Clinics in Surgery

Research Article
Published: 10 Aug, 2021

Safety and Effectiveness of Enhanced Recovery after Surgery (ERAS) in Patients with Hepatocellular Carcinoma Undergoing Partial Hepatectomy: A Multicentre, Randomized, Controlled Clinical Study

*Yang Xu[1], Pei-Yao Fu[1], Wei-Dong Jia[3], Qiang-Xia[4], Kui-Wang[5], Dou-Sheng Bai[6], Bo Hu[1], Hui-Chuan Sun[1], Qin-Hai Ye[1], Xiao-Ying Wang[1], Ying-Hong Shi[1], Shuang-Jian Qiu[1], Jia Fan[1,2] and Jian Zhou[1,2]**

[1]Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, China

[2]Institute of Biomedical Sciences, Fudan University, China

[3]Department of General Surgery, Anhui Provincial Hospital, China

[4]Department of Liver Surgery, Renji Hospital, Jiaotong University, China

[5]Department of Liver Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, China

[6]Department of General Surgery, Subei People's Hospital, Yangzhou, China

Abstract

Background: Enhanced Recovery after Surgery (ERAS) is a multimodal perioperative management approach that is used to accelerate recovery, reduce morbidity, and shorten hospital stay after major surgery. However, solid evidence that proves its safety and effectiveness in liver surgery for patients with Hepatocellular Carcinoma (HCC), which is always combined with liver cirrhosis and hepatitis infection in China, remains lacking. In this multicentre randomized controlled clinical trial, we compared ERAS and traditional treatment approach for HCC patients who underwent partial hepatectomy.

Methods: A total of 222 HCC patients recruited from five medical centers in China were randomly assigned to ERAS and control groups (1:1) to compare the short-term effects of ERAS and those of conventional perioperative managements.

Results: The overall complication rate in the ERAS group was significantly lower than that in the control group (25.2 *vs.* 45.9%, $p<0.01$). The mean length of postoperative hospital stays decreased from 8 to 7 days ($p<0.01$). The rates of vomiting (10.8 *vs.* 22.5%, $p=0.02$) and ascites (5.4 *vs.* 13.5%, $p=0.03$) in the ERAS group were significantly less than those in the control group. Pain and insulin resistance after surgery were significantly reduced in the ERAS group based on the visual analogue scale and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score (all $p<0.05$).

Conclusion: ERAS accelerated recovery in HCC patients who underwent partial hepatectomy, even those with liver cirrhosis.

Keywords: Enhanced Recovery after Surgery; Hepatocellular Carcinoma; Clinical Trials; Complication rate

OPEN ACCESS

Correspondence:
Jian Zhou, Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, Shanghai 200032, China,
E-mail: zhoujian@zs-hospital.sh.cn

Received Date: *12 Jul 2021*
Accepted Date: *27 Jul 2021*
Published Date: *10 Aug 2021*

Citation:
Xu Y, Fu P-Y, Jia W-D, Qiang-Xia, Kui-Wang, Bai D-S, et al. Safety and Effectiveness of Enhanced Recovery after Surgery (ERAS) in Patients with Hepatocellular Carcinoma Undergoing Partial Hepatectomy: A Multicentre, Randomized, Controlled Clinical Study. Clin Surg. 2021; 6: 3278.

Introduction

Hepatocellular Carcinoma (HCC) is one of the most common malignancies worldwide [1], and more than 50% of the new cases annually are reported in China; HCC occurs most often in people with chronic liver diseases, such as cirrhosis due to hepatitis B or hepatitis C infection. Currently, operation combined with a multidisciplinary comprehensive treatment remains the primary treatment for HCC patients [2,3]. With the progress of medical technology, traditional surgery has become more rapid, accurate, and minimally invasive. However, surgery still leads to a high complication rate and results in pain in patients due to the complicated procedure [4,5].

The concept of Enhanced Recovery after Surgery (ERAS) was first proposed by Kehlet et al. as

early as 2001 [6], which included a series of optimized perioperative measures based on evidence-based medicine to enhance patient recovery after major surgery. ERAS has attracted attention from surgeons globally [7-9]. With the aim to reduce postoperative complications and mortality, increase medical safety, shorten hospitalization, cut down expenses, and improve patient satisfaction, the ERAS procedure includes modified preoperative education, rational pain management, early food intake, and more exercise after surgery [10]. Moreover, through long-term research and observation, the ERAS procedure has been proven to be safe and effective in most surgeries and has already been widely applied in the perioperative management of colorectal surgery and pancreatoduodenectomy [7-9]. A previous study also showed that ERAS could be beneficial for patients who underwent liver surgery [11-18]. However, a relevant multicentre randomized controlled study has not been conducted.

Thus, in this study, we performed a multicentre randomized controlled clinical trial to compare ERAS and traditional treatment approach for HCC patients who underwent open partial hepatectomy.

Methods

Ethical approval

The present study was a prospective multicentre randomized controlled clinical trial. This study was conducted in accordance with the *Declaration of Helsinki* approved by the Ethics Committee of Zhongshan Hospital of Fudan University, Eastern Hepatobiliary Surgery Hospital, Renji Hospital of Shanghai Jiaotong University, Anhui Provincial Hospital, and Subei People's Hospital of Jiangsu Province [11]. All the patients' decision to participate in the study was voluntary, and informed consent for randomization and treatment were obtained. This study was registered with the clinicaltrials.gov (NCT02644603).

Study design and population

According to published literature, a 16% difference in the overall complication rate is expected to exist between the ERAS and control groups [11]. Assuming a type-I error of 5% (α=0.05), a power of 80% for a one-tailed two-sample test to determine whether the complication proportion in the ERAS group is different from that in the control group according to Chow et al. [19], and considering a 10% dropout, the sample size was 244 patients (estimated 122 patients in each group).

Eligible HCC patients between the age of 18 and 70 years who underwent partial hepatectomy from May 01st, 2016, to March 30th, 2017 in five clinical centers were enrolled in this study.

The inclusion criteria were as follows:

(1) patients clinically diagnosed as having HCC and who underwent open partial hepatectomy; (2) patients whose planned excision area involves fewer than four segments of the liver, without other major concomitant surgical procedures and with ASA (The American Society of Anesthesiologists) physical status classification system grade I-II; (3) Child-Pugh class A/B liver functional status. Patients with liver cirrhosis before operation were detected through a routine combination of laboratory and imaging tests, such as MRI, CT, and ultrasound shear wave elastography. Diagnosis of liver cirrhosis was finally confirmed by pathology after surgery, using the Ishak system which assigns scores 5 or 6 for cirrhosis.

Zhongshan Hospital and Eastern Hepatobiliary Surgery Hospital, which are the top two clinical centers of liver cancer in China, performed approximately 10,000 cases of hepatectomy annually. To make the results more precise, we only included HCC patients (intrahepatic cholangiocarcinoma confirmed by pathology after surgery was excluded) without diabetes mellitus and other concomitant diseases. Patients with surgical procedures other than open partial hepatectomy were also excluded.

Thus, the exclusion criteria were as follows:

(1) Patients with Child-Pugh class C liver functional status, and those with a serious underlying disease, including diabetes mellitus, disability, cardio-cerebrovascular disease, serious mental disease resulting in problems with cooperation, and previous abdominal surgery; (2) patients who refused to participate in this study; (3) laparoscopic partial hepatectomy, vascular reconstruction, and those with operation plan that was temporarily changed; (4) those whose postoperative pathological diagnosis was not HCC.

This study was designed as a Randomized Controlled Trial (RCT) and open to both doctors and patients. However, blind to the data collectors and assessors. Patients were randomized using a computerized telephone system for randomization at a ratio of 1:1. If the number is 1 that patient was included in the ERAS group, and 2 in the control group. An independent staff completed the entire randomization process [17].

Perioperative ERAS management and procedures

Patients randomized to the ERAS group received an enhanced recovery program, whereas the patients in the control group received conventional care (Table 1). Patients in the ERAS group were educated with basic knowledge about the first clinical point of care, postoperative exercise, and early oral feeding [18]. Patients in the control group were aware that conventional perioperative management could also be safe and beneficial [13,18].

Intraoperative surgical technique was not standardized; surgeons in participating centers were free to use their preferred technique and devices to gain intra-abdominal access, perform liver resection, and maintain vascular control [17]. Abdominal drains were routinely used in major hepatectomies but selectively placed in segmental hepatectomy as determined by intraoperative condition [13]. Patient-controlled anesthesia containing ropivacaine 375 mg, fentanyl 300 μg, and morphine 5 mg in 250 mL NS and standard postoperative fluid regimen were also employed.

Outcome measure and primary endpoints

The primary outcome measure was the overall complication rate. The secondary outcome measures were length of hospital stay, total hospitalization costs, visual analogue scale score for postoperative pain, pre- and post-operative body weight, inflammatory factors (Homeostatic Model Assessment for Insulin Resistance [HOMA-IR] score [20], interleukin-6, tumor necrosis factor-α, C-Reactive Protein (CRP)), the indexes of liver function (albumin, pre-albumin, Alanine Transferase (ALT), Aspartate Transaminase (AST), international normalized ratio), renal function (serum urea nitrogen and creatinine), serum hemoglobin and platelet. All the indexes were classified and compared separately. Complications were defined according to the Clavien-Dindo classification (grades 1 to 5) [21]. Postoperative pain was registered daily using an optimized 11-point (0-10) Newcastle-Ottawa Scale (NOS). Patients in both groups were discharged following the recommendations, which included normal

Table 1: ERAS protocol and conservative treatment of control group.

ERAS group	Conservative treatment group
Preoperative preparation	
(1) Preoperative education about ERAS: ✓ Tell patients about normal surgery and anesthesia, release their fears and anxieties about surgery. ✓ Tell patients the necessity about early exercises, early oral feeding and pain control after surgery. ✓ Tell patients the rehabilitation goal.	(1) Conventional preoperative education about postoperative anesthesia, exercise and oral feeding.
(2) Normal oral nutrition until 6 h before surgery, glucose in normal saline drinks up to 2 h before surgery and no bowel preparation.	(2) Fasting 12 h before surgery, and no drinking 6 h before surgery, regular bowel preparation.
(3) No pre-anesthetic medication and antibiotics.	(3) No pre-anesthetic medication and antibiotics.
During surgery	
(1) Application of heating blanket to prevent hypothermia.	(1) Regular drainage tube placement.
(2) Minimal use of abdominal drain.	(2) Regular abdominal incision.
(3) Try to use small incision as possible.	
After surgery	
(1) Continuous portable epidural analgesia* with selective cyclooxygenase-2 inhibitor (parecoxib) i.v., b.i.d for 3 days, after that celecoxib p.o., b.i.d for 2 days.	(1) Self-control portable epidural analgesia.
(2) Remove nasogastric tube in 24 h after surgery.	(2) Routine nasogastric tube drainage
(3) Have liquid diet about 500 mL in 24 h after surgery, semi-liquid food in 24 h to 36 h, soft diet in 36 h to 48 h.	(3) Drink limited liquid after exhaust, then gradually transition to semi-liquid and soft diet.
(4) Regular use of antiemetic drugs, suppositories glycerol and lactulose.	(4) Use of antiemetic drugs, suppositories glycerol and lactulose when needed.
(5) Remove urinary catheter in 24 h after surgery.	(5) Remove urinary catheter in 24 h to 36 h after surgery.
(6) Encourage patients do out-of-bed activity after 24 h after surgery.	(6) No intervention about doing exercise.
(7) Restricted fluid infusion after surgery, limited use of liver protecting drugs.	(7) Standard fluid infusion during surgery

ERAS: Enhanced Recovery after Surgery

or decreasing serum bilirubin, pain controlled with oral analgesic only, tolerance of solid food, no intravenous fluids, independent patient mobility, and patient's willingness to go home [11,22]. The study period ended after the first follow-up 1 month after discharge. Re-admission due to complications within 1 month after discharge was also closely monitored during the follow-up.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 (IBM, U.S). Independent t-test was used to compare continuous variables with normal distribution. Skewed variable data were analyzed with nonparametric Mann–Whitney U test. Chi-square test and Fisher's exact test were employed to compare discrete variables. For the primary outcome time to functional recovery α=0.05 (2-tailed) and for the secondary outcomes α=0.05 (2-tailed) were used to correct for multiple testing. A p-value <0.05 was considered statistically significant.

Result

Patient demographics

A total 244 HCC patients who met the inclusion criteria were recruited and were randomly assigned to the ERAS group (n=121) and control group (n=123). Eight patients in the ERAS group and nine in the control group were preoperatively excluded because their operation plan temporarily changed. Two patients in the ERAS group and three in the control group were excluded because the postoperative pathological diagnosis did not support primary liver cancer (Figure 1). The basic characteristics of the patients are shown in Table 2, no significant difference between the two groups. Only two patients were in Child B (CTP score 7), which had mild ascites and hypoproteinemia (these two patients were improved through albumin transferring and diuretic treatment before surgery), 78.8% (175/222) of the patients were confirmed as liver cirrhosis by pathology after surgery, which mostly had HBV (169/175) or HCV (4/175) infection, and 2 patients with alcohol-induced cirrhosis.

The ERAS procedures were strictly executed by doctors, nurses, and patients. Based on the ERAS protocol, the patients were encouraged to have early oral feeding and to do out-of-bed activity in 24 h after surgery. To enable patients in the ERAS group to achieve this goal, nasogastric tube and urinary catheter were removed within 24 h to 48 h after surgery and oral intake was resumed within 24 h after surgery, which is much earlier than that in the control group. No patient required reinsertion of a nasogastric tube or urinary catheter in the two groups.

Outcomes

Based on the Clavien–Dindo classification of surgical complications, the overall complication rate in the ERAS group was significantly lower than that in the control group (25.2 *vs.* 45.9%, p<0.01). The rates of both grade I (20.7% *vs.* 43.2%, p<0.01) and grade II complications (7.2% *vs.* 18.0%, p=0.01) were lower in the ERAS group than in the control group. Among the grade I-II complications, the rates of vomiting (10.8 *vs.* 22.5%, p=0.02) and ascites (5.4 *vs.* 13.5%, p=0.03) in the ERAS were significantly lower than those in the control group. Grade III-V complications were rarely seen in the two groups (Table 3). We made a stratified analysis on patients with Liver Cirrhosis (LC) and reached the same conclusion. The rates of both grade I (17.9% *vs.* 34.1%, p=0.01) and grade II complications (3.6% *vs.* 12.1%, p=0.03) and the overall complication rate (22.6% *vs.* 45.1%, p=0.01) were lower in the LC ERAS group than in the LC control group. And the rate of ascites has a more significant reduction in the LC ERAS Group (6% *vs.* 19.8%, p<0.01). No perioperative mortality or re-admission after discharge in both groups was noted. We came to the same results when stratified by different centers. No difference can be found between vascular reconstructions *vs.* non-reconstruction group.

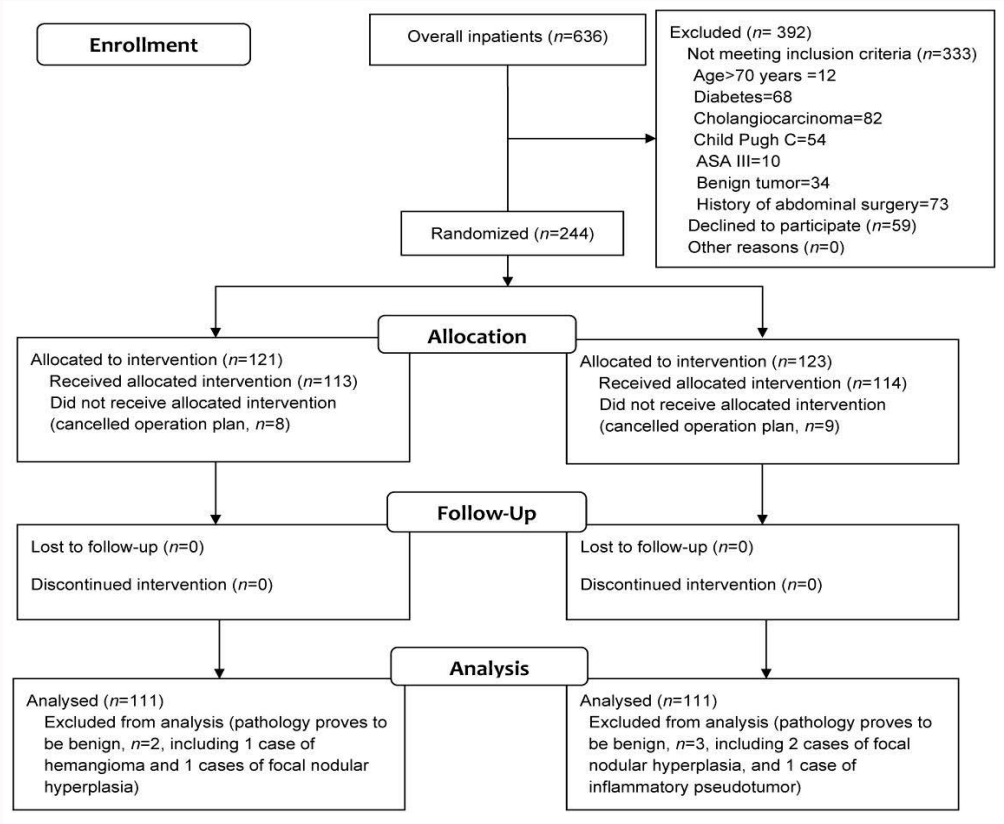

Figure 1:

Table 2: Baseline patient demographic and clinical characteristics.

Characteristics	Overall patients (n=222)		P	Patients with liver cirrhosis (n=175)		P
	ERAS (n=111)	Control (n=111)		ERAS (n= 84)	Control (n=91)	
Age [a]	54 (26, 71)	56 (27, 74)	0.46	55 (26, 71)	55 (27, 74)	0.42
Gender [b] (M/F)	86/25	92/19	0.40	63/21	74/17	0.53
HBV-DNA (yes/no) [b]	44/67	43/68	1.00	29/55	32/59	0.53
With cirrhosis (yes/no) [b]	84/27	91/20		NA	NA	NA
Pre-operative BMI [a]	23.1 (16.4, 32.3)	22.8 (18.4, 29.7)	0.21	23.1 (16.4, 32.3)	22.7 (18.4, 29.7)	0.43
Blood Insulin (mU/L)	9.8 (2.2, 168.0)	10.6 (3.0, 100.1)	0.91	8.4 (2.2, 91.5)	8.2 (3.0, 57.3)	0.95
Blood glucose (mmol/L)	5.1(3.9, 15.6)	5.2 (3.9, 11.2)	0.64	5.1 (3.9, 12.2)	5.1 (3.9, 11.2)	0.79
AFP (ng/mL)	67.0 (0.9, 60,500.0)	14.1 (4.1, 60,500.0)	0.06	69.8 (0.9, 60,500.0)	23.2 (1.3, 60,500.0)	0.19
CEA (ng/mL)	2.4 (0.7, 34.3)	2.3 (0.4, 30.4)	0.73	2.5 (0.7, 34.3)	2.5 (0.4, 30.4)	0.65
CA-199 (kU/L)	16.9 (0.6, 583.0)	14.5 (0.6, 4206.0)	0.20	15.3 (0.6, 583.0)	14.5 (0.6, 4206.0)	0.46
Hb [a] (g/L)	145.0 (94.0, 182.0)	144.0 (104.0, 174.0)	0.72	143.5 (94.0, 182.0)	144.0 (107.0, 174.0)	0.99
PLT (× 10^9/L)	156.0 (28.0, 865.0)	153.0 (48.0, 426.0)	0.68	153.0 (33.0, 865.0)	152.0 (48.0, 387.0)	0.90
WBC (× 10^9/L)	5.3 (1.3, 13.7)	5.6 (2.3, 22.9)	0.50	5.3 (1.3, 13.7)	5.5 (2.3, 22.9)	0.46
Pre-ALB (g/L)	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	1.00	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	1.00
ALB (g/L)	42.4 (30.9, 51.0)	43.0 (36.0, 50.0)	0.66	42.0 (30.9, 51.0)	42.7 (36.0, 50.0)	0.39
INR	0.98 (0.76, 1.3)	0.98 (0.78, 1.63)	0.62	1.0 (0.8, 1.3)	1.0 (0.8, 1.6)	0.10
TB (μmol/L)	12.2 (4.7, 43.4)	11.4 (3.9, 25.9)	0.44	11.6 (4.7, 32.1)	11.3 (3.9, 25.9)	0.96
DB (μmol/L)	4.9 (1.6, 15.5)	4.7 (1.5, 11.1)	0.64	4.7 (1.6, 15.5)	4.6 (1.5, 11.1)	0.94
GPT (μmol/L)	28.0 (6.0, 158.0)	26.0 (8.0, 809.0)	0.43	26.0 (6.0, 158.0)	26.0 (8.0, 809.0)	0.79
GOT (μmol/L)	26.0 (12.0, 124.0)	27.0 (10.0, 599.0)	0.53	26.0 (12.0, 124.0)	28.0 (10.0, 599.0)	0.89
Tumor number	1 (1, 5)	1 (1, 4)	0.92	1 (1, 5)	1 (1, 4)	0.83

MVI score [b]	0 (0, 2)	0 (0, 2)	0.18	0 (0, 2)	0 (0, 2)	0.39
Maximum tumor diameter (cm)	9.0 (0.8, 20)	8.8 (0.8, 19)	0.89	8.4 (0.8, 14)	8.1 (0.8, 15)	0.44
Segmental/local resection	70/41	69/42	0.99	52/32	56/35	0.54
Occlusion time (min)	12 (0, 44)	10 (0, 28)	0.13	11 (0, 30)	10 (0, 20)	0.22
Blood loss (mL)	100 (10, 1600)	100 (10, 700)	0.63	100 (30, 1600)	100 (20, 700)	0.98

Data are shown as n or median (range). [a]: Independent t-test; [b]: Fisher's exact tests; Mann-Whitney U test for all other analyses
BMI: Body Mass Index; ERAS: Enhanced Recovery after Surgery; INR: International Normalized Ratio; CRP: C-Reactive Protein; AFP: Alpha-Fetoprotein; Hb: Hemoglobin; PLT: Platelet; WBC: White Blood Cell; TB: Total Bilirubin; DB: Direct Bilirubin; ALB: Albumin; GPT: Glutamic-Pyruvic Transaminase; GOT: Glutamic-Oxaloacetic Transaminase; NA: Not Applicable

Table 3: Complications according to Clavien-Dindo classification, *n (%).*

Item [a]	Overall patients (n=222)						Patients with liver cirrhosis (n=175)				
	ERAS (n=111)	%	Control (n=111)	%	P		ERAS (n=84)	%	Control (n=91)	%	P
Grade I Complication	23 (20.7)	20.7	48 (43.2)	43.2	<0.01		15 (17.9)	17.9	41 (45.1)	45.1	<0.01
Vomiting	12	10.8	25	22.5	0.02		10	11.9	22	24.2	0.04
Diarrhea	0	0.0	4	3.6	0.04		0	0	2	2.2	0.17
Ascites, pleural effusion (<200 mL)	11	9.9	19	17.1	0.12		5	6	18	19.8	<0.01
Ascites	6	5.4	15	13.5	0.04		2	2.4	14	15.4	<0.01
Pleural effusion	7	6.3	8	7.2	0.79		5	6	7	7.7	0.65
Grade II Complication	8	7.2	20	18.0	0.02		3	3.6	14	15.4	<0.01
Post-operative infection *	6	5.4	13	11.7	0.09		2	2.4	9	9.9	0.04
Lung infection	2	1.8	4	3.6	0.41		0	0	2	2.2	0.17
Wound infection	1	0.9	2	1.8	0.56		1	1.2	3	3.3	0.35
Abdominal infection	3	2.7	6	5.4	0.31		1	1.2	4	4.4	0.20
Arrhythmia	1	0.9	3	2.7	0.31		1	1.2	3	3.3	0.35
Ischemia myocardial and angina pectoris	0	0.0	1	0.9	0.32		0	0	1	1.1	0.34
Postoperative liver failure by "50-50" criteria	1	0.9	3	2.7	0.31		0	0	1	1.1	0.34
Grade III Complication	1	0.9	1	0.9	1.00		1	1.2	1	1.1	0.96
Massive pleural effusion	1	0.9	1	0.9	1.00		1	1.2	1	1.1	0.96
Overall Complication	28	25.2	51	45.9	<0.01		19	22.6	43	47.3	<0.01

One patient might occur two or three kinds of complications
*Post-operative infection were defined as previously described [30]. ERAS: enhanced recovery after surgery

Compared with the control group, the ERAS group had a significantly lower HOMA-IR score and shorter postoperative hospital stay (median [range]: 7 [4,17] days *vs.* 8 [5,20] days, $p<0.01$) (Table 4). NOS showed notable pain reduction among patients in the ERAS group. No difference in postoperative liver function index, including ALT/AST and TB/DB, between the two groups was found.

Discussion

The ERAS program has evolved over the past 15 years and has proven effective in a variety of procedures [23]. Zhou et al. conducted the first single-centre RCT of ERAS in patients with liver cancer who underwent partial hepatectomy. In our study, we attempted to reassess the safety and efficacy of ERAS in HCC patients undergoing open partial hepatectomy *via* multicentre RCT to reduce the potential bias in a single-centre study. Most of the HBV-related HCC patients in China have cirrhosis and often have abnormal or compensated liver function when HCC is diagnosed. Therefore, promoting liver function recovery and preventing postoperative liver failure are major challenges for these patients during the perioperative period. In this study, 78.8% of patients had cirrhosis, most of whom (173/175) had compensated liver function (Child A) and were eligible for limited hepatectomy. Only 2 patients with mild ascites and hypoproteinemia (scored as CPT-7, Child B) were treated by albumin transferring and diuretic therapy prior to surgery to meet surgical safety requirements. Patients who had elevated liver transaminase (AST>400 μmol/L) or total bilirubin (TB>51.3 μmol/L) after surgery were indicated for drug intervention, which includes glycyrrhizin, glutathione, polyene-phosphatidylcholine, glucocorticoids, and other liver-protective drugs. Our study confirms that ERAS can reduce complications and stress response, shorten postoperative hospital stay, and accelerate recovery of HCC patients who underwent partial hepatectomy, especially in patients with cirrhosis. Amongst the ERAS procedures, early eating is conducive to the recovery of gastrointestinal function, thus helping gastrointestinal nutrition to be transported to the liver through the hepatic portal vein, facilitating portal vein circulation, stimulating the synthesis and metabolism of liver cells, and promoting the recovery of liver function. In addition, early ambulation can increase intestinal peristalsis and accelerate recovery of gastrointestinal function. Good postoperative analgesia and early extubation under the ERAS concept can relieve stress response and accelerate liver function recovery. However, whether intervention measures for liver dysfunction can reduce complications or mortality of high-risk patients deserves further study in the future.

Ascites is one of the most common complications after liver surgery. Hydrostatic pressure increases, plasma osmotic pressure

Table 4: Patient outcomes.

Outcomes	Overall patients (n=222)		P	Patients with liver cirrhosis (n=175)		P
	ERAS (n=111)	Control (n=111)		ERAS (n= 84)	Control (n=91)	
Postoperative hospital stays (days) [a]	7 (4, 17)	8 (5, 20)	<0.01	7 (4, 14)	8 (5, 20)	<0.01
Cost (×10^3 USD) [a]	6.05 (3.22, 10.2)	6.25 (3.19, 15.6)	0.25	6.28 (3.22, 10.2)	6.18 (3.19, 15.6)	0.25
Duration of catheter (days)	2 (0, 4)	3 (0, 5)	<0.01	2 (0, 4)	3 (0, 4)	0.28
Duration to exhaust (days)	2 (0, 4)	3 (1, 4)	<0.01	2 (0, 4)	3 (1, 4)	<0.01
Abdominal drain (days)	2 (0,6)	3 (0,8)	<0.01	1.5 (0,6)	3 (0,8)	<0.01
Visual Analog Scale						<0.01
Post-operative Day 1	3 (1, 6)	3 (1, 6)	<0.01	3 (1, 5)	3 (1, 6)	<0.01
Post-operative Day 2	2 (0. 6)	3 (1, 7)	<0.01	2 (1. 6)	3 (1, 7)	<0.01
Post-operative Day 3	2 (0, 6)	2 (0, 6)	<0.01	1 (0, 4)	2 (0, 6)	<0.01
Post-operative Day 4	1 (0, 4)	2 (1, 5)	<0.01	1 (0, 4)	2 (1, 5)	<0.01
Post-operative Day 5	1 (0, 5)	1 (0, 5)	0.03*	1 (0, 2)	1 (0, 5)	0.18
Post-operative Day 6	1 (0, 3)	1 (0, 5)	0.15	1 (0, 3)	1 (0, 5)	0.34
HOMA-IR						
Post-operative Day 1	2.4 (0.4, 62)	3.7 (0.4, 89.4)	0.06	2.4 (0.4, 62)	3.7 (0.6, 89.4)	0.61
Post-operative Day 3	2.1 (0.3, 9)	3.1 (0.4, 25.9)	0.01	2.1 (0.3, 8.9)	3.1 (0.4, 25.9)	<0.05
Post-operative Day 5	1.9 (0.4, 6.9)	2.5 (0.7, 9.8)	0.03	1.9 (0.4, 6.9)	2.5 (0.7, 9.8)	<0.05

Data are shown as n or median (range)

[a]: Student's t test; Mann-Whitney U test for all other analyses

ERAS: Enhanced Recovery After Surgery; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index

and capillary hydrostatic pressure decrease, sodium/water retention are important factors for ascites [24]. Liver surgery may seriously affect the patient's liver function, a large proportion of postoperative patients may experience hypoproteinemia due to impaired hepatic synthesis function coupled with postoperative central vein infusion, which could contribute to patients' ascites. Massive postoperative ascites could further increase the risk of abdominal infection, which seriously affects the rehabilitation of patients. Diuretics and supplement albumin were used routinely post-operation in both groups. We found it was very important to improve hypoproteinemia, increase anabolism, maintain osmotic pressure, and reduce the chance of ascites and abdominal infection [25,26]. Besides, in the ERAS group, we restricted the use of central venous infusions, including parenteral nutrition. In addition, we encourage patients to take food orally as soon as possible to increase nutrition intake, and get out of bed early to help ascites discharge. The number of ascites patients in ERAS group decreased significantly (6 *vs.* 15, p=0.03). Although it lacks statistical significance, patients in the ERAS group have less postoperative infections (6 *vs.* 13, p=0.07). In addition, early removal of abdominal drainage tube may also help reduce abdominal infection.

Multiple analgesia strategy is one of the major procedures of ERAS, including local anesthetics, selective Cyclooxygenase-2 (COX-2) inhibitor and portable epidural analgesia [27]. Postoperative pain and other discomfort make walking difficult within 24 h to 48 h after operation. Therefore, it is very important to reduce the physical and mental burden of patients to obtain better exercise results. Doctors and anesthesiologists should fully communicate with patients on multimodal analgesia. Anti-pain therapy reduces anxiety and stress, thus providing subjective comfort. Traditional analgesics, mainly opioid drugs, have well-known gastrointestinal side effects. Slow metabolism of opioids may also lead to drowsiness and even disturbance of consciousness. The combination of local anesthetics, opioids and selective COX-2 inhibitors (classified as multimodal analgesia) has been shown to improve analgesic effects in several randomized studies. The use of selective COX-2 inhibitor in this study significantly reduced the use of opioid drugs, thus reducing its associated side effects, including exhaust delay and consciousness disorders. In addition, multimodal analgesia improves the patient's pain tolerance, thus increasing daily exercise, thereby contributing to faster rehabilitation.

Compared with previous studies, our results showed no big difference in CRP and liver functions indexes after surgery between the two groups, which can be attributed to the fact that traumatic stress response is not only affected by perioperative treatment, but also mainly affected by the operation process itself. However, our trial shows that the ERAS protocol also helps reduce postoperative HOMA-IR score (p=0.06 in day 1, p=0.01 in day 3, p=0.03 in day 5), which reflects the severity of postoperative stress response [28,29]. Insulin resistance could be induced by both physiological stress, including open surgery [20,29,30], and psychological stress, such as pain [28], fear, and anxiety. A previous study pointed out that traditional preoperative care is related to significant metabolic reactions, which are mainly catabolism, leading to massive insulin resistance and protein loss, leading to major complications and prolonged recovery time [20]. The application of ERAS has been proved to significantly reduce postoperative insulin resistance, thus reducing complications and accelerating recovery [20]. This finding may be directly related to early oral feeding, ambulation and multiple analgesia [20].

Accurate assessment of a patient's general condition by the physician is crucial in the ERAS protocol. Moreover, as important implementers of the ERAS protocol, nurses should have access to the patient's condition to enable them to conduct better patient education and provide instructions and nursing and dietary management, and they are extremely helpful in monitoring and reporting analgesic effects. It is equally important to update patients'

understanding, as they, based on their previous experience, tend to be concerned over the new protocol that advocates early ambulation and feeding. Appropriate patient education is, therefore, vital for patient cooperation, and physicians should timely assess any changes in the patient's condition and adjust the treatment scheme accordingly.

ERAS are a continuously developing program subject to improvements. In addition to the aforementioned interventions, precise and minimally invasive surgery, such as laparoscopic and da Vinci surgeries are very helpful for postoperative recovery of HCC patients. Future studies should also focus on the safety and efficacy of ERAS in patients with diabetes, elderly patients, and cholangiocarcinoma. In addition, as the request by the investigators, we also closely monitored all the patients enrolled in this study for another 11 months. So far, there's no re-admission case due to complications, and no difference was found in 1-year recurrence rate and overall survival between the two groups. According to our results, the cost of the ERAS group was slightly lower than that of the control group, but there was no significant difference. We found that the multi-mode analgesia treatment in the ERAS group was costly and could compensate for the reduction in hospitalization cost.

In conclusion, ERAS is an advanced concept for the perioperative treatment of HCC patients. The ERAS protocol could effectively relieve pain of the patients, and reduce insulin resistance and complication rate (ascites and vomiting) through multimodal analgesia, limited central vein infusion, and patient encouragement to do early out-of-bed activity and have early oral feeding, thereby shortening the length of postoperative hospital stay and reducing the mental and economic burden for the patients. For patients with severe liver cirrhosis, active perioperative treatment to protect liver function is helpful to accelerate postoperative recovery.

Funding

This work was supported by grants from the National Science and Technology Major Project (No. 2013ZX10002011-004 and 2018ZX10203204-006-002), and the National Key Research and Development Program (No. 2016YFC0902400).

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.
2. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379:1245-55.
3. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-90.
4. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248(2):189-198.
5. Kehlet H. Surgery: Fast-track colonic surgery and the 'knowing-doing' gap. Nat Rev Gastroenterol Hepatol. 2011;8(10):539-40.
6. Wilmore DW, Kehlet H. Management of patients in fast track surgery. Bmj. 2001;322(7284):473-6.
7. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery after Surgery (ERAS®) Society recommendations. Clin Nutr. 2012;31:783-800.
8. Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery after Surgery (ERAS®) Society recommendations. Clin Nutr. 2012;31(6):801-16.
9. Mortensen K, Nilsson M, Slim K, Schafer M, Mariette C, Braga M, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery after Surgery (ERAS(R)) Society recommendations. Br J Surg. 2014;101(10):1209-29.
10. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: A review. JAMA Surg. 2017;152(3):292-8.
11. Ni CY, Yang Y, Chang YQ, Cai H, Xu B, Yang F, et al. Fast-track surgery improves postoperative recovery in patients undergoing partial hepatectomy for primary liver cancer: A prospective randomized controlled trial. Eur J Surg Oncol. 2013;39(6):542-7.
12. Dunne DF, Jones RP, Lythgoe DT, Pilkington FJ, Palmer DH, Malik HZ, et al. Cardiopulmonary exercise testing before liver surgery. J Surg Oncol. 2014;110(4):439-44.
13. Dunne DF, Yip VS, Jones RP, McChesney EA, Lythgoe DT, Psarelli EE, et al. Enhanced recovery in the resection of colorectal liver metastases. J Surg Oncol. 2014;110(2):197-202.
14. Savikko J, Ilmakunnas M, Makisalo H, Nordin A, Isoniemi H. Enhanced recovery protocol after liver resection. Br J Surg. 2015;102(12):1526-32.
15. Page AJ, Gani F, Crowley KT, Lee KH, Grant MC, Zavadsky TL, et al. Patient outcomes and provider perceptions following implementation of a standardized perioperative care pathway for open liver resection. Br J Surg. 2016;103(5):564-71.
16. Yip VS, Dunne DF, Samuels S, Tan CY, Lacasia C, Tang J, et al. Adherence to early mobilisation: Key for successful enhanced recovery after liver resection. Eur J Surg Oncol. 2016;42(10):1561-7.
17. Wong-Lun-Hing EM, van Dam RM, van Breukelen GJ, Tanis PJ, Ratti F, van Hillegersberg R, et al. Randomized clinical trial of open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery after surgery programme (ORANGE II study). Br J Surg. 2017;104(5):525-35.
18. Tufo A, Dunne DFJ, Manu N, Joshi H, Lacasia C, Jones L, et al. Hepatectomy for octogenarians with colorectal liver metastasis in the era of enhanced recovery. Eur J Surg Oncol. 2018;44(7);1040-7.
19. Chow S SJ, Wang H. Sample size calculations in clinical research. Taylor & Francis, 2007.
20. Ljungqvist O. Jonathan E. Rhoads lecture 2011: Insulin resistance and enhanced recovery after surgery. JPEN J Parenter Enteral Nutr. 2012;36(4):389-98.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
22. Van Dam RM, Hendry PO, Coolsen MM, Bemelmans MH, Lassen K, Revhaug A, et al. Initial experience with a multimodal enhanced recovery programme in patients undergoing liver resection. Br J Surg. 2008;95(8):969-75.
23. Kehlet H. Fast-track hip and knee arthroplasty. Lancet. 2013;381:1600-2.
24. Mayberry JC, Welker KJ, Goldman RK, Mullins RJ. Mechanism of acute ascites formation after trauma resuscitation. Arch Surg. 2003;138(7):773-6.
25. Haynes GR, Navickis RJ, Wilkes MM. Albumin administration--what is the evidence of clinical benefit? A systematic review of randomized controlled trials. Eur J Anaesthesiol. 2003;20(10):771-93.
26. Morrell BJ, Vinden C, Singh RN, Kornecki A, Fraser DD. Secondary abdominal compartment syndrome in a case of pediatric trauma shock resuscitation. Pediatr Crit Care Med. 2007;8(1):67-70.
27. Paech MJ, Salman S, Ilett KF, O'Halloran SJ, Muchatuta NA. Transfer of parecoxib and its primary active metabolite valdecoxib *via* transitional breast milk following intravenous parecoxib use after cesarean delivery:

A comparison of naive pooled data analysis and nonlinear mixed-effects modeling. Anesth Analg 2012;114(4):837-44.

28. Low LA, Bauer LC, Pitcher MH, Bushnell MC. Restraint training for awake functional brain scanning of rodents can cause long-lasting changes in pain and stress responses. Pain. 2016;157(8):1761-72.

29. Xu XJ, Apovian C, Hess D, Carmine B, Saha A, Ruderman N. Improved insulin sensitivity 3 months after RYGB surgery is associated with increased subcutaneous adipose tissue AMPK activity and decreased oxidative stress. Diabetes. 2015;64(9):3155-9.

30. Czubkowski P, Wierzbicka A, Pawlowska J, Jankowska I, Socha P. Obesity, lipid profiles and oxidative stress in children after liver transplantation. Acta Biochim Pol. 2017;64(4):661-5.

31. Jastreboff AM, Sinha R, Lacadie C, Small DM, Sherwin RS, Potenza MN. Neural correlates of stress- and food cue-induced food craving in obesity: Association with insulin levels. Diabetes Care. 2013;36(2):394-402.