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Original Article

Efficacy and safety analysis of enhanced recovery after partial hepatectomy for hepatocellular carcinoma: a controlled study with propensity score matching

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Abstract: *Background:* The aim of this study was to compare outcomes between patients with hepatocellular carcinoma (HCC) who received enhanced recovery after surgery (ERAS) or conventional care after partial hepatectomy. *Methods:* ERAS patients were paired with conventional recovery patients through propensity score matching to reduce potentially confounding bias due to preoperative differences. Propensity-matched patients were compared in terms of peri- and postoperative clinical outcomes, complications, and mortality. *Results:* ERAS patients tended to show better liver function recovery between postoperative days 3 and 7, and they showed significantly earlier abdominal drain removal ($P = 0.038$), shorter time to first flatus ($P < 0.001$), earlier mobilization out of bed ($P = 0.015$), and shorter postoperative hospital stay ($P = 0.001$). The two patient groups were similar in rates of complications and mortality. *Conclusion:* Our results suggest that ERAS can accelerate postoperative recovery without compromising patient safety following partial hepatectomy for HCC.

Keywords: Enhanced recovery after surgery, partial hepatectomy, hepatocellular carcinoma, propensity score matching

Introduction

Enhanced recovery after surgery (ERAS), introduced in the 1990s, aims to incorporate evidence-based practices into perioperative care in a standardized fashion in order to regain baseline preoperative physiology as quickly as possible while attenuating the negative effects of surgical inflammation. ERAS can shorten postoperative length of stay and reduce hospital costs following colorectal [1], vascular [2], obstetric [3], urologic [4], and pediatric [5] surgical procedures. Whether ERAS can improve outcomes after hepatic surgery is unclear. This is an important question to address because partial hepatectomy is often performed on patients with hepatocellular carcinoma (HCC), but it carries a high risk of postoperative mortality and complications.

Based on studies of ERAS in liver surgery [6-9], we hypothesized that ERAS could shorten postoperative length of hospital stay without increasing postoperative complications or mortality following partial hepatectomy. Therefore we compared various outcomes of patients who received ERAS or conventional care following partial hepatectomy for HCC. Since the two interventions were assigned to patients nonrandomly, we sought to reduce patient selection bias in our analysis by matching patients receiving ERAS or conventional recovery based on propensity scoring.

Methods

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Affiliated Tumor Hospital of Guangxi Medical University. All participants gave written informed consent for their clinical records to be used in approved medical research.

Table 1. ERAS and conventional (control) recovery programs applied to HCC patients following partial hepatectomy

ERAS group	Control group
Day before surgery	
Patient education about ERAS	Standard patient education
No pre-anesthetic medication	Pre-anesthetic medication
No bowel preparation	Routine bowel preparation
Day of surgery	
CVP monitoring (CVP < 5 mmHg)	Not monitored
Carbohydrate drinks up to 2 h before surgery	No intake of oral carbohydrate drinks on the day of surgery
Placement of thoracic epidural catheter (T8-T9 level) with continuous infusion of bupivacaine 0.125% with fentanyl 1-2 lg/ml at a rate of 4-6 mL/h until day 3, plus intravenous paracetamol or NSAIDs	Combined tracheal intubation and general anesthesia
Nasogastric tube removed within 24 h after surgery	Routine nasogastric tube drainage
Minimal use of abdominal drain	Standard use of abdominal drains
Active warming with a warmer coat and warmed fluids	Not monitored
Antibiotic prophylaxis 30 min before surgery	Antibiotic prophylaxis 3 days before surgery
Postoperative day 1	
Continue portable epidural analgesia or analgesia via a fentanyl transdermal system	Patient-controlled intravenous analgesia pump
Mobilization in bed < 2 h	No mobilization scheme
Physical therapy four times per day	No physical therapy scheme
Reduction of intravenous fluids	Intravenous infusion of 2.5-3.0 L
Patient drinks at least 1.0 L liquid	No oral application scheme until first flatus
Simo decoction combined with acupuncture at the *tsu-sanli* acupoint until first flatus	No intervention
Postoperative day 2	
Continue portable epidural analgesia or analgesia via fentanyl transdermal system	Patient-controlled intravenous analgesia pump
Try to mobilize out of bed and mobilize in bed < 4 h	Mobilization in bed
Reduction of intravenous fluids	Continue as on day 1
Drink at least 1.5 L of liquid	No oral application scheme until first flatus
Remove drainage of peritoneal cavity	-
Simo decoction combined with acupuncture at the *tsu-sanli* acupoint until first flatus	No intervention
Postoperative day 3	
Epidural catheter removed, NSAIDs started	Patient-controlled intravenous analgesia pump
Mobilization out of bed < 6 h	Encourage patients to mobilize out of bed
Continuous reduction of intravenous fluids	Continue as above
Semiliquid diet	Start oral intake until first flatus
-	Remove nasogastric tube drainage
Postoperative day 4	
Control pain with oral analgesia only	Stop intravenous analgesia pump
Mobilization out of bed > 6 h	Encourage patient to mobilize out of bed
Switch all medications to oral route	-
Discontinuation of intravenous fluids	Reduction of intravenous fluids
Normal diet	Start oral intake until first flatus
-	Remove drainage of peritoneal cavity with output < 50 mL within 24 h

Postoperative day 5	
Encourage full mobilization	Encourage patients to mobilize out of bed
Control pain with oral analgesia only	-
Normal diet	Start oral intake until first flatus
Postoperative day 6	
Encourage full mobilization	Encourage patients to mobilize out of bed
Normal diet	Start oral intake until first flatus
Start to check discharge criteria	-
Postoperative day 7	
Full mobilization	Mobilization out of bed
Normal diet	Start oral intake
Check discharge criteria	-
Postoperative day 8	
Continue as on day 7	Continue as on day 7

Abbreviations: CVP, central venous pressure; ERAS, enhanced recovery after surgery; HCC, hepatocellular carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs.

Patients

This retrospective study included 205 patients who were diagnosed with primary HCC and underwent partial hepatectomy between January 2016 and September 2016 at the Department of Hepatobiliary Surgery in the Affiliated Tumor Hospital of Guangxi Medical University. The inclusion criteria for this study were as follows: (1) the patient had a tumor in the right or left hemi-liver, and partial hepatectomy involved hemi-hepatectomy or less; (2) the patient underwent initial partial hepatectomy at our hospital; (3) diagnosis was verified based on postoperative pathology; (4) the patient had Child-Pugh stage A or B liver functional status; (5) no metastasis was detected at the time of diagnosis; and (6) the patient had not received any HCC treatment at the time of study enrollment, such as chemotherapy, radiotherapy, supportive care, or sorafenib.

Postoperative recovery

The measures applied to patients receiving ERAS or conventional care after surgery are summarized in **Table 1**. ERAS involves a multidisciplinary team of surgeons, nurses, physical therapists, and operating room personnel. Patients were first educated about ERAS preoperatively, and they did not need to prepare their bowels beforehand. On the day before surgery, they were actively warmed with a coat, their central venous pressure was confirmed to be < 5 mmHg, and they received warm fluids. Postoperatively, delivery of intravenous fluid was reduced and discontinued earlier than in conventional care; in addition, nasogastric tubes were removed earlier and the peritoneal cavity was drained earlier in the ERAS group. Patients resumed drinking and oral feeding and were encouraged to become mobile earlier than in conventional care. In addition, ERAS patients received simo decoction and acupuncture at the *tsusanli* acupoint, which we have found to reduce incidence of postoperative ileus and shorten hospital stay in HCC patients after hepatectomy [10]. ERAS patients also received continuous portable analgesia epidurally or via a fentanyl transdermal system instead of via a patient-controlled intravenous analgesia pump.

Propensity score matching

The patients in our study were assigned to receive ERAS or conventional postoperative care based on clinical criteria or patient preference, rather than through randomization. Therefore, to minimize confounding in our analysis due to baseline differences between the two groups of patients, we generated pairs of ERAS and control patients based on propensity score matching [11]. Analyses were conducted with propensity score-matched pairs as indicated.

Propensity scores were estimated using a logistic regression model based on the following characteristics of patients and HCC: age, sex,

Table 2. Preoperative baseline characteristics of patients in ERAS and control groups before and after propensity score matching

	Before propensity score matching				After propensity score matching			
Parameter	ERAS (n = 105)	Control (n = 100)	Standardized difference, %	*P* value	ERAS (n = 74)	Control (n = 74)	Standardized difference, %	*P* value
Age, year	46.5 ± 11.3	45.8 ± 11.6	6.3	0.656	46.1 ± 10.6	45.2 ± 11.7	4.9	0.596
Sex				0.732				0.806
ASA grade				0.717				1.000
I	62 (59.0)	64 (64)	10.2		37 (50.0)	37 (50.0)	0	
II	28 (26.7)	22 (22)	10.5		11 (14.9)	11 (14.9)	0	
III	14 (13.3)	13 (13)	1.0		26 (35.1)	26 (35.1)	0	
Male, n (%)	92 (87.6)	86 (86.0)	4.9		65 (87.8)	64 (86.5)	4.1	
Female, n (%)	13 (12.4)	14 (14.0)	4.9		9 (12.2)	10 (13.5)	4.1	
Tumor size, cm	6.9 ± 3.5	6.3 ± 2.9	17.6	0.172	6.4 ± 2.8	6.4 ± 3.1	3	0.827
HbsAg (+), n (%)	89 (84.8)	86 (86.0)	3.4	0.802	89 (84.8)	86 (86.0)	7.5	
Child-Pugh class, n (%)				0.865				1.000
A	97 (92.4)	93 (98.0)	2.3		68 (91.9)	68 (91.9)	0	
B	8 (7.6)	7 (7.0)	2.3		6 (8.1)	6 (8.1)	0	
Cirrhosis, n (%)	89 (84.8)	83 (83.0)	4.9	0.732	61 (82.4)	61 (82.4)	0	1.000
Type of hepatectomy, n (%)				0.562				0.868
Right	54 (51.4)	54 (54.0)	5.1		39 (52.7)	37 (50.0)	5.4	
Left	36 (34.3)	28 (28.0)	13.2		22 (29.7)	25 (33.8)	8.5	
Segmentectomy	15 (14.3)	18 (18.0)	10.6		13 (17.6)	12 (16.2)	3.8	
AFP (ng/ml), n (%)				0.403				1.000
≥ 400	47 (44.8)	39 (39.0)	11.5		34 (45.9)	34 (39.0)	0	
≤ 400	58 (55.2)	61 (61.0)	11.5		40 (54.1)	40 (61.0)	0	
Total bilirubin, μmol/L	15.6 ± 7.0	13.6 ± 6.8	28.9	0.037	14.5 ± 5.6	14.3 ± 7.0	9.9	0.881
ALT, U/L	50.7 ± 52.4	63.6 ± 44.5	1.4	0.931	58.1 ± 54.0	56.8 ± 73.5	2.4	0.909
AST, U/L	60.6 ± 40.9	56.0 ± 35.4	3	0.828	56.1 ± 37.2	59.2 ± 73.1	4.6	0.755
Prothrombin time, s	12.8 ± 1.8	13.6 ± 1.8	40.9	0.004	13.2 ± 1.4	13.0 ± 1.8	9.3	0.388
Albumin, g/L	39.2 ± 3.7	38.5 ± 4.2	21.2	0.156	38.6 ± 3.5	38.6 ± 4.0	1.8	0.912
Platelet count, 10^9/L	189.4 ± 72.2	190.0 ± 73.1	0.9	0.951	188.1 ± 70.6	186.3 ± 73.0	2.5	0.881
BCLC stage, n (%)				0.141				0.929
A	73 (69.5)	69 (69.0)	1		56 (75.7)	54 (73.0)	7.1	
B	16 (15.2)	23 (23.0)	21.5		11 (14.9)	12 (16.2)	3.7	
C	16 (15.2)	8 (8.0)	13.2		7 (9.5)	8 (10.8)	3.7	

Values are mean ± SD or n (%). *Abbreviations:* AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERAS, enhanced recovery after surgery; BCLC, Barcelona clinic liver cancer; PSM, propensity score matching.

Table 3. Liver function before and after surgery in propensity score-matched patients

Parameter	ERAS (n = 74)	Control (n = 74)	*P* value
Total bilirubin (μmol/L)			
Day before surgery	14.5 ± 5.6	14.3 ± 7.0	0.881
Postoperative day 1	25.1 ± 21.1	23.7 ± 21.8	0.645
Postoperative day 3	20.5 ± 19.5	23.0 ± 23.0	0.471
Postoperative day 5	17.3 ± 11.3	19.0 ± 13.9	0.451
Postoperative day 7	16.3 ± 9.0	17.8 ± 13.4	0.425
Albumin (g/L)			
Day before surgery	38.6 ± 3.5	38.6 ± 4.0	0.912
Postoperative day 1	32.0 ± 4.5	31.8 ± 3.9	0.708
Postoperative day 3	31.6 ± 4.6	31.5 ± 3.9	0.908
Postoperative day 5	31.8 ± 3.5	32.2 ± 3.2	0.447
Postoperative day 7	33.2 ± 6.1	33.2 ± 3.3	0.981
Prothrombin time (s)			
Day before surgery	13.2 ± 1.4	13.0 ± 1.8	0.388
Postoperative day 1	14.6 ± 1.9	14.8 ± 1.7	0.532
Postoperative day 3	14.5 ± 1.6	14.9 ± 1.8	0.220
Postoperative day 5	13.9 ± 1.4	14.2 ± 1.3	0.257
Postoperative day 7	13.8 ± 1.5	14.8 ± 1.6	0.001

ERAS, enhanced recovery after surgery.

American Society of Anesthesiologists (ASA) grade; tumor size, HBeAg status, Child-Pugh class, presence or absence of cirrhosis, type of hepatectomy, presence or absence of alpha-fetoprotein (AFP) ≥ 400 ng/ml, platelet count, prothrombin time and levels of total bilirubin, albumin, alanine transaminase (ALT), and aspartate transaminase (AST). One-to-one matching without replacement was performed using a 0.1 caliper width. Standardized differences were calculated to obtain a balance between the ERAS and conventional groups, with good balance indicated by a difference < 0.1 [12].

Outcomes

Outcome measures were the following: changes in liver function between the day before surgery and a given postoperative day, with function assessed in terms of serum levels of total bilirubin, albumin and prothrombin time; postoperative complications in-hospital and within 30 days of discharge; 30- and 90-day mortality; and postoperative length of hospital stay, defined as the interval from the day of surgery until the day of discharge. General complications included liver failure, puncture hematoma, bile fistula, incision dehiscence, abdominal infection, hydrothorax, intestinal obstruction, bleeding, wound infection and pulmonary infection.

Discharge criteria

Functional recovery was defined as adequate pain control requiring only oral analgesia, adequate oral intake with no intravenous fluid requirement, independent mobility sufficient to perform activities of daily living, and blood tests of liver function and inflammatory markers indicating a return to normal ranges [6]. Patients were assessed daily against these criteria. An experienced clinician determined readiness for hospital discharge.

Statistical analysis

Data for continuous variables were expressed as mean ± standard deviation and compared between ERAS and control groups using the independent-samples *t* test. Data for continuous variables were compared between ERAS and control groups using the paired *t* test. Inter-group differences in categorical data were compared using the chi-squared or Fisher exact tests. All statistical analyses were performed in SPSS 22.0 (IBM, Chicago, IL, USA). For all tests, $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The clinicopathological characteristics of ERAS and control groups were compared without propensity score matching (**Table 1**). The two groups were similar for all parameters analyzed, except that the control group had longer prothrombin time ($P = 0.004$). However, the two groups showed standardized differences > 10% for most variables, indicating that the two groups were not well matched for most baseline characteristics.

Propensity score matching

Propensity score matching generated 74 pairs of patients, for which baseline characteristics

Table 4. Operating details and outcomes for propensity score-matched patients

Parameter	ERAS (n = 74)	Control (n = 74)	*P* value
Operating time (min)	228.3 ± 71.6	209.6 ± 42.7	0.270
Intraoperative blood loss (mL)	366.7 ± 344.6	346.4 ± 274.0	0.647
Patients transfused, n (%)	5 (6.8)	8 (10.8)	0.384
Intraoperative transfusion, packs of red cell (units)	4.0 ± 1.4	6.3 ± 2.7	0.101
Duration of abdominal drain (days)	4.5 ± 1.7	5.7 ± 3.2	0.038
Duration to first flatus (days)	1.7 ± 0.7	2.9 ± 0.8	< 0.001
Duration to first mobilization out of bed and walking (days)	3.6 ± 0.9	4.2 ± 1.4	0.015
Intensive care unit stay (days)	2.0 ± 1.2	2.2 ± 1.5	0.451
Postoperative hospital stay (days)	11.8 ± 2.0	13.6 ± 4.1	0.001

Values are mean ± SD or n (%). ERAS, enhanced recovery after surgery.

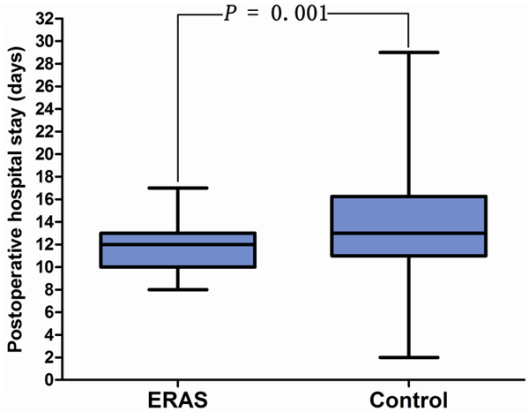

Figure 1. Total length of postoperative hospital stay in enhanced recovery after surgery (ERAS) and control groups.

showed no significant differences ($P > 0.05$) and for which the standardized difference was < 10% for all parameters (**Table 2**). The resulting score-matched pairs were used in subsequent analyses.

Liver function recovery

Changes in liver function from the day before surgery until postoperative day 7 are presented in **Table 3**. The ERAS group showed better liver function recovery than the control group between postoperative days 3 and 7, although these differences did not achieve significance. Only the level of prothrombin time on postoperative day 7 differed significantly between the groups ($P = 0.001$).

Outcomes

Outcome data are summarized in **Table 4**. Duration of the abdominal drain was 4.5 ± 1.7 days in the ERAS group and 5.7 ± 3.2 days in the control group ($P = 0.038$). Mean time to first flatus was 1.7 ± 0.7 days in the ERAS group and 2.9 ± 0.8 days in the control group ($P < 0.001$). Mean time until the first mobilization out of bed was 3.6 ± 0.9 days in the ERAS group and 4.2 ± 1.4 days in the control group ($P = 0.015$). Postoperative hospital stay was 11.8 ± 2.0 days in the ERAS group and 13.6 ± 4.1 days in the control group ($P = 0.001$; **Figure 1**).

Safety

The ERAS and control groups showed similar postoperative 30-day mortality (0 *vs.* 1.4%, $P = 1.000$) and 90-day mortality (1.4% *vs.* 1.4 %, $P = 1.000$; **Table 5**).

Postoperative complications occurred in 18 patients in the ERAS group (16.4%) and 14 (23.0%) in the control group ($P = 0.424$). In the ERAS group, liver failure occurred in 3 patients; puncture hematoma, 2; bile fistula, 1; incision dehiscence, 2; abdominal infection, 1; hydrothorax, 4; bleeding, 1; wound infection, 1; and pulmonary infection, 1. In the control group, liver failure occurred in 2 patients; bile fistula, 3; incision dehiscence, 2; intestinal obstruction, 1; bleeding, 2; wound infection, 3; and pulmonary infection, 1. Detailed complications in the two groups are listed in **Table 5**.

Discussion

The results of the present study suggest that ERAS can accelerate postoperative recovery without compromising patient safety following partial hepatectomy for HCC. These results support previous reports of the efficacy and safety of ERAS after hepatic surgery [6-9].

Table 5. Surgical complications for propensity score-matched patients

	ERAS (n = 74)	Control (n = 74)	*P* value
30-day mortality, n (%)	0 (0)	1 (1.4)	1.000
90-day mortality, n (%)	1 (1.4)	1 (1.4)	1.000
Postoperative complications, n (%)	18 (23.0)	14 (16.4)	0.424
Liver failure, n (%)	3 (4.1)	2 (2.7)	1.000
Puncture hematoma, n (%)	2 (2.7)	0 (0)	0.477
Bile fistula, n (%)	1 (1.4)	3 (4.1)	0.612
Incision dehiscence, n (%)	2 (2.7)	2 (2.7)	1.000
Abdominal infection, n (%)	1 (1.4)	0 (0)	1.000
Hydrothorax, n (%)	4 (5.4)	0 (0)	0.128
Intestinal obstruction, n (%)	0 (0)	1 (1.4)	1.000
Bleeding, n (%)	1 (1.4)	2 (2.7)	1.000
Wound infection, n (%)	2 (2.7)	3 (4.1)	1.000
Pulmonary infection, n (%)	1 (1.4)	1 (1.4)	1.000

Our results in the present study are consistent with our previous work suggesting that simo decoction combined with acupuncture at the *tsusanli* acupoint may reduce incidence of postoperative ileus and shorten hospital stay in HCC patients after hepatectomy. In fact, the present study may provide a more rigorous assessment of this idea because we used propensity score matching to reduce patient selection bias.

Our results suggest that ERAS is as safe as conventional recovery care despite its association with shorter postoperative hospitalization, drainage period and time to mobilization out of bed. We observed no significant difference in 30- or 90-day mortality between ERAS and the control groups, and the mortality rates in the ERAS group (0-1.4%) were similar to the rates reported in previous studies involving ERAS after hepatic surgery (0-1.8%) [6-9]. The two groups in our study showed similar incidence of complications, and the incidence in the ERAS group (23%) was slightly lower than that reported in studies of ERAS after hepatic surgery (28-46.4%) [6-9].

The ERAS program at our hospital included monitoring central venous pressure preoperatively to ensure that it was < 5 mmHg. Our results showing ERAS efficacy are consistent with several studies of open hepatic resection [13-16] suggesting that maintenance of low central venous pressure can reduce overall perioperative morbidity, shorten postoperative hospital, and possibly improve survival. Low central venous pressure has also been associated with reduced back-bleeding during parenchymal transection and lower risk of excessive administration of intravenous fluids [17-19]. Our results may contrast with those of one study [20] suggesting that low central venous pressure may not be beneficial for patients undergoing minor hepatectomies. Further work is needed to assess the benefits of low central venous pressure for patients undergoing minor or major hepatectomies.

Although ERAS was associated with shorter postoperative hospital stay than conventional care in our study, mean hospital stay in the ERAS group (11.8 ± 2.0 days) was longer than the mean or median values of 5-8 days reported in studies examining ERAS following hepatic surgery [6-9]. This may reflect the fact that the proportion of ASA grade III patients in our study (35.1%) was higher than the proportions of 5-19.6% in those studies.

The current study has some limitations. First, its retrospective design increases the risk of bias that cannot be eliminated even after propensity score matching. Second, our sample was relatively small, so our results should be verified and extended in larger, preferably prospective and randomized studies.

Despite these limitations, the current study suggest that ERAS can be more effective than conventional care and similarly safe when applied to patients undergoing partial hepatectomy for HCC. ERAS can accelerate postoperative recovery for such patients and thereby shorten their hospital stay.

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Disclosure of conflict of interest

None.

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