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ORIGINAL ARTICLE

Application value of ERAS in perioperative period of precise hepatectomy for hepatocellular carcinoma patients

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Summary

Purpose: *To explore the efficacy and reliability of enhanced recovery after surgery (ERAS) applied in the perioperative period of precise hepatectomy for hepatocellular carcinoma (HCC).*

Methods: *The propensity score matching and a retrospective cohort study were employed. The clinical and pathological data of 122 hepatocellular carcinoma (HCC) patients with surgical indications admitted to our hospital from March 2014 to March 2016 were collected. These 122 patients were subjected to propensity score matching and divided into ERAS group and Control group. The surgical situation, postoperative recovery [postoperative alanine aminotransferase (ALT), total bilirubin (TBiL) and C-reactive protein (CRP) levels], postoperative complications, postoperative hospital stay, hospitalization costs and patient satisfaction score were observed and compared between the two groups. All patients were followed up to record their postoperative survival.*

Results: *The average drainage tube removal time, bowel sound time, postoperative flatus time and postoperative hospital stay of patients were overtly shorter in ERAS group than in Control group. Besides, the postoperative numerical rating scale (NRS) score and the incidence rate of moderate and severe pain after surgery were lower in ERAS group than in Control group. The total hospitalization cost was significantly lower in ERAS group than in Control group. The patient satisfaction score was obviously higher in ERAS group than in Control group. ERAS group had fewer cases of postoperative vomiting, abdominal distension, biliary fistula, intestinal obstruction, large-volume ascites, liver failure, wound infection, pulmonary infection and abdominal infection than Control group, but the differences were not statistically significant. The ALT, TBiL and CRP levels of patients were notably lower in ERAS group than in Control group at d 7 after surgery. Based on the follow-up results, there was no significant difference in overall survival between the two groups*

Conclusion: *ERAS applied in the perioperative period of HCC patients receiving precise hepatectomy is reliable and effective and has positive significance for the promotion of postoperative rehabilitation, which is worthy of popularization in clinical practice.*

Key words: *ERAS, hepatocellular carcinoma, precise hepatectomy, perioperative period*

Introduction

Precise hepatectomy, which has small trauma, quick postoperative recovery and good short-term prognosis in the treatment of hepatocellular carcinoma (HCC) in comparison conventional hepatectomy, has become the leading surgical approach for treatment of HCC at present [1]. Enhanced recovery after surgery (ERAS), first proposed by Kehlet et al of the University of Copenhagen in Denmark in 1997, refers to a series of perioperative optimization measures proved through evidence-based medicine that alleviate surgical trauma, relieve postoperative pain and accelerate postoperative

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recovery in patients undergoing hepatectomy, which has been confirmed to be effective in shortening postoperative hospital stay and reducing hospitalization costs of surgical patients [2,3]. At present, the concept of ERAS has been applied in many disciplines including colorectal surgery, cardiothoracic surgery, urinary surgery, orthopedics, and gynaecology and obstetrics, with remarkable efficacy [4-8]. However, the application of ERAS in precise hepatectomy is still in the clinical exploration stage in China and foreign countries due to the high complexity and risk of operation on liver.

In this study, therefore, ERAS was included in the perioperative diagnosis and treatment scheme for patients receiving precise hepatectomy for HCC, and its reliability and efficacy in hepatic surgery were investigated by comparing with the conventional perioperative diagnosis and treatment scheme.

Methods

General data

The propensity score matching and retrospective cohort study were utilized. The clinical and pathological data of 122 patients with HCC treated in our hospital from March 2014 to March 2016 were collected.

Inclusion criteria

Patients receiving precise hepatectomy for liver cancer for the first time and no treatments such as interventions before surgery, those definitely diagnosed with HCC via postoperative pathological examination, those without extrahepatic organ metastasis, those with well controlled preoperative hypertension and diabetes, Child-Pugh grade A or B preoperative liver function and no nutritional support, and those with complete clinical and pathological data.

Exclusion criteria

Patients with apparent abnormal function of important organs such as the heart, lungs and kidneys, those with Child-Pugh grade C preoperative liver function, those undergoing palliative surgery or open radiofrequency ablation, those with a history of intestinal surgery, those with severe preoperative constipation, or those with incomplete clinical or pathological data. A total of 122 patients were enrolled in this study, including 83 males and 39 females. They were aged 23-71 years with a mean of 54.65±10.33 years. As to tumor location, 46 cases were in the right hepatic lobe, 39 cases in the left hepatic lobe and 37 cases located in the middle lobe. The baseline data including age, gender, tumor diameter, tumor location, Child-Pugh grade liver function, levels of alanine aminotransferase (ALT), total bilirubin (TBiL) and C-reactive protein (CRP) and ASA score exhibited no statistically significant differences between the two groups ($p>0.05$), which were comparable (Table 1). All patients enrolled were informed of and signed the informed consent in accordance with Declaration of Helsinki. This study was approved by the Ethics Committee of No.215 Hospital of Shaanxi Nuclear Industry.

Table 1. Demographics and general clinical data of all studied patients

Data	*ERAS group (n=61)*	*Control group (n=61)*	*p value*
Age (years)	55.21±9.83	53.44±10.53	0.339
Gender (Male/Female)	39/22	44/17	0.438
Tumor diameter (cm)	6.3±2.9	5.7±3.2	0.280
Tumor location, n			0.837
Right lobe	24	22	
Left lobe	20	19	
Middle lobe	17	20	
ASA grade, n (%)			0.168
1	56 (50.8)	51 (61.0)	
2	5 (49.2)	10 (39.0)	
Child-Pugh class, n (%)			0.191
A	55 (72.9)	50 (81.4)	
B	6 (27.1)	11 (18.6)	
AFP (ng/ml), n (%)			0.338
≥400	18 (23.7)	23 (16.9)	
<400	43 (76.3)	38 (83.1)	
ALT (U/L)	53.4±9.4	55.7±10.3	0.200
TBil (μmol/L)	13.5±2.2	14.2±2.7	0.119
CRP (mg/L)	4.7±0.8	4.9±0.9	0.197

ERAS: enhanced recovery after surgery; ASA: American Society of Anesthesiologists; AFP: alpha fetoprotein; ALT: alanine transaminase; TBil: total bilirubin; CRP: C-reactive protein

Surgical methods

In ERAS group, the education was conducted for patients 2 days before surgery to relieve their nervousness and anxiety and gain understanding and support from patients. The patients were fasted for 6 h and orally administered 250 mL of 10% glucose 2 h before surgery, without preanesthetic medication. Bowel preparation and gastric intubation were not performed before surgery, while a urinary catheter was inserted after anesthesia and be removed within 12 h after surgery. Tracheal + epidural anesthesia was used. During hepatectomy, the central venous pressure was controlled at 3-5 cm H_2O (1 cm H_2O=0.098 kPa), and color Doppler ultrasonography was carried out to confirm the blood flow of the normal liver and the vascular occlusion of the affected liver without blocked or dissected porta hepatis. In addition, the infusion volume was <1.500 mL, and the body temperature was kept within the normal range. After surgery, 25 cal/g fat emulsion was injected at a dose of ≤2.500 mL/d, maintaining water-electrolyte-acid-base balance, and a precise individualized, multimodal and preemptive analgesia regimen of intravenous patient-controlled analgesia pump combined with non-steroidal anti-inflammatory drugs was routinely performed, in which the pump was removed 3 days after surgery. The patients started ambulation from 12 h after surgery, with at least 4 times of off-bed ambulation on day 1 after surgery. Besides, the frequency of ambulation gradually rose. 30-50 mL of enteral nutrition powder (1×10^6 cal/L) was eaten every 2-3 h on day 1 after surgery and 100-200 mL every 2-3 h on day 2, and then semi-liquid diet was added based on the tolerance of the patients until the normal diet was restored. The drainage tube was placed unconventionally after surgery, which was removed if there was no bile leakage or bleeding on day 1 after surgery.

In the control group, the patients were informed of the surgical methods and precautions one day before surgery, subjected to conventional preanesthetic medication, given no food for 8 h and drink for 6 h before surgery, and orally administered with sodium phosphate on the eve of surgery for bowel preparation. In addition, a gastric tube was indwelt before surgery and removed after postoperative flatus, and a urinary catheter was conventionally indwelt and removed after postoperative off-bed ambulation. Intratracheal anesthesia was employed, and there was no strict requirement for central venous pressure, infusion volume and body temperature control. After surgery, 3.000-3.500 mL of 0.9% sodium chloride solution were infused and the epidural catheter-controlled analgesia pump was utilized for continuous analgesia for 48 h (10% ropivacaine, sufentanil 0.05 mg and normal saline 85 ml with pump, pumping speed 2ml/h). There was no requirement for the time on patient's off-bed ambulation after surgery. Enteral nutrition powder (1×10^6 cal/L) was eaten after flatus, and liquid diet was gradually added until the normal diet was assumed. The drainage tube was placed conventionally after the operation, which was removed if there was no bile leakage or bleeding at 3-4 days after surgery.

Observation indexes

Surgical situation: operation time, intraoperative blood loss and intraoperative blood transfusion volume. Postoperative recovery: postoperative bowel sound recovery time, postoperative first flatus time, postoperative drainage tube removal time, numerical rating scale (NRS) score for pain at 24 and 48 h after surgery, levels of ALT, TBiL and CRP on days 1 and 7 after surgery, postoperative complications, postoperative hospital stay, hospitalization costs and patient satisfaction score [6].

Postoperative pain was assessed via NRS, a visual analogue scale that is most commonly used in evaluating postoperative pain in China and abroad [4,5]. The postoperative moderate and severe pain (highest score t>4 points) was included in postoperative pain identification.

Postoperative complications: general complications (postoperative nausea & vomiting, intestinal obstruction, wound infection, urinary tract infection, delayed gastric emptying, deep venous thrombosis or pulmonary embolism, myocardial infarction and renal insufficiency) and surgical complications (postoperative hemorrhea, bile leakage, large-volume ascites, intra-abdominal abscess formation and liver failure).

Discharge criteria: patients with basic ability of daily living, those with relieved pain or well controlled pain by oral administration of analgesics, those with capacity of normal eating and free flatus and defecation, those with Child-Pugh grade A liver function and well healed wound without infection (without the needs of taking out stitches), or those agreeing and hoping to discharge.

All patients were followed up at 1, 2, 3, 4, 5, 6, 9 and 12 month(s) after discharge to record their postoperative survival. The patients who survived for over 1 year were followed up every 6 months. The follow-up was ended in March 2019.

Statistics

SPSS 22.0 was utilized for statistical analyses. Measurement data were expressed as mean ± standard deviation (SD), and t-test was employed for the comparison between the two groups. Enumeration data were expressed as ratio (%), and x^2 test was used for comparison between groups. P<0.05 suggested that the difference was statistically significant. Survival curves were plotted by Kaplain-Meier method. Log-rank test was applied to verify statistically significant difference in progression-free survival between groups, and p<0.05 indicated a statistically significant difference.

Results

General information before surgery

Comparisons of surgical indexes between the two groups of patients

The specific surgical procedures in ERAS group (n=61) and Control group (n=61) are shown in Table 2, and the differences were not statistically significant between two groups (p=0.850). There were no statistically significant differences in the operation time, intraoperative blood loss and blood transfusion volume between the two groups of patients [(140±20) min *vs.* (145±23) min, p=0.203, (354±92) mL *vs.* (332±102) mL, p=0.213, and (1.2±1.3) U *vs.* (1.1±1.4) U, p=0.683] (Table 2).

Comparison of postoperative recovery between the two groups of patients

The abdominal drainage tube was indwelt in 24 patients in ERAS group and 49 patients in Control group after surgery. The average drainage tube removal time was 2.8±1.0 days and 4.3±1.4 days in ERAS group and Control group, respectively, and the difference was statistically significant (p<0.001). In ERAS group, 15 patients started off-bed ambulation on day 1 after surgery, 24 patients on day 2 after surgery, and 22 patients on day 3 or above after surgery. In Control group, there were 3 patients starting off-bed ambulation 1 day after surgery, 16 patients 2 days after surgery, and 42 patients 3 days or above after surgery. The postoperative bowel sound recovery time, postoperative flatus time, and postoperative hospital stay were remarkably shorter in ERAS group than those in Control group (p=0.011, p=0.039, p=0.030). The mean NRS score at 24 and 48 h after surgery was 3.79 and 2.91 in ERAS group, which was significantly lower than 4.65 and 4.01 in Control group (p<0.001). There were 10 and 22 patients with moderate and severe pain after surgery in the two groups, respectively, and the incidence rate of postoperative moderate and severe pain was lower in ERAS group than that in Control group (p=0.023). The total hospitalization cost of patients was clearly lower in ERAS group than that in Control group (p<0.001). The patient satisfaction score was markedly higher in ERAS group than that in Control group (p=0.024) (Table 3).

Table 2. Comparison of parameters related to surgery of the studied patients in two different groups

Parameters	*ERAS group (n=61)*	*Control group (n=61)*	*p value*
Surgical method, n (%)			0.850
Left lateral lobectomy	16 (26.2)	13 (21.3)	
Left hemihepatectomy + Cholecystectomy	15 (24.6)	14 (23.0)	
Right hemihepatectomy + Cholecystectomy	21 (34.4)	22 (36.1)	
Segmental hepatectomy/ Hepatic lobectomy	9 (14.8)	12 (19.6)	
Operation time (min)	140±20	145±23	0.203
Blood loss (mL)	354±92	332±102	0.213
Blood transfusion (U)	1.2±1.3	1.1±1.4	0.683

ERAS: enhanced recovery after surgery

Table 3. Comparison of postoperative recovery parameters of the studied patients in two different groups

Parameters	*ERAS group (n=61)*	*Control group (n=61)*	*p value*
Hospital stay after surgery (d)	8.4±0.8	8.8±1.1	0.030
Drainage tube removal time (d)	2.8±1.0	4.3±1.4	0.001
Borborygmus appears after surgery (h)	48±9	52±8	0.011
Gas passage after surgery (d)	2.6±0.6	4.0±0.8	0.039
Hospitalization expense (Ten thousand yuan)	3.9±0.3	4.2±0.5	0.001
Patient satisfaction score (points)	8.6±1.1	8.1±1.3	0.024
Complications, n (%)			
Vomiting	5 (8.2)	7 (11.5)	0.543
Bloating	4 (6.6)	6 (9.8)	0.509
Biliary fistula	2 (3.3)	2 (3.3)	1.000
Ileus	3 (4.9)	2 (3.3)	0.648
Large volume ascites	1 (1.6)	3 (4.9)	0.619
Hepatic failure	1 (1.6)	1 (1.6)	1.000
Incision infection	2 (3.3)	4 (6.6)	0.402
Pulmonary infection	2 (3.3)	3 (4.9)	0.648
Intraperitoneal infection	1 (1.6)	4 (6.6)	0.171

ERAS: enhanced recovery after surgery

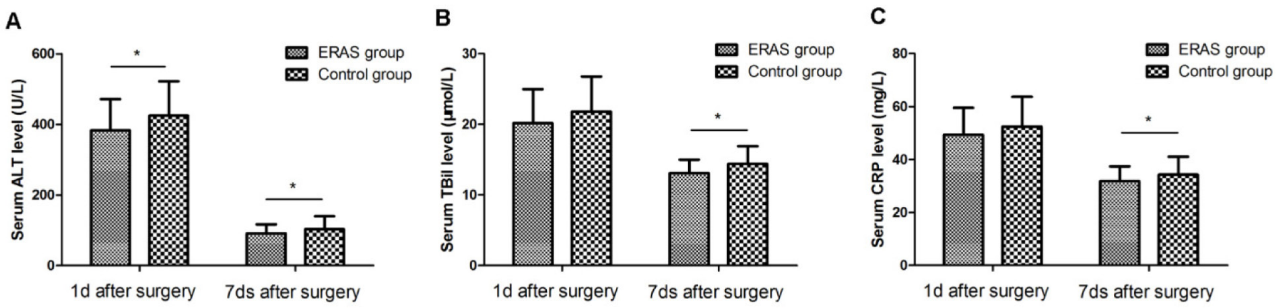

Figure 1. Comparison of serum ALT, TBil, CRP levels of patients in the two studied groups. The difference of 1 day posttreatment serum TBil **(B)** and CRP **(C)** levels of patients in ERAS group and Control group had no statistical significance (p=0.074, p=0.114). The serum ALT level **(A)** on 1 day posttreatment was significantly lower in patients in ERAS group than in Control group (p=0.014). Seven days after treatment, serum ALT **(A)**, TBil **(B)** and CRP **(C)** levels were significantly lower in patients in ERAS group than in Control group (p=0.040, p=0.002, p=0.027).

Comparisons of postoperative complications of patients between the two groups

The following complications were mainly observed in patients in ERAS group and Control group, respectively: postoperative nausea and vomiting in 5 and 7 cases, abdominal distension in 4 and 6 cases, incision infection in 2 and 4 cases, bile leakage in 2 and 2 cases, intestinal obstruction in 3 and 2 cases, large-volume ascites in 1 and 3 case(s), abdominal infection in 1 and 4 case(s), pulmonary infection in 2 and 3 cases, and liver failure in 1 and 1 case. The incidence rate of postoperative complications had no statistically significant differences between the two groups (p>0.05) (Table 3).

Comparisons of postoperative serum ALT, TBiL and CRP levels of patients between the two groups

The serum ALT level of patients was 383±89 U/L and 91±26 U/L at 1 and 7 days after surgery in ERAS group, which was significantly lower than 425±97 U/L and 103±37 U/L in Control group (p=0.014, p=0.040). The serum TBiL level was 20.2±4.8 μmol/L and 21.8±5.0 μmol/L on day 1 and 13.1±1.9 μmol/L and 14.4±2.5 μmol/L on day 7 after treatment in ERAS group and Control group, respectively, The serum TBiL level exhibited no statistically significant difference on day 1 after surgery between the two groups, but it was significantly lower in ERAS group than in Control group 7 days after surgery (p=0.074, p=0.002). The serum CRP content of the patients was 49.3±10.2 mg/L in ERAS group and 52.4±11.3 mg/L in Control group on day 1 after surgery, showing no statistically significant difference (p=0.114), while it was distinctly lower in ERAS group than in Control group 7 days after surgery [(31.8±5.6) mg/L *vs.* (34.3±6.7) mg/L, p=0.027)] (Figure 1).

Results of patient survival

The patients were followed up for 6-36 months (median 27 months). There was 1 case lost to follow-up in ERAS group at 12 months after surgery, and 2 cases in Control group at 18 and 24 months after surgery, respectively. During follow-up, 10 patients in ERAS group died of cerebral infarction, respiratory failure and tumor recurrence-induced multiple organ failure at 11, 15, 23, 27, 27, 28, 29, 29, 33 and 35 months after surgery, respectively, while in Control group, 13 patients died of myocardial infarction, tumor recurrence-induced multiple organ failure, metastasis of liver cancer to lungs, cerebral infarction, and respiratory failure at 10, 14, 18, 19, 24, 26, 26, 28, 29, 30, 31, 32 and 34 months after surgery. The Kaplan-Meier overall survival curves of the two groups of patients are shown in Figure 2. The Log-rank test for the overall survival of patients in two groups revealed that the difference was not statistically significant (p=0.318).

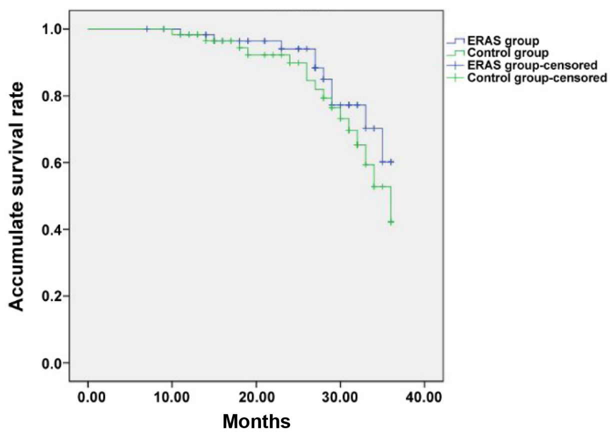

Figure 2. Kaplan-Meier survival curves of the studied patients. The difference of overall survival rate of patients in ERAS group and Control group had no statistical significance (p=0.318).

Discussion

ERAS serves as a novel perioperative management model in clinical practice, of which the core is to mitigate the trauma and stress of patients. Besides, it is patient-centered and intended to accelerate postoperative rehabilitation, reduce postoperative complications, shorten hospital stay and lower hospitalization costs, which is a synergistic effect of combined effective measures [9,10]. Precise hepatectomy integrates, applies and innovates a series of modern medical theories, enhanced recovery concepts, surgical techniques and imaging technologies in the field of liver surgery. The liver tumors and liver vasculature are accurately evaluated through radiography before surgery, liver function reserve and residual liver volume after hepatectomy are assessed, and hepatic blood flow is not blocked or selectively blocked. The liver is precisely dissected, and the cutting surface is finely treated to more effectively resect the lesion and reduce bleeding, thus maximally preserving residual liver function and decreasing postoperative complications to achieve better long-term clinical prognosis [11,12].

In this study, it was found that the postoperative bowel sound recovery time and postoperative first flatus time were clearly shorter in ERAS group than in Control group (p=0.011, p=0.039), making it possible for patients to eat early after surgery and promote the recovery of the body after surgery, which is in line with the findings of research conducted by Wohler et al [13]. In comparison with Control group, ERAS group displayed overtly lowered postoperative pain score, shortened hospital stay, reduced costs and enhanced patient satisfaction, suggesting that ERAS is notably effective in the perioperative period of precise hepatectomy. Attention was paid to psychological counseling of the patients in ERAS group, reducing negative emotions of patients such as the fear before surgery and preoperative anxiety, which provides positive psychological support for accelerating rehabilitation. Improving confidence in liver cancer healing and subjectivity in postoperative rehabilitation of the patients shortens the average hospital stay, reduces hospitalization costs, and improves patient satisfaction to a certain extent [14,15]. Preoperative nutritional support is conductive to surgery-induced trauma and stress of the patients, reducing catabolism, avoiding hypoglycemia and hypovolemia caused by long fasting of water and food, and reducing the volume of fluid infusion during surgery [16,17].

According to this study, the incidence rates of postoperative vomiting, abdominal distension and pulmonary infection were lower in ERAS group than in Control group, but the differences were not statistically significant. The possible reason is that ERAS encourages patients to eat and ambulate at the early stage after surgery, which can facilitate the recovery of the body. Early feeding after surgery is able to increase organ blood flow, promote gastrointestinal tract movement, reduce catabolism, protect intestinal mucosal barrier, and prevent intestinal infection. Intestinal nutrients are absorbed and then enter the liver through the portal vein, which is beneficial to improving liver function, stimulating protein synthesis in the liver, and accelerating the recovery of the body [18,19]. Preoperative cardiopulmonary exercise and early postoperative ambulation are capable of improving blood circulation, preventing muscle disuse atrophy, alleviating ventilation disorders, avoiding long-term bed-induced hypostatic pneumonia, facilitating sputum excretion, and reducing pulmonary complications. Furthermore, comprehensive temperature maintenance strategies adopted during surgery can effectively keep body temperature normal during surgery and reduce chills and agitation upon resuscitation as well as postoperative complications [20-22]. The follow-up results revealed that there was no statistically significant difference in long-term survival between the two groups of patients (p=0.318).

This study had a small sample size and short-term and incomplete follow-up. Subsequently, improving and perfecting the surgical methods and conducting comprehensively prospective comparative studies are the focuses. The conclusions of this study need to be verified through multicenter randomized controlled studies with a large sample size.

Conclusions

For HCC patients undergoing precise hepatectomy, ERAS in the perioperative period is reliable and effective and has positive significance for promoting postoperative rehabilitation, which is worthy of popularization in the clinic.

Conflict of interests

The authors declare no conflict of interests.

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