Original Article

Randomized Controlled Trial: ERAS Program on Colorectal Cancer Surgery Decrease the Length of Patients' Hospital Stay

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Background: Colorectal carcinoma is the third leading cause of cancer-related deaths in Thailand. Complete surgical resection is one of the main options for curative treatment. Enhanced recovery after surgery (ERAS) programs can decrease the length of hospital stay by two to three days, and decrease postoperative complications by 30 to 50% when compared to traditional programs. The aim of this study is to compare the ERAS program to the traditional program after surgery in the length of hospital stay, postoperative complications, and rate of revisits within 30 days of the patients being discharged.

Objective: To evaluate how different lengths of hospital stays, post operative complications, readmission rates, postoperative nausea vomiting, pain between traditional and ERAS program in colorectal cancer patients admitted to Ramathibodi Hospital to adapt the ERAS protocol in practical use in Ramathibodi patients who underwent surgery.

Materials and Methods: The authors randomized patients with colorectal carcinoma who underwent surgery followed by ERAS program and traditional program, between 1 June 2015 and 18 May 2017 in Ramathibodi Hospital. The inclusion criteria were elective colorectal surgery, patients' age between 18 to 75 years old, clinical and pathological diagnosis colorectal cancer, American Society of Anesthesiologist classification 1 to 3, and patients who had signed a consent form. Exclusion criteria included previous abdominal surgery, immobilized patients, and patients who refused to join the program or did not return for follow-up appointments.

Results: Forty-six patients with colorectal carcinoma underwent surgery. Twenty-two patients were treated with the traditional program, and twenty-four patients were treated with the ERAS program. The average age was 62±8.17 years old in the traditional program, and 63±9.05 years old in the ERAS program. The median length of hospital stay was 8 days (7 to 9) in the traditional program, and 6 days (5 to 6.5, $p<0.0001$) in the ERAS program. Postoperative complications, pain score, post-operative nausea vomiting and revisit rate in both programs were not different.

Conclusion: The ERAS program showed benefits in decreased length of hospital stays for colorectal cancer surgery patients. Postoperative complications, pain score, post-operative nausea vomiting and revisit rate within 30 days after discharge in both groups were not different.

Keywords: Colorectal surgery, Enhanced recovery after surgery, Length of hospital stay

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Colorectal carcinoma is the third leading cause of cancer-related deaths in Thailand. In 2014, the incidence was 11,496 cases/year and the mortality rate was 6,845 cases/year[1]. Surgery is the mainstay of treatment[2]. In traditional programs, patients were allowed to eat solid food until midnight and take the mechanical bowel preparation the day prior to surgery. Postoperative phase, they received strong opioids to control pain and eat nothing until the fifth to seventh postoperative days. The Enhanced Recovery After Surgery (ERAS) program can reduce the length of hospital stay in colorectal patients and increase the opportunity for other patients to receive surgery earlier due to reduced waiting lists. It also improves the outcome of the disease, and shortens the recovery phase for the patients who need adjuvant chemotherapy[2-4]. ERAS program is widely used in elective colorectal patients in the modern era. It began in 1990 by Henrik Kehlet[3] showing that patients experienced earlier recovery by 2 to 3 days, decreasing the length of hospital stay when compared to the traditional program, and 30 to 50% decrease in postoperative complications[4]. In the ERAS program, patients receive information and recommendations

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to prepare for the operation: approximate length of stay, pre-operative fasting, early ambulation, and postoperative feeding. During the intra-operative period the anesthesiologist reduces drug doses by using an epidural block to reduce the rate of postoperative bowel ileus[5]. Patients are encouraged to participate in early mobilization[6]. This study is a randomized controlled trial in patients who were scheduled for elective colorectal surgery in Ramathibodi Hospital comparing the traditional program to the Enhanced Recovery After Surgery (ERAS) program. The primary outcome was the length of hospital stay after surgery. Secondary outcomes were postoperative complications, pain scores and rates of revisit within thirty days of discharge.

Materials and Methods

Ethical approval was obtained from Ramathibodi Hospital, Mahidol University review board and Thai Clinical Trial Registration number TCTR20180129009. Patients who were diagnosed with colorectal carcinoma and met the inclusion criteria between 1 June 2015 and 18 May 2017.

Inclusion criteria

1) Elective colorectal surgery
2) Age 18 to 75 years old
3) Colorectal cancer stage I-IV
4) American Society of Anesthesiologist classification I-III
5) Patient signed a consent form

Exclusion criteria

1) Previous abdominal surgery
2) Immobilized patients
3) Patients who refuse to join the program or are lost during follow-up.

The authors explained the pros and cons in this trial. When the patients committed to join the present study, they were randomized one by one into control groups (Traditional program) and the intervention group (ERAS program). All patients had routine standard guidelines for preoperative procedures.

Pre-operative phase

Traditional program

Fasting from midnight

Taking mechanical bowel preparation with polyethylene glycol (2 liters) or sodium phosphate (90 milliliters).

Prophylaxis antibiotic 30 minutes before surgery: Cefoxitin or Ceftriaxone and/or Methonidazole. In penicillin allergy cases, Ciprofloxacin was used instead.

ERAS program

Fasting from 3.00 am

No mechanical bowel preparation

Prophylaxis antibiotic 30 minutes before surgery: Cefoxitin or Ceftriaxone and/or Methonidazole. In penicillin allergy cases, Ciprofloxacin was used instead.

Intraoperative phase

Traditional program

General anesthesia

In patients suspected of having bowel obstruction or ileus, the surgeon may have inserted a nasogastric tube.

ERAS program

Combined general and epidural at T7-8 level anesthesia

In patients suspected of having bowel obstruction or ileus, the surgeon may have inserted a nasogastric tube.

Postoperative phase

Traditional program

Fasting 5 to 7 days postoperative

Control pain with strong opioids

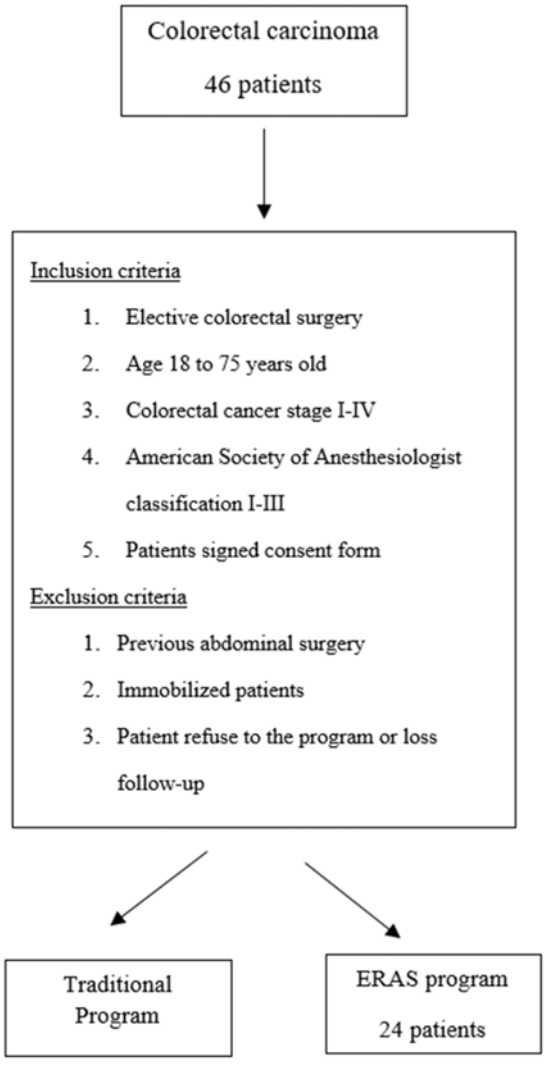

Figure 1. Flow chart of study selection based on inclusion and exclusion criteria.

ERAS program

Started with liquid diet within twenty-four hours

Patients were encouraged to ambulate within six hours of surgery

Control pain with epidural block and Paracetamol. Adding weak opioids when pain score became equal to or greater than four.

All patients' data were recorded. Patients were followed-up in the out-patient department during the first and fourth week after discharge.

Outcome measures

The primary outcome was the length of hospital stay. Secondary outcomes were postoperative complications, pain scores and rates of revisit within thirty days after patients were discharged. All patients' data were recorded with Microsoft Excel program and analyzed with Stata version 14.

Statistical analysis

T-test (continuous, normal distribution), Wilcoxon-Mann-Whitney test (continuous, non-normal distribution), Chi-square and Fisher's exact test were used to compare demographic and clinical variables between groups. A two-tailed *p*-value of <0.05 was considered significant.

Results

There were forty-six patients with colorectal carcinoma who underwent surgery between 1 June 2015 to 18 May 2017 in Ramathibodi Hospital. Twenty-two patients were randomized to the traditional program and twenty-four were randomized to the ERAS program. In the traditional program, there were 9 males (40.91%) and 13 females (59.09). In the ERAS program, there were 10 males (41.67%) and 14 females (58.33%). The average patients' age was 62±8.17 years old in the traditional program and 63±9.05 years old in the ERAS program. Patients' characteristics are shown in Table 1.

Regarding underlying diseases and cancer staging, there were two types of operation: open and laparoscopic. In the traditional group open surgery was performed more than the ERAS group ($p = 0.017$) but the type of operation showed no difference in the two groups ($p = 0.237$). The type of operation is shown in Table 2.

Average operative times were 210 minutes (145 to 260) in the traditional program and 225 minutes (175 to 317.5) in the ERAS program ($p = 0.1244$). The length of skin incisions was 6 centimeters (5 to 9) in the traditional program and 4.5 centimeters (3.5 to 6.5) in the ERAS program ($p = 0.054$). Blood loss was 100 milliliters (70 to 300) in the traditional program and 100 milliliters (50 to 200) in the ERAS program ($p = 0.1147$). There was no overall difference in operative time, length of skin incision or blood loss between the two groups. Perioperative data is shown in Table 3.

There was no difference in ASA classification, prophylaxis antiemetic drug and blood component replacement, but the total perioperative fluid replacement in the ERAS program was significantly less than the traditional

Table 1. General characteristic

	Traditional program n = 22	ERAS program n = 24	*p*-value
Sex			
Male	9 (40.91)	10 (41.67)	0.958
Female	13 (59.09)	14 (58.33)	
Age	62±8.17	63±9.05	0.700
BMI (mean ± SD)	24.13±4.13	23.35±3.53	0.496
Underlying disease			
DM	5 (22.73)	6 (25.00)	0.857
HT	9 (40.91)	9 (37.50)	0.813
IHD	3 (13.64)	1 (4.17)	0.255
CKD	0	1 (4.17)	1.000
DLP	9 (7.2)	6 (7.8)	0.250
Other	8 (36.36)	7 (29.17)	0.755
CEA level (ng/mL) (IQR)	9.2 (2.4 to 24.8)	3.8 (2 to 8.5)	0.151
AJCC Staging edition 8			
0	1 (4.55)	0	0.394
I	2 (9.09)	4 (16.67)	
IIA	2 (9.09)	5 (20.83)	
IIB	2 (9.09)	1 (4.17)	
IIC	0	0	
IIIA	3 (13.64)	1 (4.17)	
IIIB	8 (36.36)	12 (50)	
IIIC	0	0	
IVA	2 (9.09)	1 (4.17)	
IVB	2 (9.09)	0	

program ($p = 0.021$). Post-operative data are shown in Table 4.

Post-operative pain scores were assessed at five periods after surgery: 1 to 2 hours, 12 hours, 24 hours, 48 hours, and 72 hours. In the traditional program; pain scores were 2 (2-2), 2 (2-2), 2.5 (2-4), 3 (3-4), 3 (3-4). In the ERAS program pain scores were 2 (2-2), 2(2-2), 2 (2-2), 2 (1-2), 2 (1-2), respectively. Post-operative nausea vomiting (PONV)

Table 2. Operative data

	Traditional program n = 22	ERAS program n = 24	*p*-value
Type of operation			
Open	16 (72.73)	9 (37.50)	0.017
Laparoscopy	6 (27.27)	15 (62.50)	
Operation			
Right hemicolectomy	4 (18.18)	5 (20.83)	0.237
Extended right hemicolectomy	5 (22.73)	1 (4.17)	
Left hemicolectomy	2 (9.09)	1 (4.17)	
Extended left hemicolectomy	1 (4.55)	0	
Sigmoidectomy	3 (13.64)	4 (16.67)	
Anterior resection	3 (13.64)	6 (25)	
LAR	3 (13.64)	6 (25)	
APR	0	1 (4.17)	
Subtotal colectomy	1 (4.55)	0	
Operative time Median (IQR)	210 (145 to 260)	225 (175 to 317.5)	0.1244
Length of skin incision (cm) (IQR)	6 (5 to 9)	4.5 (3.5 to 6.5)	0.054
Blood loss	100 (70 to 300)	100 (50 to 200)	0.1147

Table 3. Perioperative data

	Traditional program n = 22	ERAS Program n = 24	*p*-value
ASA classification			
I	1 (4.55)	2 (8.33)	0.905
II	10 (45.45)	12 (50)	
III	11 (50)	10 (41.67)	
Antiemetic prophylaxis	13 (61.9)	15 (62.5)	0.967
Perioperative fluid administration (mean ± SD)	2,355.90±1,050.62	1,688.33±842.38	0.021
Blood component			
PRC	2 (9.09)	0	0.131
FFP	1 (4.76)	0	0.28
LPPC	-	-	

Table 4. Postoperative data

	Traditional program n = 22	ERAS program n = 24	*p*-value
PACU time (mins) median (IQR)	65 (60 to 95)	67.5 (60 to 85)	0.898
Postoperative nausea and vomiting (PONV)			
24 hour	1 (4.55)	0	0.291
48 hour	1 (4.55)	0	0.291
Pain score median (IQR)			
1 to 2 hour	2 (2 to 2)	2 (2 to 2)	0.170
12 hour	2 (2 to 2)	2 (2 to 2)	0.181
24 hour	2.5 (2 to 4)	2 (2 to 2)	0.0002
48 hour	3 (3 to 4)	2 (1 to 2)	0.0000
72 hour	3 (3 to 4)	2 (1 to 2)	0.0000

was recorded in 2 periods: 24 and 48 hours after surgery. 24 hours after surgery, PONV was detected in 1 patient (4.55%) in the traditional program and no patients (0%) in the ERAS program. 48 hours after surgery, PONV was detected in 1 patient (4.55%) in the traditional program and no patients (0%) in the ERAS program. There was no difference in pain score and PONV in both groups.

The length of hospital stay was 8 days (7 to 9) in the traditional program and 6 days (5 to 6.5, $p<0.0001$) in the ERAS program. Postoperative complications in the traditional program were a surgical site infection 1 case (4.55%), ileus 1 case (4.55%), medical complication 1 case (4.55%), and other complication 1 case (4.55%). Postoperative complications in the ERAS program were a surgical site infection 1 case (4.17%), other complication 3 cases (12.5%). Rate of revisit within thirty days of discharge was 1 case (4.55%) in the traditional program and 3 cases (12.5%, $p = 0.609$) in the ERAS program. There was no difference in complications and rate of revisit in both groups.

Discussion

There are various practicing programs in postoperative care colorectal cancer patients. In the past numerous surgeons were familiar with traditional program that involved fasting at midnight and using mechanical bowel preparation with polyethylene glycol (2 liters) or sodium phosphate (90 milliliters), and 5 to 7 postoperative fasting days and controlling pain with strong opioids. However, nowadays there is an ERAS program that allows a shorter fasting period and does not require mechanical bowel preparation. In addition, postoperative feeding starts earlier, within twenty four hours. These two programs seem very different in practice and this study shows different outcomes in length of hospital stay, postoperative complication, revisiting rates.

46 patients with colorectal carcinoma underwent surgery in Ramathibodi Hospital between 1 June 2015 and 18 May 2015. There was no difference in baseline characteristics: sex, age, average CEA, surgical procedure, ASA classification, operative time (210 mins vs. 225 mins $p = 0.1244$), length of skin incision (6 cm vs. 4.5 cm, $p = 0.054$), intra-operative blood loss (100 milliliters vs. 100 milliliters, $p = 0.1147$), post-anesthetic care unit time (65 vs. 67.5 min, $p = 0.898$) between the traditional group and the ERAS group.

In our study there is a significant difference in the length of hospital stays, with the traditional program being longer than the ERAS program (8 days vs. 6 days, $p<0.001$). Similar to the study of Henrik Kehlet[3] in 1990 showing that patients had earlier recovery, decreased by 2-3 days length of hospital stay when compared to the traditional program, and a 30 to 50% decrease in postoperative complications[4]. In the study of El Nakeeb et al[7] postoperative stays for the early feed group was shorter (6.2 ± 0.2) compared to the traditional method (6.9 ± 0.5, $p = 0.05$). The benefit of the ERAS program that is found in the present study is significantly-decreased length of hospital stay that enables reduced costs of medical and non-medical treatment. This is especially the case in private hospitals where patients can save on the cost of treatment. Public hospitals such as Ramathibodi, have lower rates than private hospitals but get referrals from other hospitals in area around Bangkok. The ERAS program will help the hospital with quicker recovery, earlier discharge, and is, therefore, easier to get referrals from other rural hospitals.

Twenty-two randomized controlled trials with 2,270 patients showed a reduction in the fasting time to 2 hours for clear fluids and 6 hours for solids and do not increase the risk of regurgitation or pulmonary complications in patients who are healthy. The study of El Nakeeb et al[7] did not find a difference in wound complications, anastomotic leakage, or abnormalities in serum electrolytes, as in our study, showing that there is no significant between the two groups. In the traditional program there was a surgical site infection 1 case (4.55%), ileus 1 case (4.55%), medical complication 1 case (4.55%), and other complication 1 case (4.55%). Postoperative complications in the ERAS program were surgical site infection 1 case (4.17%), other complication 3 cases (12.5%). Rate of revisits within thirty days of discharge was 1 case (4.55%) in the traditional program and 3 cases (12.5%, $p = 0.609$) in the ERAS program. However there are several confounding factors that effect postoperative complications, such as patient performance status, condition of patient at the time of operation, type of operation and postoperative care that has the missing data or some parameters that the authors cannot control in the present study.

Post-operative nausea vomiting (PONV) was recorded in 2 periods: 24 and 48 hours after surgery. 24 hours after surgery, PONV was detected in 1 patient (4.55%) in the traditional program and no patients (0%) in the ERAS program ($p = 0.291$). 48 hours after surgery, PONV was detected in 1 patient (4.55%) in the traditional program and no patients (0%) in the ERAS program ($p = 0.291$). But the outcome of postoperative nausea vomiting from Ramathibodi Hospital patients was not different between the two groups, due to the patients in the ERAS program having a shorter period of fasting time, which may cause less fluid and electrolyte imbalance when compared with the conventional program. Moreover, the ERAS program will encourage patients to ambulate sooner which will help normal bowel function earlier. Other reasons that make the lower rate of postoperative nausea vomiting in the ERAS program are due to the pain management of the ERAS program using epidural block and Paracetamol and weak opioids when the pain score was equal to or greater than four, but the traditional program uses stronger opiods that may cause nausea vomiting and ileus.

The ERAS program shows the benefits in decreasing the length of hospital stay, and that safety and complication risks are no different from the traditional program. However there are some limitations in the present study. First, the small number of patients that were included in the present study. If there were more patients in both the

traditional program and ERAS groups and subgroup analysis in each type of operation and each type of tumor staging, there would be some useful information to adapt in practice in each type of patient. Second, there are some differences between the traditional program and ERAS program in the type of surgery. The traditional program was 72.73% open surgery and 27.27% laparoscopic. Whereas the ERAS program was 37.50% open surgery and 62.50% laparoscopic. This may have caused the conventional program patients delayed recovery when compared to the ERAS program. Third, some surgeons are more familiar with the traditional program, which may have led to limitation about the information of the ERAS group. In the future, however, if the ERAS program were more commonly used and there were a greater sample size, this study would show some useful information for practicing in the future.

Conclusion

The ERAS program showed a decrease in the length of hospital stays compared to the traditional program, whereas post-operative nausea vomiting, postoperative complications, and revisit rate within 30 days after discharge in both groups showed no difference. This information will encourage surgeons to use the ERAS program on patients to enable quicker recovery times and earlier discharge. This is especially beneficial in public hospitals, where there are limited resources, many patients, and referrals from other rural hospitals.

What is already known on this topic?

ERAS 2 to 3 days decrease length of hospital stay when compared to traditional program;

30 to 50% decrease postoperative complications;

Prophylactic abdominal drain does not prevent anastomotic dehiscence or allow for early detection of clinical leakage. But may increase the incidence of both wound infection and clinical leakage;

Postoperative vomiting occurring more frequently in the early feed group (25% and 10%, $p = 0.05$).

What this study adds?

In our study there is significant different in length of hospital stays in traditional program are longer than ERAS program (8 vs. 6, $p<0.001$).

Post op complication in our study is not significant between the two groups. ERAS did not reduce postoperative complications;

Post-operative nausea vomiting (PONV) was not different between two groups due to the patients in ERAS program get short period of fasting time that may cause less fluid and electrolyte imbalance when compared with conventional program, moreover, the ERAS program will enhance patients to early ambulation that will help patient to return to bowel function earlier. Other reasons that make the lower rate of postoperative nausea vomiting in ERAS program due to the pain management of ERAS program using epidural block and paracetamol adding weak opioid when pain score greater than or equal to four but in conventional program using strong opiod that may cause nausea vomiting and ileus.

Potential conflicts of interest

There is some different between conventional program and ERAS program in type of surgery, conventional program open surgery 72.73%, laparoscopy 27.27% where as ERAS program open surgery 37.50% and laparoscopy 62.50% this may cause conventional program delay recover when compare to ERAS program.

Postoperative pain control was different between the two groups, which may cause the traditional group nausea vomiting more than the ERAS program.

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