgery until 10 pm
(11)	Oral intake of 500 ml water on the day of surgery	More than 500 ml water is allowed after complete awakening from anesthesia unless PONV is found
(12)	Encouraging chewing gum on the day of surgery	Patients with dentures do not always have to use chewing gum
(13)	Oral nutritional supplement on POD1	–
(14)	Routine postoperative laxative	Giving magnesium oxide postoperatively
(15)	Removal of urethral catheter on POD1	Removal of the Foley catheter on POD 1, except in high-risk patients such as those with a history of benign prostatic hyperplasia, prostate surgery, bladder injury, rectal surgery, or postoperative urinary retention
(16)	Ambulation on POD 1	Physiotherapists lead ambulation and rehabilitation
(17)	Discontinuation of c.i.v. on POD 1	Maintenance intravenous fluid discontinued. Fluid bolus allowed

The conventional care group did not receive "Preadmission education", "PONV measures", "No preoperative MBP", "Taking Elental on the day of surgery", "Sitting position on the day of surgery", and "Oral intake of 500 ml water on the day of surgery". With a few exceptions, drinking was generally initiated on POD1 and eating on POD2, and the timing of discontinuation of c.i.v. was determined according to the amount of food intake. There are no clear rules regarding the amount of intraoperative fluids, when to remove the drain and NG tube, the use of a routine postoperative laxative, when to remove the urethral catheter, and when to start ambulation, which were left to the discretion of the individual surgeon

PONV postoperative nausea and vomiting, *POD* postoperative day, *MBP* mechanical bowel preparation, *TAP* transversus abdominis plane, *PCA* patient-controlled analgesia, *NG* nasogastric, *c.i.v.* continuous intravenous infusion

discontinuation of food intake once started, and resumption of continuous infusion [1]. Patients who deviated from the ERAS protocol were also included in the statistical analysis as part of the ERAS protocol group.

Propensity score (PS) matching

A higher proportion of laparoscopy was expected in the ERAS group. Because the laparoscopic surgery group was more recent than the open surgery group, an imbalance in crucial covariates related to outcomes could have biased the estimation of the effect of laparoscopic surgery. To address the selection bias, we performed a PS analysis. The PS included 12 effective covariates, including age, sex, surgical approaches, procedure classification, pathological stage, cardiovascular disease or hypertension, respiratory disease, liver disease, urinary tract disease, diabetes mellitus, cerebral vascular disease, and American Society of Anesthesiologists physical status (ASA-PS). The PS for each patient was estimated using a logistic regression model, and we used the PS to match patients who were treated by the ERAS protocol with corresponding control patients who were treated conventionally. For more plausible matching, we applied one-to-one pair matching. The caliper width for PS matching was 0.2.

Statistical analysis

Data are presented as means and standard deviation or median and range. The Mann–Whitney *U* test, Pearson's chi-squared test, or Fisher's exact test were used to investigate the relationship between the ERAS protocol and conventional care. The association between the clinical variables and LOHS was examined using multiple regression analysis. Logistic regression analysis was also used to examine the association of the clinical variables with complications. Factors were included in the models based on existing knowledge of the factors related to LOHS and with $p < 0.05$ in the univariate regression analysis. We selected the factors using the forced entry method and likelihood ratios. Multicollinearity among the included variables was examined using variance inflation factors. Factors with $p < 0.05$ were also considered significant in the multivariate analysis. We conducted this analysis using version 28.0.0 of SPSS software (IBM, NY, USA). To examine the relationship between compliance and overall complications, or between compliance and LOHS, trend analyses were performed using the Jonckheere-Terpstra trend test.

Results

Patient characteristics and perioperative outcomes

Table 2 compares the patient characteristics and perioperative outcomes between the ERAS group and the conventional care group. We found no significant differences in age, gender, colectomy rate, comorbidity, or ASA grade between the groups, but the ERAS group had a significantly higher rate of laparoscopy and a significantly lower median volume of intraoperative fluid. In terms of postoperative outcomes, we found no significant difference in Clavien–Dindo grade, time to first flatus, or time to first stool between the groups, although food intake recommenced significantly earlier in the ERAS group. We also found no significant differences between the groups in the rates of postoperative death, reoperation, or readmission within 30 days after surgery.

As the percentage of laparoscopic surgery was significantly higher in the ERAS group than in the conventional care group, we performed PS matching to compare the perioperative outcomes of 73 patients from both groups with a percentage of laparoscopy of 87.7%. Even after matching, the volume of intraoperative fluid given was significantly less in the ERAS group (median 765 ml [range 80–3800 ml] vs. 1600 ml [500–3400 ml], $p < 0.001$). In terms of postoperative outcomes, we found no significant difference in Clavien–Dindo grade between the two groups ($p = 0.314$), although the infusion was discontinued significantly earlier in the ERAS group, on POD 1 [range POD 1–34] vs. POD 3 [1–77]; $p < 0.001$). LOHS was significantly shorter in the ERAS group at a median of 9 days [range 3–43 days] vs. 12 days [4–44 days]; $p < 0.001$), and there were no significant differences in the rates of postoperative death, reoperation, or readmission within 30 days after surgery between the groups ($p = 1.000$, 1.000, and 0.366, respectively).

The accomplishment rate of the ERAS protocol was 77.2% (223/289). Table 3 lists the complications in the two groups. There were no significant differences in the incidences of the major complications of paralytic ileus ($p = 0.139$), anastomotic leakage ($p = 0.769$), outlet obstruction ($p = 1.000$), or port site hernia ($p = 0.574$).

Compliance with each ERAS intervention

Figure 1 compares compliance with each ERAS intervention between the ERAS protocol and conventional care groups. Compliance rates were much higher in the ERAS group for all items except the use of routine postoperative laxatives because some items that were not part of

Table 2 Patient characteristics and perioperative outcomes before and after propensity score matching between the enhanced recovery after surgery (ERAS) and conventional care groups

	Before matching			After matching		
	ERAS protocol ($n=289$)	Conventional care ($n=99$)	p value	ERAS protocol ($n=73$)	Conventional care ($n=73$)	p value
Age, years	74 (32–94)	74 (30–92)	0.824	72 (48–94)	73 (44–92)	0.969
Female: male (%female)	131: 158 (45.3%)	44: 55 (44.4%)	0.879	31: 42 (42.5%)	31: 42 (42.5%)	1.000
Procedure classification, colectomy: proctectomy (%colectomy)	208: 81 (72.0%)	75: 24 (75.8%)	0.464	58: 15 (79.5%)	56: 117 (76.7%)	0.842
Surgical approach, laparoscopy: open (%laparoscopy)	279: 10 (96.5%)	64: 35 (64.6%)	< 0.001	64: 9 (87.7%)	64: 9 (87.7%)	1.000
Stage			0.399			0.962
0	23 (7.96%)	11 (11.1%)		7 (9.59%)	9 (12.3%)	
I	89 (30.8%)	27 (27.2%)		23 (31.5%)	24 (32.9%)	
II	95 (32.9%)	26 (26.3%)		16 (21.9%)	15 (20.6%)	
III	62 (21.5%)	24 (24.2%)		22 (30.1%)	19 (26.0%)	
IV	20 (6.92%)	11 (11.1%)		5 (6.85%)	6 (8.22%)	
Concomitant disease						
Cardiac/hypertension	116 (40.1%)	49 (49.5%)	0.104	34 (46.6%)	40 (54.8%)	0.321
Respiratory	28 (9.69%)	5 (5.05%)	0.153	4 (5.48%)	4 (5.48%)	1.000
Liver	24 (8.30%)	9 (9.09%)	0.809	4 (5.48%)	5 (6.85%)	1.000
Urinary tract	35 (12.1%)	9 (9.09%)	0.414	4 (5.48%)	6 (8.22%)	0.745
Diabetes mellitus	52 (18.0%)	14 (14.1%)	0.379	11 (15.1%)	11 (15.1%)	1.000
Cerebral vascular	27 (9.34%)	9 (9.09%)	0.941	7 (9.59%)	7 (9.59%)	1.000
ASA grade			0.371			0.604
I	45 (15.6%)	8 (8.08%)		4 (5.48%)	7 (9.59%)	
II	195 (67.5%)	76 (76.8%)		60 (82.2%)	56 (76.7%)	
III	49 (17.0%)	14 (14.1%)		9 (12.3%)	10 (13.7%)	
IV	0 (0.00)	1 (1.01%)		0 (0.00)	0 (0.00)	
Blood loss, ml	13 (0–2400)	10 (5–1600)	0.001	20 (0–2400)	5 (5–520)	0.861
Intraoperative fluid, ml	850 (80–3800)	1600 (500–3470)	< 0.001	765 (80–3800)	1600 (500–3400)	< 0.001
Intraoperative urine output, ml	200 (0–1450)	250 (20–1500)	0.013	200 (0–1200)	250 (80–1500)	0.182
Operation time, min	254 (83–679)	224 (95–620)	0.004	255 (86–660)	229 (104–417)	0.083
Clavien–Dindo grade, 0, I, II, IIIa, IIIb, IVa, IVb, V	201, 40, 39, 4, 5, 0, 0, 0	65, 12, 18, 3, 0, 0, 0, 1	0.226	41, 16, 14, 1, 1, 0, 0, 0	50, 9, 11, 2, 0, 1, 0, 0	0.314
Clavien–Dindo grade 2 or higher complications	48 (16.6%)	22 (22.2%)	0.227	16 (21.9%)	14 (19.2%)	0.838
Postoperative day of oral food intake	1 (1–21)	2 (1–22)	< 0.001	1 (1–9)	2 (1–16)	< 0.001
Time to first flatus, days	1 (0–7)	1 (0–4)	0.786	1 (1–4)	2 (0–4)	0.696
Time to first stool, days	2 (1–7)	3 (0–12)	0.162	2 (1–6)	3 (0–8)	0.202
Postoperative day for discontinuation of continuous infusion	1 (1–102)	3 (1–77)	< 0.001	1 (1–34)	3 (1–77)	< 0.001
Length of hospital stay, days	9 (3–104)	14 (4–44)	< 0.001	9 (3–43)	12 (4–44)	< 0.001
Postoperative death	0 (0.00)	1 (1.01%)	0.255	0 (0.00)	1 (1.37%)	1.000
Reoperation	6 (2.08%)	0 (0.00)	0.345	1 (1.37%)	0 (0.00)	1.000
Readmission	7 (2.42%)	4 (4.04%)	0.482	1 (1.37%)	4 (5.48%)	0.366

Values are expressed as the median (range) or n (%) unless otherwise noted. p values were determined by the chi-squared test, Fisher's exact test, or Mann–Whitney U test

Table 3 Complications in the enhanced recovery after surgery (ERAS) protocol and conventional care groups

	ERAS protocol ($n=289$)	Conventional care ($n=99$)	p value
Paralytic ileus	20 (6.9%)	12 (12.1%)	0.139
Anastomotic leakage	12 (4.2%)	3 (3.0%)	0.769
Outlet obstruction at ileostomy	3 (1.0%)	1 (1.0%)	1.000
Port site hernia	3 (1.0%)	0 (0%)	0.574
Intra-abdominal abscess	1 (0.3%)	1 (1.0%)	0.446
Neurogenic bladder	1 (0.3%)	1 (1.0%)	0.446
Urinary tract infection	1 (0.3%)	0 (0%)	1.000
PONV	1 (0.3%)	0 (0%)	1.000
Bronchitis	1 (0.3%)	0 (0%)	1.000
Atrial fibrillation	1 (0.3%)	0 (0%)	1.000
Lymphorrhea	1 (0.3%)	0 (0%)	1.000
Restriction of shoulder joint range of motion	1 (0.3%)	0 (0%)	1.000
Progressive anemia of unknown cause	1 (0.3%)	0 (0%)	1.000
Elevated inflammatory response of unknown cause	1 (0.3%)	0 (0%)	1.000
Postoperative bleeding	0 (0%)	1 (1.0%)	0.255
Intestinal ischemia	0 (0%)	1 (1.0%)	0.255
Aspiration pneumonia	0 (0%)	1 (1.0%)	0.255
Leg edema	0 (0%)	1 (1.0%)	0.255

Values are given as n (%). p values were determined by chi-squared test, Fisher's exact test, or Mann–Whitney U test

Complications were defined as Clavien–Dindo grade 2 or higher

Surgical site infections developed in four patients in the ERAS protocol group and six in the conventional care group, all of which were classified as Clavien–Dindo grade 1

"Paralytic ileus" is a condition in which the bowel is not mechanically obstructed, but intestinal peristalsis is clearly reduced on physical and radiological findings

PONV postoperative nausea and vomiting

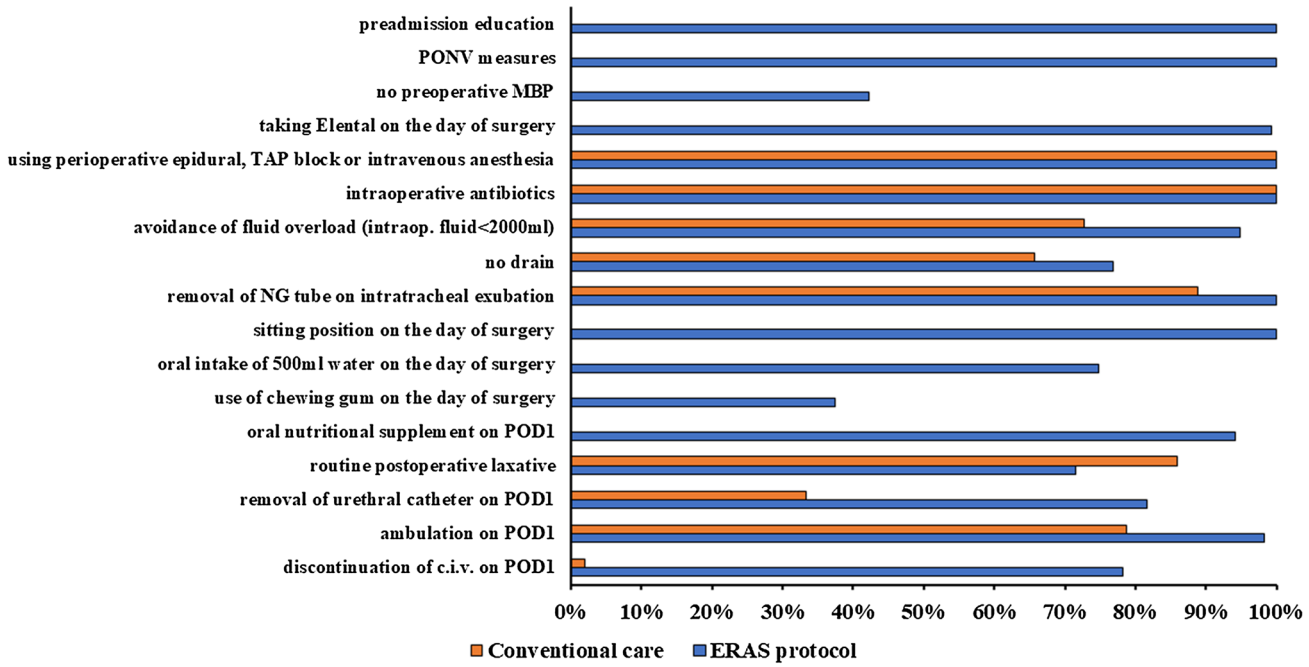

Fig. 1 Compliance with each 'enhanced recovery after surgery' (ERAS) protocol. *PONV* postoperative nausea and vomiting, *MBP* mechanical bowel preparation, *TAP* transversus abdominis plane, *intraop.* Intraoperative, *NG* nasogastric, *c.i.v.* continuous intravenous infusion

conventional care were included. These comprised pre-admission education, PONV measures, no preoperative mechanical bowel preparation, taking Elental on the day of surgery, sitting upright on the day of surgery, oral intake of 500 ml water on the day of surgery, use of chewing gum on the day of surgery, and giving an oral nutritional supplement on POD1. Giving laxatives from POD1 was forgone in the left-sided colon surgery or rectal surgery in the ERAS group, based on evidence that severe diarrhea on POD1 may cause anastomotic leak.

Relationship between compliance rate and complication rate or LOHS

We compared the complication rate (Fig. 2) and median LOHS (Fig. 3) with the extent to which patients could comply with the ERAS items (< 70% compliance, 70–80%, 80–90%, and > 90%). The higher compliance rate showed a significantly lower complication rate and shorter LOHS (both $p < 0.001$). To examine the influence on compliance of age, ASA-PS, or surgical procedure, we conducted a subgroup analysis of compliance rates for colectomy ERAS ($n = 208$) and proctectomy ERAS ($n = 81$), non-elderly ERAS (< 75 years old, $n = 151$) and elderly ERAS (≥ 75 years old, $n = 138$), and ASA-PS of 1 ($n = 45$) and

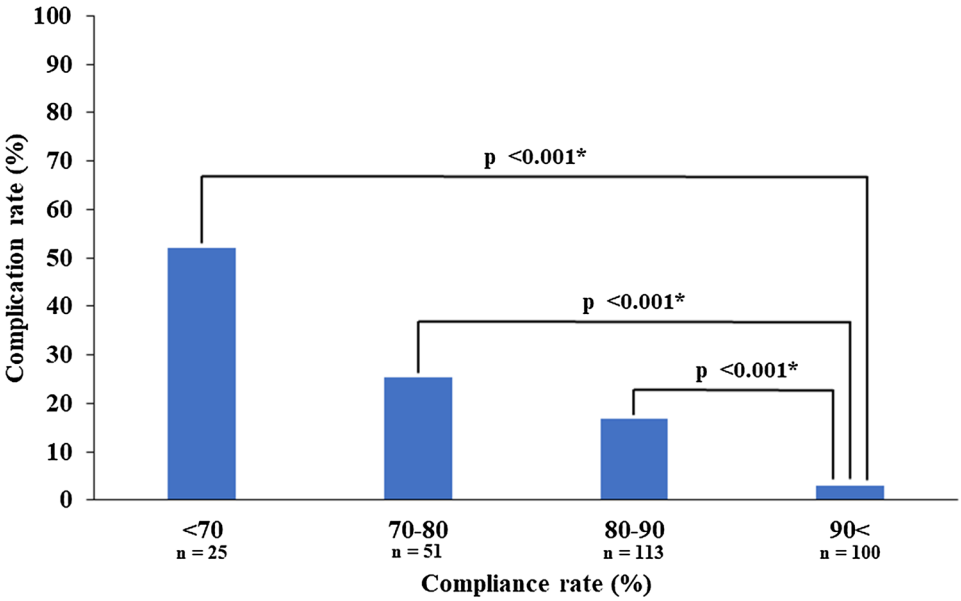

Fig. 2 Relationship between compliance rate and complication rate. *p* values were determined by the Jonckheere–Terpstra trend test, or for comparison between two groups, the Mann–Whitney *U* test

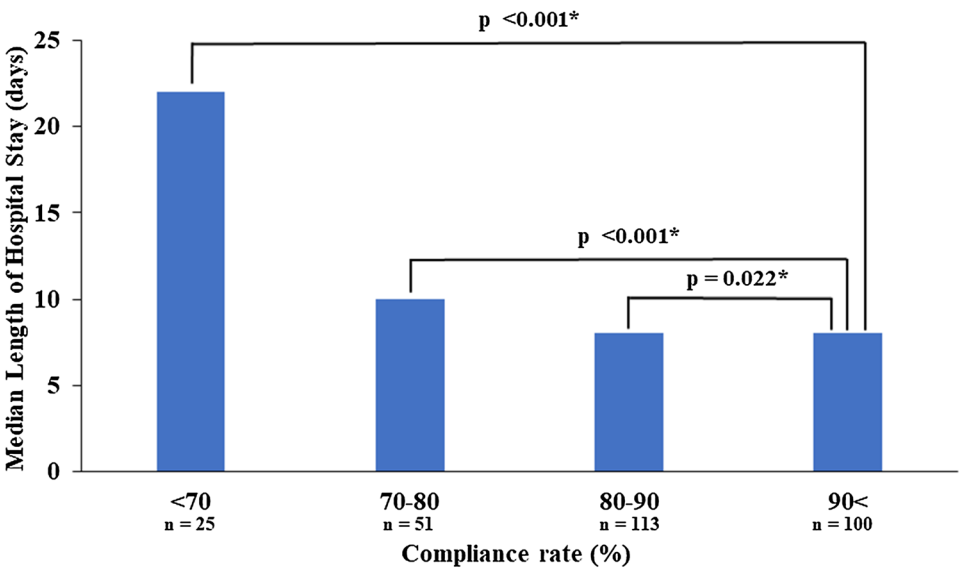

Fig. 3 Relationship between compliance rate and length of hospital stay. *p* values were determined by the Jonckheere–Terpstra trend test, or for comparison between two groups, the Mann–Whitney *U* test

Table 4 Logistic regression analysis of the association between factors and complication rate

Factors	Complications	No complications	Univariate		Multivariate	
	$n=48$	$n=241$	OR_{Crude} (95% CI)	p value	OR_{Adj} (95% CI)	p value
Age, years	74.8 ± 10.2 (46–93)	72.4 ± 10.4 (32–94)	1.02 (0.99, 1.06)	0.147	1.01 (0.96, 1.05)	0.746
Female: male (%female)	15:33 (31.3%)	116:125 (48.1%)	0.49 (0.25, 0.95)	0.034	0.89 (0.35, 2.23)	0.798
Procedure classification, colectomy: proctectomy (%colectomy)	24:24 (50.0%)	184:57 (76.3%)	0.31 (0.16, 0.59)	< 0.001	0.35 (0.10, 1.26)	0.109
Surgical approach, laparoscopy: open (%laparoscopy)	43: 5 (89.6%)	236: 5 (97.9%)	0.18 (0.51, 0.66)	0.009	1.35 (0.17, 11.02)	0.777
Concomitant disease						
Cardiac/hypertension	18 (37.5%)	98 (40.7%)	0.88 (0.46, 1.66)	0.683		
Respiratory	8 (16.7%)	20 (8.3%)	2.21 (0.91, 5.36)	0.080		
Liver	4 (8.3%)	20 (8.3%)	1.00 (0.33, 3.08)	0.994		
Urinary tract	5 (10.4%)	30 (12.4%)	0.82 (0.30, 2.23)	0.694		
Diabetes mellitus	7 (14.6%)	45 (18.7%)	0.74 (0.31, 1.77)	0.502		
Cerebral vascular	8 (16.7%)	19 (7.9%)	2.34 (0.96, 5.70)	0.062		
Operation time ≥ 300 min	28 (58.3%)	61 (25.3%)	4.13 (2.17, 7.86)	< 0.001	1.71 (0.56, 5.19)	0.342
ASA grade II or more	43 (89.6%)	201 (83.4%)	1.71 (0.64, 4.59)	0.286		
Discontinuation of c.i.v. on POD1	8 (16.6%)	218 (90.4%)	0.021 (0.009, 0.050)	< 0.001	0.025 (0.009, 0.067)	< 0.001
Taking Elental on the day of surgery	46 (95.8%)	241(100%)	NA[a]	NA[a]		
No preoperative MBP	17 (14.6%)	105 (43.6%)	0.71 (0.37, 1.35)	0.298		
Avoidance of fluid overload (intraoperative fluid < 2000 ml)	38 (79.2%)	236 (97.9%)	0.08 (0.03, 0.25)	< 0.001	0.53 (0.07, 3.78)	0.527
No drain	28 (58.3%)	194 (80.5%)	0.34 (0.18, 0.65)	0.001	1.28 (0.34, 4.81)	0.716
Oral intake of 500 ml water on the day of surgery	31 (64.6%)	185 (76.7%)	0.55 (0.28, 1.07)	0.079		
Use of chewing gum on the day of surgery	14 (29.2%)	94 (39.0%)	0.64 (0.33, 1.26)	0.201		
Oral nutritional supplement on POD1	42 (87.5%)	230 (95.4%)	0.33 (0.12, 0.95)	0.041	0.62 (0.13, 2.83)	0.534
Routine postoperative laxative	28 (58.3%)	179 (74.3%)	0.48 (0.26, 0.92)	0.027	1.08 (0.37, 3.14)	0.894
Removal of urethral catheter on POD1	32 (66.7%)	204 (84.7%)	0.36 (0.18, 0.73)	0.004	0.80 (0.25, 2.53)	0.701
Ambulation on POD1	45 (93.8%)	239 (99.2%)	0.13 (0.02, 0.77)	0.025	1.73 (0.09, 34.41)	0.718

Values are expressed as means ± SD (range) or n (%) unless otherwise noted. p values were determined by logistic regression analysis

OR_{Crude} crude odds ratio, *CI* confidence interval, OR_{Adj} adjusted odds ratio, *c.i.v.* continuous intravenous infusion, *POD* postoperative day, *MBP* mechanical bowel preparation

[a]The item "Taking Elental on the day of surgery" was removed from the multivariate analysis because of complete separation

ASA-PS of 2 or higher ($n=244$). We found significant differences between colectomy ERAS and proctectomy ERAS (89.2% vs. 75.0%, $p<0.001$), but not between non-elderly ERAS and elderly ERAS patients (85.0% vs. 85.4%, $p=0.991$) or ASA-PS of 1 and ASA-PS of 2 or higher (85.5% vs. 85.2%, $p=0.628$).

Factors related to complications

Table 4 shows univariate and multivariate analyses of the association between factors and complications. Univariate analysis identified sex, procedure classification (%colectomy), surgical approach (%laparoscopy), operation time ≥ 300 min, discontinuation of the intravenous infusion (c.i.v.) on POD 1, avoidance of fluid overload (intraoperative fluid < 2000 ml), no drain, oral nutritional supplementation on POD 1, routine postoperative laxative, removal of urethral catheter on POD 1, and ambulation on POD 1 as significantly associated with complications. According to binomial logistic regression analysis, "Discontinuation of c.i.v. on POD1" alone was significantly associated with complications (odds ratio = 0.025; 95% confidence interval [CI] 0.009, 0.067; $p<0.001$).

Factors related to LOHS

Table 5 shows univariate and multivariate analyses of the association of various factors with the LOHS. Univariate

Table 5 Multiple regression analysis of the association between factors and the length of hospital stay

Factors	Univariate		Multivariate			
	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value	Std Beta	VIF
Age	0.13 (0.03, 0.23)	0.008	0.1 (0, 0.2)	0.048	0.1	1.1
Female sex	− 1.44 (− 2.48, − 0.4)	0.007	0.07 (− 0.93, 1.08)	0.888	0.01	1.07
Colectomy	− 3.34 (− 4.47, − 2.22)	< 0.001	− 1.26 (− 2.75, 0.23)	0.098	− 0.11	1.92
Laparoscopy	− 4.42 (− 5.99, − 2.86)	< 0.001	1.62 (− 1.62, 4.87)	0.326	0.06	1.5
Concomitant disease						
Cardiac/hypertension	− 0.77 (1.82, − 0.28)	0.151				
Respiratory	1.29 (− 0.57, 3.15)	0.173				
Liver	− 1.31 (− 3.17, 0.55)	0.168				
Urinary tract	0.31 (− 1.33, 1.95)	0.712				
Diabetes mellitus	− 0.29 (− 1.68, 1.09)	0.680				
Cerebral vascular	2.44 (0.66, 4.22)	0.007	0.51 (− 1.22, 2.24)	0.561	0.03	1.09
Operation time ≥ 300 min	3.31 (2.07, 4.55)	< 0.001	0.74 (− 0.53, 2.01)	0.251	0.07	1.47
ASA grade II or more	1.26 (− 0.39, 2.9)	0.135				
Discontinuation of c.i.v. on POD1	− 6.71 (− 7.93, − 5.48)	< 0.001	− 5.43 (− 6.74, − 4.12)	< 0.001	− 0.43	1.26
Taking Elental on the day of surgery	1.92 (− 5.31, 9.15)	0.602				
No preoperative MBP	− 1.06 (− 2.27, 0.15)	0.085				
Avoidance of fluid overload (intraoperative fluid < 2000 ml)	− 6.80 (− 8.33, − 5.27)	< 0.001	− 3.89 (− 6.76, − 1.01)	0.008	− 0.17	1.74
No drain	− 3.56 (− 4.69, − 2.43)	< 0.001	− 1.41 (− 3.02, 0.21)	0.088	− 0.11	1.99
Oral intake of 500 ml water on the day of surgery	− 1.58 (− 2.95, − 0.22)	0.023	0.62 (− 0.59, 1.83)	0.317	0.05	1.19
Use of chewing gum on the day of surgery	− 1.15 (− 2.38, 0.08)	0.068				
Oral nutritional supplement on POD1	− 0.10 (− 2.65, 2.45)	0.938				
Routine postoperative laxative	− 1.62 (− 2.81, − 0.42)	0.008	− 0.59 (− 1.78, 0.6)	0.329	− 0.05	1.23
Removal of urethral catheter on POD1	− 2.00 (− 3.53, − 0.47)	0.011	0.65 (− 0.77, 2.06)	0.369	0.05	1.28
Ambulation on POD1	− 3.66 (− 8.24, 0.92)	0.117				

p values were determined by multiple regression analysis

CI confidence interval, *Std Beta* standardized regression coefficient, *VIF* variance inflation factor, *c.i.v.* continuous intravenous infusion, *POD* postoperative day, *MBP* mechanical bowel preparation

analysis identified sex, procedure classification (%colectomy), surgical approach (%laparoscopy), cerebral vascular disease, operation time ≥ 300 min, discontinuation of c.i.v. on POD1, avoidance of fluid overload (intraoperative fluid < 2000 ml), no drain, oral intake of 500 ml water on the day of surgery, routine postoperative laxative, and removal of the urethral catheter on POD1 as significantly associated with LOHS. Multiple regression analysis was performed in the same way. "Discontinuation of c.i.v. on POD1" and "Avoidance of fluid overload" were significantly associated with LOHS (coefficient = -5.43; 95% CI − 6.74, − 4.12; $p < 0.001$; and coefficient = − 3.89; 95% CI − 6.76, − 1.01; $p = 0.008$, respectively). "Discontinuation of c.i.v. on POD1" had a greater impact than "Avoidance of fluid overload" ($\beta = -0.43$ and -0.17, respectively). The residuals had normal distribution.

Discussion

The findings of this study demonstrated that the ERAS protocol at our hospital was safe and effective for elective colorectal cancer surgery and that greater compliance contributed to shorter LOHS and fewer complications. While these results reconfirm general evidence from previous reports, we also identified the most important ERAS items. Notably, compliance with ERAS items related to perioperative fluid management had a strong influence on these outcomes. We think that identifying this will help facilitate successful implementation of the ERAS protocol in colorectal surgery.

Ota et al. reported that the ERAS protocol can promote early discharge without increasing the complication

rate, more effectively than conventional care [1]. Despite reports that stoma creation interfered with postoperative recovery from rectal cancer surgery [9, 10], there was no difference in the proportion of patients in the ERAS group and in the conventional care group, who had a stoma created after PS matching (11 of 73 patients in each group, data not shown). In the present study, compliance with ERAS items correlated with complication rates and LOHS, but the compliance rate may be influenced by other factors, such as age, ASA-PS, or proctectomy. Although proctectomy had a significantly worse compliance rate than colectomy, there was no difference in terms of age and ASA-PS. A detailed analysis of the impact of such factors on compliance rate, accomplishment rate, complication rate, and LOHS will be the subject of future studies.

Although we did not investigate the issue of cost in our study, other reports have shown that the application of ERAS not only shortens the LOHS, but it also reduces costs for patients after colorectal surgery [11] and laparoscopic cholecystectomy [12]. Some studies have focused on the importance of perioperative nutritional management [13], whereas others have focused on perioperative fluid management [14–20]. The ERAS Compliance Group [2] reported that LOHS can be shortened by preoperative carbohydrate drinks, optimal fluid loading, and intravenous anesthesia instead of epidural anesthesia.

Our results showed that the discontinuation of c.i.v. on POD 1 contributed to reducing the complication rate, and that the avoidance of fluid overload and discontinuation of c.i.v. on POD 1 helped minimize the LOHS. Both of these items are associated with perioperative infusion management. Intraoperative infusion tends to vary among anesthesiologists, probably in consideration of postoperative outcomes [14]. It is thought that administering the appropriate amount of IV fluids without excess or deficiency can shorten the LOHS, reduce costs, and prevent postoperative ileus [15]. In this study, the most prevalent complication was paralytic ileus, which also tended to be more frequent in the conventional care group than in the ERAS group, although the complication rates did not differ significantly between the two groups, being 6.9% vs. 12.1% in the ERAS protocol vs. conventional care groups, respectively; $p = 0.139$; Table 3). We emphasized the importance of restriction to optimize perioperative fluid infusion. Within the ERAS group, paralytic ileus occurred in only 2 of 226 patients (0.9%) for whom "Discontinuation of c.i.v on POD 1" was achieved, but in 18 of 63 patients (28.6%) for whom it was not achieved ($p < 0.001$, data not shown). These data suggest that excessive or unnecessary fluid infusion postoperatively may cause bowel edema, leading to reduced bowel peristalsis. Because of the small number of patients in this series, it was not possible to evaluate whether achieving "Discontinuation of c.i.v. on POD1" affected the incidence of other complications.

According to our analysis, avoidance of fluid overload (intraoperative fluid < 2000 ml) was significantly associated with a shorter LOHS (Table 5). As shown in Table 1, the ERAS protocol generally recommends 3 ml/kg/h of intraoperative crystalloid and colloid fluid for low-risk surgery, so there may be skepticism about 2000 ml of intraoperative fluid being the boundary between optimal fluid and volume overload. However, we consider > 2000 ml intraoperative fluid to be excessive, because even when following the 3 ml/kg/h guideline, the intraoperative fluid volume for a 7-h operation on a patient weighing 100 kg, would be 2100 ml. Most of the patients in this series weighed less than 100 kg and the operation times were less than 7 h, so 2000 ml was used as the boundary and > 2000 ml was defined as fluid overload in this study. The multivariate analysis also included an operation time ≥ 300 min as an independent variable, which mitigates the bias by operation time. Fluid overload was unable to be avoided in 15 patients, with a median infusion rate of 4.87 ml/kg/h (range 2.26–8.65 ml/kg/h) and exceeding 4 ml/kg/h in 12. Complications of Clavien–Dindo grade 2 or higher occurred in 10 of these 15 patients, all of which were related to paralytic ileus (data not shown). Considering that the incidence of paralytic ileus in the entire ERAS protocol group was 6.9% (Table 3), the incidence was much higher in patients given intraoperative fluid > 2000 ml. Although maintaining an infusion rate of 3 ml/kg/h for low-risk patients according to the ERAS protocol is ideal, considering the reality of clinical practice, we think that our proposed fluid overload boundary can serve as a simple indicator to prevent excessive infusion in general colorectal cancer surgery.

This study has some limitations. First, it was a single-center retrospective study, and the data collected in the conventional care group (April, 2014 to June, 2015) were in a different period to the data for the ERAS protocol group (June, 2015 to April, 2021). Therefore, the ERAS protocol group could have had a higher implementation rate of laparoscopic surgery than the conventional care group and, naturally, had better postoperative outcomes [21]. Although we eliminated that bias by performing PS matching, even after matching, the ERAS group had better postoperative outcomes than the conventional care group. As surgical techniques improve over time, it is undeniable that they will have had some influence on postoperative outcomes.

In conclusion, this study showed that the ERAS protocol can be implemented safely for elective colorectal cancer surgery without increasing the complication rate, and that a higher compliance rate with the ERAS protocol is dose-dependently associated with a lower complication rate and shorter LOHS. Among the ERAS items, perioperative fluid

management had a crucial impact on lowering complication rates and shortening the LOHS.

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Declarations

Conflict of interest Hiromichi Sato, Hirofumi Ota, Koji Munakata, Yusuke Matsuura, Makoto Fujii, Noriko Wada, Daisuke Takiuchi, Naoki Hama, Kou Takachi, and Masao Yukawa declare that they have no conflicts of interest.

Ethical statement The protocol for this research project was approved by the Institutional Review Board of Ikeda City Hospital and conforms to the provisions of the Helsinki Declaration of 1964 and later versions. Approval no. A21011. The requirement for acquisition of informed consent from patients was waived because of the retrospective design of this study and anonymized data.

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