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Enhanced Recovery Program Versus Traditional Care in Laparoscopic Hepatectomy

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Abstract: Enhanced recovery after surgery (ERAS) has shown effectiveness in terms of reducing the hospital stay and cost associated with open liver resection. However, the benefit of ERAS in patients undergoing laparoscopic liver resection is still unclear, and clinical studies on this topic are limited.

The ERAS program for laparoscopic liver resection was used in a group of 80 patients (ERAS group). The results were compared with those in a control group of 107 patients. All patients underwent laparoscopic liver resection. The primary endpoints were the postoperative hospital stay, defined as the number of days from surgery to discharge, and the hospitalization expense. The secondary endpoints were resumption of oral intake, readmissions, and complications.

The median postoperative hospital stay was 6.2 ± 2.6 days in the ERAS group, which was significantly shorter than that in the control group (9.9 ± 5.9 d; $P < 0.001$). The hospitalization cost was $\$6871 \pm 2571$ in the ERAS group and $\$7948 \pm 3630$ in the control group ($P = 0.020$). The morbidity rate was 22.5% (18 of 80 patients) in the ERAS group and 43.9% (47 of 107 patients) in the control group ($P = 0.002$). There were no significant differences the in rate of readmission between the 2 groups.

Enhanced recovery after surgery for laparoscopic liver resection is safe and effective. Patients in the ERPS group had a shorter hospital stay, fewer complications, and lower hospital costs.

(*Medicine* 95(8):e2835)

Abbreviations: ASA = American Society of Anesthesiologists, DVT = deep vein thrombosis, ERAS = enhanced recovery after surgery, LPMOD = laparoscopic Peng multifunctional operative dissector, PCIA = patient-controlled intravenous analgesia, VAS = visual analog scale.

Editor: Perbinder Grewal.
Received: December 1, 2015; revised: January 19, 2016; accepted: January 20, 2016.
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The authors have no funding or conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002835

INTRODUCTION

Laparoscopic liver resection was first introduced in the 1990s. During the past 20 years, many studies have shown that laparoscopic hepatectomy has become a safe and feasible surgical procedure for liver disease. Numerous studies comparing laparoscopic hepatectomy and open hepatectomy have revealed no differences in the width of the resection margins for malignant lesions or overall survival, and outcomes after resection for hepatocellular cancer or colorectal cancer liver metastases.[1,2] However, liver surgery is associated with a high rate of complications (15%–48%),[3,4] and in 1 study, the postoperative hospital stay after liver resection was 8 days.[5]

Enhanced recovery after surgery (ERAS) was first introduced by Kehlet[6] in 1997, and was shown to reduce the complication rate and hospital stay duration after colorectal surgery.[7] During the past 2 decades, ERAS has rapidly evolved with the application of various effective methods, including perioperative education, improved anesthetic and analgesic methods, and early oral intake and mobilization. Using these procedures, ERAS can relieve patients' pain, promote patients' recovery, and reduce complications and cost.[8]

All studies to date on the application of ERAS in liver resection show that ERAS is safe and feasible.[9,10] However, the evidence for the use of ERAS in laparoscopic hepatectomy remains insufficient. Therefore, we performed the present study to determine the application of ERAS in laparoscopic hepatectomy at Sir Run Run Shaw Hospital, Medical College of Zhejiang University.

METHODS

Patients

From June 2014 to July 2015, 187 patients aged 14 to 80 years, who presented for laparoscopic liver resection at the Second Department of General Surgery, The Sir Run Run Shaw Hospital, Medical College of Zhejiang University, were considered for inclusion in the study. Our surgery department has 2 medical teams, both of which can perform high-volume laparoscopic liver surgery. One team followed the ERAS protocol and the other administered conventional perioperative care (Table 1). The patients were randomized to one of the 2 medical teams and were blinded to the intervention. The ERAS group comprised 80 patients, and the control group (conventional perioperative care) comprised 107 patients. With respect to patient characteristics, the 2 groups were similar in age, sex, Child–Pugh classification, and American Society of Anesthesiologists (ASA) physical status (Table 2).

The inclusion criteria were as follows: partial hepatectomy or half liver resection, body mass index of 18 to 35 kg/m^2, tumor (if present) in either the right or left lobe, Child–Pugh class A or

TABLE 1. Summary of Enhanced Recovery After Surgery Program

	ERAS Group	Control Group
Day before surgery	Perioperative education, including mobilization and dietary goals	No
	No routine bowel preparation	Normal bowel preparation
	Normal oral nutrition	No
Day of surgery	Carbohydrate drinks until 2 h before surgery (250 mL)	No
	Combined tracheal intubation and general anesthesia local anesthesia (0.2% ropivacaine)	Combined tracheal intubation and general anesthesia
	No nasogastric tube or removed as early as possible	Routine nasogastric tube drainage
	Less abdominal drain used	Standard use of abdominal drains
Postoperative day 0	Drink water 6 h after surgery	Fast
	Restricted intravenous fluid 2000 to 2500 mL	No
	Pain control: PCIA + 40 mg ParecoxibNa (Dynastat) i.v. per 12 h	Only PCIA or ParecoxibNa (Dynastat)
Postoperative day 1	Oral nutritional supplements (liquid)	No diet plan
	Mobilization twice daily	Bed rest
	Urinary catheter removed	No
	Reduce intravenous fluid	No
Postoperative day 2	Stop intravenous anesthetics and use oral Tramadol or Celecoxib	PCIA or ParecoxibNa (Dynastat)
	Oral semiliquid diet	Liquid
	Stop maintenance intravenous fluid	No
	Mobilization 4 times daily	Mobilization on bed
	Remove CVC	No
	Remove abdominal drainage tube if volume of drainage <30 mL	No
Postoperative day 3	Stop anesthetics if pain controlled well	Stop PCIA
	Normal mobilization	Encourage to mobilization out of bed
	Normal diet	Liquid or semiliquid diet
	Check the discharge criteria	Remove urinary catheter
Postoperative day 4: home	Continue the events as day 3	Continue the events as day 3
	Check the discharge criteria	Remove abdominal drainage tube if volume of drainage <30 mL
	Education for discharge and recovery plan at home	Encourage to more mobilization
		Check the discharge criteria

CVC = Central Venous Catheter, ERAS = enhanced recovery after surgery, PCIA = patient-controlled intravenous analgesia.

B liver functional status, and ASA physical status of I to III. The exclusion criteria were as follows: pregnant or lactating women, unwillingness to participate, inability to give written informed consent, Child–Pugh class C liver functional status, ASA physical status of IV or V, tumor invasion of the inferior vena cava or confluence of the hepatic vein, and decompensated liver cirrhosis.

Laparoscopic Hepatectomy

All operations were performed under general anesthesia. The laparoscopic Peng multifunctional operative dissector (LPMOD) was used in each operation to transect the liver parenchyma by curettage and aspiration. The patient was placed in the supine position.[11] A Veress needle was inserted directly under the umbilicus to allow for the flow of carbon dioxide into the peritoneal cavity. With the pneumoperitoneum inflated to 12 to 14 mm Hg CO_2, the large vessels and bile ducts were ligated with clips via laparoscopic instruments. Regional hepatic vascular exclusion was used in these cases.

Clinical Pathway

Preoperative

Patients in the control group underwent routine care, such as nothing by mouth for 8 hours before surgery, bowel preparation, and no oral nutritional supplements. The doctors and nurses were familiar with the medical records of the patients and provided them with conventional preoperative and psychological education.

Patients in the ERAS group received a more detailed explanation of the perioperative care and ERAS program when they made the decision to undergo surgery. The nurses provided the patients a checklist showing the rehabilitation plan, and daily mobilization and nutritional goals. Patients received 250 mL of an oral carbohydrate solution 2 hours before surgery.

Intraoperative and Anesthesia

The same conventional anesthetic protocol (combined intravenous and inhalation anesthesia) was used in both groups.

TABLE 2. Patient Demographics

	ERAS Group	Control Group	*P*
Age, y	53.4 ± 13.5	55.5 ± 12.8	0.290*
Sex (male/female)	37/43	50/57	0.950
Primary disease			
Cirrhosis	13	29	0.070
Hypertension	8	20	
Diabetes mellitus	3	12	
Cardiovascular disease	4	11	
Others	15	20	
Child–Pugh class (A/B)	78/2	103/4	0.630
ASA physical status (I/II)	35/45	49/58	0.780
Type of hepatectomy			
Right hepatectomy	5	12	0.240
Left hepatectomy	12	17	0.870
Segmentectomy	22	27	0.730
Local resection	41	51	0.630
Liver pathology			
Hepatocellular carcinoma	38	46	0.540
Metastatic hepatic carcinoma	9	6	
Cholangiocellular carcinoma	4	3	
Hepatolithiasis	10	16	
Hepatic hemangioma	14	30	
Others	5	6	

Values are presented as mean (standard deviation) or n.
ASA = American Society of Anesthesiologists, ERAS = early recovery after surgery.
* *t* test; all remaining *P* values, chi-square test.

Patients in the ERAS group received additional 0.2% ropivacaine for local anesthesia around the trocar incision and patient-controlled intravenous analgesia. During the operation, patients in the control group routinely underwent placement of an indwelling nasogastric tube and abdominal cavity drainage tube.

In the ERAS group, the temperature of the operation room was maintained at >25°C, and a warm air blower and heated peritoneal washing liquid were used to keep the patients warm. Additionally, the use of nasogastric tubes and abdominal cavity drainage tubes was minimized. Fluid administration was strictly restricted (crystalloid + colloid < 2000 mL). Routine antibiotic prophylaxis was administered.

Postoperative

Patients in the ERAS group were given water or liquids 6 hours after surgery. If gastrointestinal tract peristalsis, flatus, and defecation were restored, the patients were given liquid food on postoperative day 1, then a semiliquid diet on postoperative day 2. Fluid infusion was managed by clinical parameters such as the CVP, urine output, and heart rate (maintenance fluids were controlled at 2000–2500 mL/d). The patients received patient-controlled intravenous analgesia and 40 mg of parecoxib sodium (Dynastat) intravenously every 12 hours. If pain persisted, 50 mg of oral tramadol was added 3 times daily. The patients were encouraged to do mobilization and walk around the ward on postoperative day 1 to avoid deep venous thrombosis (DVT). The urinary catheter was removed 1 day after surgery, and the abdominal drainage tube was removed as soon as possible. Details of the ERAS program are shown in Table 1.

The discharge criteria were as follows: normal temperature, good pain control with oral analgesia only, tolerance of food, no intravenous fluids, and willingness to be discharged.

The primary endpoint of the study was the postoperative hospital stay, defined as the number of days from surgery to discharge, and the hospitalization cost. The secondary endpoints were resumption of oral intake, the pain score, readmissions, and complications (evaluation by Clavien–Dindo classification[12]). The pain score was evaluated by a visual analogue scale (VAS) that ranged from 0 to 10 cm (0 cm, no pain; and 10 cm, worst pain).[13] All of the patients were asked to state the severity of their pain during and immediately after the procedure using the VAS. A detailed explanation about the VAS and its application was given personally to each patient before the procedure. A VAS score of ≥4 was accepted as severe pain.

All data were collected during hospitalization and at the 30-day follow-up. This study was a retrospective study with effective and safe measures; therefore, ethical approval was not necessary.

Statistical Analysis

Data on patient characteristics, intraoperative parameters, and postoperative courses were collected. Continuous data with a normal distribution were statistically tested for group differences using a 2-sample Student *t* test. Data without a normal distribution were analyzed using the Mann–Whitney *U* test. Readmission, complication, and mortality rates were analyzed using the chi-square test or Fisher exact test. A *P* value of <0.050 was considered to be statistically significant. Statistical analyses were performed with SPSS for Windows, version 19 (IBM Corp., Armonk, NY).

RESULTS

In total, 187 patients were included in the 2 groups. The 107 patients in the control group received standard care, and the 80 patients in the ERAS group underwent the ERAS program. The patient characteristics of the 2 groups were similar in age, sex, Child–Pugh classification, and ASA physical status. All patients in both groups underwent laparoscopic hepatectomy. The types of liver resection performed are shown in Table 2. There were also no significant differences in the pathological findings between the 2 groups (Table 2).

The operative details and outcomes are shown in Table 3. The operative time was 172.6 ± 86.0 minutes in the ERAS group and 190.8 ± 90.1 minutes in the control group ($P = 0.260$). The intraoperative blood loss volume was 268.2 ± 416.0 mL in the ERAS group and 328.0 ± 426.2 mL in the control group ($P = 0.380$), and blood transfusion was needed during the operation in 8 patients in the ERAS group and 13 in the control group ($P = 0.650$). A nasogastric decompression tube was used in 19 of 80 patients in the ERAS group and in 40 of 107 patients in the control group ($P = 0.047$). The duration of nasogastric tube placement was 0.9 days in the ERAS group and 1.6 days in the control group ($P < 0.001$). In the ERAS group, abdominal drainage tubes were used for 0.9 ± 0.6 days and removed 2.7 ± 2.1 days postoperatively. This was significantly less frequent than in the control group (1.5 ± 0.5 and 8.0 ± 3.9 days, respectively; $P < 0.001$ for both). Urinary catheters were removed 1.0 ± 0.3 days postoperatively in the ERAS group and 2.0 ± 1.2 days postoperatively in the control group ($P < 0.001$). Oral intake was usually resumed within

TABLE 3. Operative Details and Outcomes

	ERAS Group	Control Group	*P*
Operative time, min	172.6 ± 86.0	190.8 ± 90.1	0.260
Intraoperative blood loss, mL	268.2 ± 416.0	328.0 ± 426.2	0.380
Blood transfusion	8	13	0.650
Pain score			
Postoperative day 1	1.9 ± 0.5	2.6 ± 1.0	<0.001
Postoperative day 3	1.3 ± 0.6	2.4 ± 1.0	<0.001
Postoperative day 5	0.8 ± 0.6	1.8 ± 0.7	<0.001
Duration of urinary catheters, d	1.0 ± 0.3	2.0 ± 1.2	<0.001
Duration nasogastric tube			0.047*
No	61	67	
Yes	19	40	
Duration of nasogastric tube, d	0.9	1.6	<0.001
Duration of abdominal drainage tube	0.9 ± 0.6	1.5 ± 0.5	<0.001
Abdominal drainage tube removal (postoperative day)	2.7 ± 2.1	8.0 ± 3.9	<0.001
Semiliquid diet after surgery, d	1.7 ± 0.7	4.5 ± 2.9	<0.001
C-reactive protein concentration*			
Postoperative day 1	41.9 ± 32.7	44.0 ± 35.2	0.790
Postoperative day 3	88.3 ± 51.4	88.2 ± 44.7	0.960
Postoperative day 5	37.4 ± 22.9	55.3 ± 54.9	0.100
Postoperative hospital stay, d	6.2 ± 2.6	9.9 ± 5.9	<0.001
Time to function recovery, d	5.0 ± 2.3	8.5 ± 4.4	<0.001
Readmission (<30 d)	3	5	0.600*
Cost (US dollar)	$6871 ± 2571	$7948 ± 3630	0.020

Values are presented as mean ± standard deviation or n unless otherwise indicated.
ERAS = early recovery after surgery.
* Chi-square test; all other *P* values, *t* test.

TABLE 4. Surgical Complications by Clavien–Dindo Classification

Overall Complications	ERAS Group (n = 80)	Control Group (n = 107)	*P*
No complications	62 (77.5)	60 (56.1)	0.002
Grade I			
Nausea/vomiting	3 (3.75)	5 (4.7)	0.760
Wound infection	2 (2.5)	3 (2.8)	0.900
Deep vein thrombosis	0 (0.0)	6 (5.6)	0.030
Grade II			
Postoperative liver failure	8 (10)	10 (9.3)	0.880
Grade IIIa			
Pleural effusion	1 (1.25)	6 (5.6)	0.120
Bile leakage	2 (2.5)	6 (5.6)	0.300
Intraperitoneal inflammation	1 (1.25)	7 (6.5)	0.080
Grade IIIb			
Hemorrhage >1000 mL and reoperation	1 (1.25)	2 (1.9)	0.740
Grade IVa	0 (0.0)	1 (0.9)	0.390
Grade IVb	0 (0.0)	1 (0.9)	0.390
Grade V	0 (0.0)	0 (0.0)	N/A

Values are presented as n (%). All *P* values were measured by the chi-square test.
ERAS = enhanced recovery after surgery.

6 hours after surgery in the ERAS group. The median time until semiliquid diet resumption was 1.7 ± 0.7 days in the ERAS group and 4.5 ± 2.9 days in the control group ($P < 0.001$). The readmission rates (<30 d were similar in the ERAS and control groups (3 vs 5 patients, respectively; $P = 0.600$).

Complications are shown in Table 4. There was no perioperative mortality in the 2 groups. The complications were evaluated using the Clavien–Dindo classification. The morbidity rate was 22.5% (18 of 80 patients) in the ERAS group and 43.9% (47 of 107 patients) in the control group ($P = 0.002$). No patient in the ERAS group developed DVT, but 6 patients did in the control group ($P = 0.030$). Grade II to V complications occurred in 16.3% of patients in the ERAS group, which was significantly lower than the rate in the control group (30.8%; $P = 0.020$). One patient in the ERAS group underwent a reoperation because of hemorrhage. Two patients in the control group underwent reoperations; 1 had liver failure, and the other was diagnosed with multiple organ dysfunction and stayed in the intensive care unit for 2 weeks.

The pain scores were used to evaluate the effect of analgesia (Table 3). On days 1, 3, and 5, the mean pain score in the ERAS group was significantly lower than that in the control group (all $P < 0.001$) (Table 3, Figure 1). The serum C-reactive protein concentrations on days 1, 3, and 5 are shown in Table 3. The C-reactive protein concentration in the control group was higher than that in the ERAS group, but not significantly so (all $P > 0.050$). The median postoperative hospital stay was 6.2 ± 2.6 days in the ERAS group, which was significantly shorter than that in the control group (9.9 ± 5.9; $P < 0.001$) (Figure 2). The cost of hospitalization was $6871 ± 2571 in the ERAS group and $7948 ± 3630 in the control group ($P = 0.020$).

DISCUSSION

Recent studies have shown that ERAS is widely used in the perioperative period and leads to significantly shorter hospital stays after surgery and lower hospitalization costs.[14–16] We searched the PubMed database and found 3 studies about the ERAS program in laparoscopic hepatectomy. He et al[17] reported a study including 86 patients, in which the postoperative hospital stay after laparoscopic hepatectomy was 6 (range 4–8) days among patients who underwent ERAS, which was 2 days shorter than that in the control group; the hospitalization

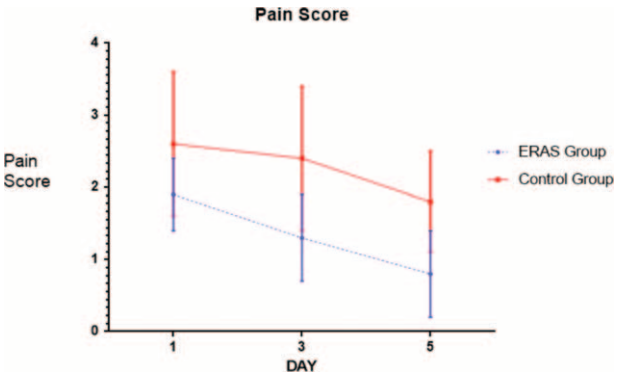

FIGURE 1. Pain score in the control group (red line) was higher than that in the early recovery after surgery (ERAS) group (blue line). The pain score was significantly different between the 2 groups on days 1, 3, and 5 (all $P < 0.001$). The *P* values were measured by the *t* test.

cost was also lower in the ERAS group ($7742 ± 1200 vs $9740 ± 1540, respectively; $P = 0.030$). Stoot et al[18] performed a study of 26 patients who underwent ERAS after laparoscopic hepatectomy and reported similar conclusions. Sánchez-Pérez et al[19] showed that 80.8% of patients who underwent ERAS (26 patients) left the hospital within the first 3 days after surgery (58.8% in the control group including 17 patients).

Our study has some differences from these studies. Our study involved 187 patients with different liver diseases, such as liver cancer, hepatolithiasis, benign tumors, and others. Our sample size and diseases are more convincing. Additionally, many studies of the application of ERAS reported that the use of epidural analgesia was an effective solution to control pain after surgery.[17–20] However, these methods increase the risk of complications. In our study, we gave patients 0.2% ropivacaine for local anesthesia around the trocar incision intraoperatively and used 40 mg of parecoxib sodium (Dynastat) intravenously every 12 hours with patient-controlled intravenous analgesia after surgery. Good pain control was achieved. Moreover, we used a visual analog scale for assessment of pain. Finally, our study shows that our ERAS protocol is suitable and useful for laparoscopic hepatectomy. Therefore, we applied for a randomized controlled trial (NCT02533193), and it is currently underway.

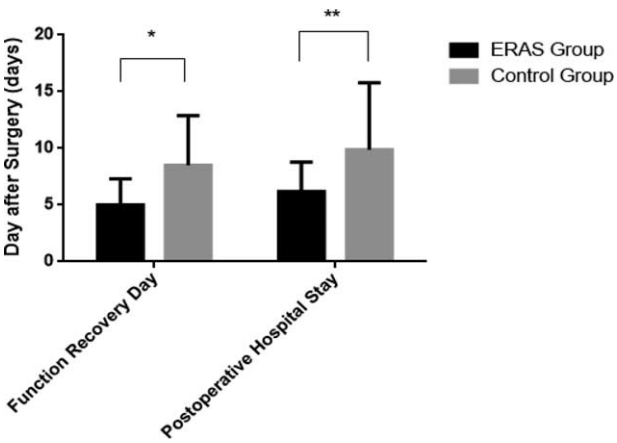

FIGURE 2. Functional recovery after surgery was achieved at 5.0 ± 2.3 days in the early recovery after surgery (ERAS) group and 8.5 ± 4.4 days in the control group ($^{*}P < 0.001$). The postoperative hospital stay was 6.2 ± 2.6 days in the ERAS group and 9.9 ± 5.9 days in the control group ($^{**}P < 0.001$). The *P* values were measured by the *t* test.

In our study, patients in the ERAS group left the hospital at 6.2 ± 2.6 days, and the hospitalization cost was $6871 ± 2571. Both of these parameters were significantly lower than those in the control group (9.9 ± 5.9 d and $7948 ± 3630, respectively; both $P < 0.050$). In the ERAS protocol of this study, perioperative patient education, early postoperative mobilization, less use of drainage tubes, enhanced pain control, intravenous fluid restriction, and oral nutrition played important roles in reducing patients' stress and promoting rapid recovery.[21]

Perioperative patient education is an important factor throughout the ERAS program. Before the operation, it is necessary for patients to understand the ERAS program and follow the doctors' or nurses' advice. With good cooperation of patients, implementation of the ERAS program can relieve patients' anxiety, fear, and stress, all of which may increase the hospital stay and cost. After the operation, patient education reinforces the daily goals of the ERAS procedures and improves patients' physical and psychological recovery. Additionally, an efficient, professional, and united team comprising doctors, anesthetists, nurses, and pharmacists is a powerful tool with which to maintain the ERAS program and provide patients with the best care.[22,23]

In the ERAS program, patients are able to drink fluids (250 mL of a glucose–sodium solution) within 2 hours of surgery and have liquid food 6 hours after surgery. Some authors have reported that 2 hours of fasting can avoid aspiration pneumonia during surgery. Drinking 250 mL of a glucose–sodium solution 2 h before surgery helps patients to improve tolerance to surgery and reduce anxiety, hunger, and insulin resistance.[24] Use of no gastric tube or early gastric tube removal allows patients to drink water within 6 hours after surgery, and have a liquid diet on postoperative day 1 and a semiliquid diet on postoperative day 2. Routine bowel preparation and intake of an early normal oral diet help to promote the resumption of gastrointestinal function, reducing catabolism, stress, and complications such as vomiting, nausea, and distension.

Pain control is crucial in patients undergoing ERAS. Good pain control can reduce the hospital cost and duration of stay, and patients are much more comfortable. Many studies on the application of ERAS have reported that the use of epidural analgesia is an effective solution to control pain after surgery. In the present study, however, patients in the ERAS group received a local anesthetic during surgery. Patient-controlled intravenous anesthesia and intravenous parecoxib sodium (Dynastat) every 12 hours were used after surgery, and oral analgesics replaced intravenous analgesia if good pain control was achieved. The pain scores were significantly lower in the ERAS than in the control group on days 1, 3, and 5 (1.9 vs 2.6, 1.3 vs 2.4, and 0.8 vs 1.8, respectively; all $P < 0.001$). Epidural analgesia may improve the risk of complications such as bleeding, infection, and an extended operation time.

In this study, patients were required to perform movements in bed on the operation day. On postoperative day 1, the patients were encouraged to get up from their bed and walk around the wards twice daily with the help of others. Less drainage tube use, good pain control, and early removal of the urethral catheter are important for early mobilization. Early mobilization can reduce complications such as DVT and intestinal obstruction. In the present study, DVT occurred in no patients in the ERAS group and in 6 patients in the control group. Patients who are able to ingest a normal diet, are mobile postoperatively,

and have no nausea/vomiting or other complications feel more comfortable and are willing to go home. This results in a shorter hospital stay and decreases the economic burden on patients.[21]

Reducing complications may also influence recovery because complications reduce patients' comfort and even survival.[25,26] Some studies showed that the ERAS program can improve short and long-term outcomes by reducing stress. In the present study, the ERAS group had a significantly lower rate of complications. The readmission rate (<30 d was similar in the ERAS and control groups.

Laparoscopic hepatectomy has become widely used for treatment of both benign and malignant liver diseases.[27,28] Many studies have shown that laparoscopic hepatectomy is safe and feasible with low morbidity and mortality. Meanwhile, laparoscopic hepatectomy is a minimally invasive surgery that causes less stress and trauma. It can improve patients' recovery and shorten their hospital stay and cost. Therefore, laparoscopic liver resection is an important part of the ERAS program in patients undergoing liver resection.

CONCLUSIONS

Laparoscopic hepatectomy, as a safe and feasible surgery for patients, can promote recovery after liver resection. The ERAS program is also considered to be more effective and safer than conventional care for liver resection. However, more studies on the use of ERAS in laparoscopic hepatectomy are needed, especially randomized prospective studies.

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