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Individualized Enhanced Recovery After Surgery (Eras) Protocols for Patients with Hepatocellular Carcinoma: A Retrospective Study

*Yu Zhang[1], Xin Cheng[3], Lei Zhang[1], Zhongling Xu[2], Zihan Feng[3], Zeyin Chen[3], Zhong Chen[1]**

ABSTRACT

Background: Hepatocellular carcinoma (HCC) patients often undergo curative liver resection to treat this form of cancer. Hepatectomy is, however, a form of major surgery associated with many significant risks including prolonged hospitalization, high costs, impaired physiological function, and high postoperative complication rates. Enhanced recovery after surgery (ERAS) is a multidisciplinary approach that seeks to expedite postoperative recovery in patients undergoing major surgeries in order to lower postoperative complication rates. Prior studies have successfully employed ERAS approaches in the context of gynecological, urological, and cardiovascular surgeries. However, HCC is a complex disease and affected patients may also suffer from pre-existing liver disease, making it essential that they be administered appropriate individually tailored treatments. This study was thus designed to assess the efficacy and safety of individualized ERAS approaches in patients undergoing hepatectomy.

Methods: In total, we retrospectively analyzed data from 90 HCC patients that underwent hepatectomy between October 2018 and August 2019. All patients met the study enrolment criteria and provided written informed consent to participate. All studies were approved by the Hospital Research Ethics Committee and were consistent with the Declaration of Helsinki. Patients were randomly divided into two groups (n=45 each) based on the employed perioperative treatment strategies: a conventional treatment group and an ERAS treatment group. Key outcomes were then compared between groups, including postoperative pain scores, duration of postoperative hospitalization, medical costs, and rates of readmission. Quantitative data are given as `x±s and were compared via Student's t-tests, whereas categorical data were compared via chi-squared tests and Fisher's exact test.

Results: ERAS treatment was associated with lower postoperative pain scores at 24, 48, and 72 h post-treatment (P<0.05), with a shorter postoperative hospitalization duration (8.16 days vs.10.49 days; P<0.004), and with lower medical costs (P<0.004) as compared to traditional treatment. No significant differences in complication rates (P>0.05) or readmission rates (P>0.557) were observed between these groups.

Conclusion: Individualized ERAS improves patient postoperative recovery more effectively than traditional treatment in patients undergoing hepatectomy.

INTRODUCTION

In patients with hepatocellular carcinoma (HCC), liver resection remains the first-line approach to curative treatment. At present, such treatment of liver cancer is associated with relatively tolerable perioperative mortality rates (~5%), and 5-year survival rates for HCC patients continue to improve Palavecino et al. (2010). Even so, hepatectomy is a major surgery associated with significant perioperative stress, prolonged postoperative recovery, and extended hospitalization. Indeed, surgical complications affect between 12 and 46% of patients that undergo liver resection Damania et al. (2017). Enhanced recovery after surgery (ERAS) is a multidisciplinary collaborative approach that seeks to expedite patient recovery by minimizing postoperative stress and complication rates. ERAS approaches have improved outcomes associated with colorectal surgery Gouvas et al. (2009), and are also commonly employed in the context of gynecological, urological, cardiothoracic surgeries and head&neck surgery Persson et al. (2015), Findlay et al. (2015), Imai et al. (2020), Schneider et al. (2020). Treatment of HCC can be highly complex owing to intratumoral heterogeneity, inter-tumor heterogeneity, and high rates of other pre-existing liver conditions such as cirrhosis and hepatitis in affected patients Komarova et al. (2015).

[1]Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China.
[2]Department of Anaesthesiology, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China.
[3]Medical school of Nantong University, Nantong 226001, Jiangsu Province, China.

Correspondence to: Professor Zhong Chen, Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China. E-mail: chenzhong9806@sina.com

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It is thus essential that individualized treatments and rehabilitative approaches be made available to patients undergoing surgical treatment for HCC. The present study thus retrospectively analyzed outcomes from HCC patients that underwent hepatectomy at the Affiliated Hospital of Nantong University. Clinical data from these patients were reviewed in order to explore the relative safety and efficacy of individualized perioperative ERAS treatment as a means of improving outcomes in liver cancer patients undergoing respective surgery.

MATERIALS AND METHODSs

Patients

We retrospectively analyzed data from 90 hepatocellular carcinoma patients that underwent hepatobiliary and pancreatic spleen surgery in the Affiliated Hospital of Nantong University between October 2018 and August 2019. All patients provided written informed to participate, and all studies were conducted in accordance with appropriate ethical guidelines. All patients met the study enrollment criteria and provided written informed consent to participate. All studies were approved by the Hospital Research Ethics Committee and were consistent with the Declaration of Helsinki. Our surgery department has 2 medical teams. One team followed the ERAS protocol Jia et al. (2019) and the other administered conventional care. The patients were randomized to one of the 2 medical teams and were blinded to the intervention. Each group was comprised of 45 patients.

Patients included in the present study met the following criteria: (1) patients were between the ages of 18 and 70; (2) patients had not undergone any preoperative local treatments for tumors; (3) primary liver cancer was confirmed via pathological examination of excised tumor sections, and patients had severe systemic disease; (4) patients had good preoperative blood pressure and blood glucose levels; (5) patients exhibited Child-Pugh Grade A or B preoperative liver function, with a 15-minute indocyanine green excretion rate of < 10%; (6) patients had ECOG scores of 0-1 points; (7) patients did not require special nutritional support; (8) patients underwent smooth open R0 liver tumor resection.

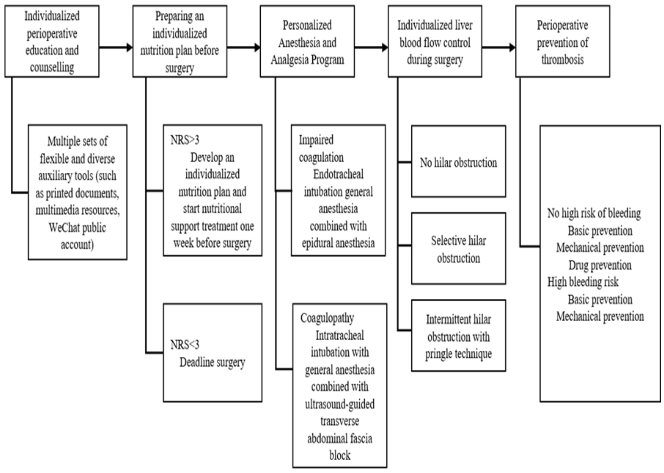
Patients were excluded from this study if they met the following criteria: (1) Liver resection was conducted as an emergency procedure; (2) patients exhibited metastatic liver cancer; (3) surgery was palliative or open-frequency radiofrequency ablation; (4) patients had a history of prior gastrointestinal surgeries; (5) incomplete patient data were available.

Patients were discharged when they met the following criteria: (1) good organ functional recovery was observed; (2) patients were able to take care of themselves; (3) patient pain was well-controlled with oral medication; (4) patients were able to partake of a normal diet; (5) patient defecation was normal; (6) patient bilirubin levels were normal; and (7) the incision site was well-healed. Patients were then able to request discharge. At one-month post-discharge, patients were assessed in an outpatient clinic and were asked to discuss their pain and any other post-discharge complications.

Clinical Pathway

Traditional perioperative treatments were administered to patients in the control group, whereas patients in the ERAS group underwent both conventional and individually-tailored ERAS treatment interventions (Table1, Figure1).

Figure 1 Individualized ERAS strategy



Statistical Analysis

An initial sample size of 40 cases per group was estimated to be necessary based on the following assumptions: class I error $\alpha = 0.05$ and test power $\beta = 0.2$. As an estimated 10% of patients were expected to be lost to follow-up, the final sample size per group was 45 patients (90 total patients) in order to enable us to resolve significant differences between groups. Data were compared using SPSS 19.0. Quantitative data are given as `x±s and were compared via Student's t-tests, whereas categorical data were compared via chi-squared tests and Fisher's exact test. $P < 0.05$ was the significance threshold.

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Table 1: Conventional perioperative treatment plan.

Treatment plan	**ERAS Group**	**Control group**
Preoperative management measures		
Fasting water and carbohydrate preload before surgery	Fasting for no more than 6 hours before surgery and drinking water 2 hour before anesthesia. Carbohydrate intake one night before surgery and 2 hours before anesthesia	Fast for 12 hours before surgery and 8 hours for water
Bowel preparation	No bowel preparation	Preoperative oral relieving agent and saline enema
Gastric tube	No gastric tube	Indwelling before surgery, remove after venting
Intraoperative management measures		
Urinary catheter	Placement before anesthesia, removal on the first day after surgery	Placement before anesthesia, removal after 3-4 days
Prophylactic antibiotics	Intravenous antibiotics once before skin incision	No
Liquid management	Minimize blood transfusion, use balanced crystal fluid to maintain blood volume, measure central venous pressure to control fluid replacement, central venous pressure <5mmHg	Normal rehydration, no special restrictions
Body temperature control	Electric blankets, infusion warmers to warm liquids, warm saline or sterilized water for injection to wash the abdominal cavity and control the operating room temperature	No special treatment
Abdominal drainage tube	Irregular placement	Placement of abdominal drainage tube
Postoperative management measures		
Liquid management	Control the amount of fluid replacement within 2500ml, adjust the amount of fluid replacement with reference to the amount of bleeding and urine during the operation. Reduce the amount of fluid replacement gradually after eating	no request

Abdominal drainage tube	Abdominal drainage tube was bloodless and bile fluid, removed 2 days after operation	Removal of abdominal drainage tube without drainage fluid
Postoperative analgesia	Intravenous self-controlled analgesia pump + selective Cox2 inhibitor intravenous infusion	Intravenous self-controlled analgesia pump, on-demand analgesia
Reduce stress response	Use proton pump inhibitors and broad-spectrum hydrolase inhibitors to reduce the body's inflammatory response	No special treatment
Diet	Start drinking water on the first day after surgery, and gradually change from liquid to general food after venting	Eat after venting
Moving target	Sit up for 1h on the first day after surgery, move for 1h on the lower limbs, sit up for 2h on the second day after surgery, and move on for 30 minutes at the bed.	Encourage early patient activity, voluntary patient activity
Regulate blood glucose after surgery	Routinely check blood sugar levels after surgery and use insulin to control hyperglycemia	Postoperative blood glucose testing for diabetics

RESULTS

Table 2: Comparison of baseline data of patients in the ERAS group and the control group.

Clinical parameters	**ERAS group**	**Control group**	**Test value**	**P-value**
Age（year,x±s)	57.24±10.47	63.64±10.47	2.901	0.373
Gender [n,(%)]				
male	12（26.7)	29（64.4)	0.829	0.362
female	33（73.3)	16（35.6)		
Surgery method				
Partial liver resection	33	27	4.489	0.106
Lobectomy	7	13		
Hepatectomy	5	5		
Tumor diameter (cm, x±s)	4.46±2.38	4.62±2.21	0.326	0.279
Operation time (min, x±s)	138.56±48.68	127.11±49.81	-1.102	0.8
Intraoperative blood loss (ml, x±s)	287.56±310.87	267±268.77	-0.336	0.696
Intraoperative blood transfusion	12	11	0.058	0.809

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In total, 90 patients were included in the two groups. Baseline comparisons between groups are shown in Table 2. We observed no significant differences between the ERAS and traditional treatment groups with age and gender. The types of liver resection performed are shown in Table 2. The average tumor diameter was 4.46±2.38 cm in the ERAS group and 4.62±2.21 cm in the control group (P =0.279). The average operation time was 138.56±48.68 minutes in the ERAS group and 127.11±49.81 minutes in the control group (P =0.8). The average intraoperative blood loss volume was 287.56±310.87 ml in the ERAS group and 267±268.77 minutes in the control group (P =0.696), while the average number of units of intraoperative blood transfusion required was 12 in the ERAS group and 11 in the control group (P =0.809).

As shown in Table 3, we observed significant differences between the ERAS and traditional treatment groups with respect to earliest postoperative bedtime, duration of ventilation, postoperative pain scores, time to abdominal drainage tube removal, postoperative hospitalization duration, and Hospital costs (P < 0.05).

In the ERAS group, the earliest postoperative bedtime was significantly reduced relative to the control group (21.29±6.29h vs. 56.67±9.08h, P=0.016). The duration of initial ventilation was 30.20±5.27h in the ERAS group and 60.42±7.8h in the control group (P=0.028).

Significant changes were observed in postoperative pain scores between groups at 24h, 48h, and 72h post-operation (P=0.007, P=0.001, P=0.02).

Extraction of the abdominal drainage tube in the ERAS group also occurred earlier on average relative to the control group (3.33±0.98d vs. 5.76±1.85d, P=0.009). Postoperative hospital stay in the ERAS group was only 8.16±1.54d vs. 10.49±3.72d in the control group (P =0.001). Hospital costs in the control were higher than in the ERAS group (￥44032±10707 vs. ￥50795±10953, P=0.004). Readmission rates were similar in both groups (1 vs. 2, P =0.577). in rates of postoperative complications between groups (P＞0.05) (Table 3).

Discussion

The ERAS approach was first proposed in 1997 by Professor Henrik Kehlet of Denmark. ERAS seeks to serve as a multidisciplinary evidence-based clinical approach to optimizing perioperative patient care through coordination of surgery, nursing care, anesthesia, and patient nutrition in order to reduce psychological and physical stress, to decrease functional impairment, and to accelerate patient discharge and recovery Basse et al. (2000). Liver resection is a complex surgery associated with substantial risk. Liver reserve function varies between patients, as do the surgical techniques employed and the resection ranges. Perioperative ERAS guidelines for liver surgery were first released in 2016 Melloul et al. (2016). Owing to this variability, while a number of different accelerated rehabilitation strategies have been proposed to date, none are suitable for all patients. It is thus essential that appropriate ERAS intervention plans be developed on an individualized basis for each patient.

Table 3: Comparison of postoperative conditions between the ERAS group and the control group

Clinical parameters	ERAS group	Control group	Test value	P-value
Early time to get out of bed after surgery (h, x±s)	21.29±6.29	56.67±9.08	21.472	0.016
First ventilation time（h, x±s）	30.20±5.27	60.42±±7.8	21.539	0.028
Postoperative pain score (point, x±s)				
24h	2.42±1.10	5.58±1.60	10.9	0.007
48h	0.98±0.75	3.24±1.17	10.921	0.001
72h	0.36±0.57	1.29±0.87	6.022	0.02
Extraction time of abdominal drainage tube（d, x±s）	3.33±0.98	5.76±1.85	7.772	0.009
Postoperative hospital stay（d, x±s）	8.16±1.54	10.49±3.72	3.888	0.001
Hospital costs（yuan, x±s）	44032±10707	50795±10953	2.962	0.004
Readmission	1	2	0.345	0.557
Postoperative complications [n (%)]				
Ascites	2 (4.4)	3 (6.7)	0.212	0.645
Pleural fluid	5 (11.1)	3 (6.7)	0.549	0.459
Lung infection	2（4.4)	1（2.2)	0.345	0.557
Incision fat liquefaction	4（8.9)	7（15.6)	0.932	0.334
Pulmonary embolism	0	1（2.2)	1.011	0.315
Liver failure	0	1（2.2)	1.011	0.315

Liver cancer is also a complex disease and commonly occurs in the context of other comorbid conditions such as hepatitis or liver cirrhosis, necessitating multidisciplinary treatment and diagnosis. Selecting an inappropriate ERAS plan has the potential to not only fail to expedite recovery, but also to potentially cause further harm to the patient. However, certain controversies remain regarding optimal ERAS approaches for patients undergoing hepatectomy. Key issues of concern include whether or not epidural anesthesia should be performed, whether patients should undergo postoperative anticoagulant therapy, and how issues such as intraoperative blood loss, thrombus formation, postoperative organ dysfunction, and low central venous pressure should be managed Agarwal et al. (2019). Herein, we propose an individualized plan for accelerated rehabilitation surgery. In addition to the conventional ERAS, individualized ERAS clinical strategies should be formulated based upon the specific condition of each hepatocellular patient, with the aim of improving the application of ERAS in patients with liver cancer undergoing hepatectomy. Given the risks associated with liver surgery, patients and their families typically suffer from substantial anxiety that can adversely impact both preoperative preparation and postoperative recovery. While no studies have specifically evaluated appropriate preoperative education and counseling for patients undergoing liver resection, studies in other surgical contexts have found individualized preoperative education and psychological counseling to be independent predictors of ERAS success. Given the substantial variability with respect to patient age, background, and education level, it is important that a range of flexible auxiliary tools be used to properly inform and guide patients and their loved ones. The goals of these interventional tools should be to educate patients regarding their disease, perioperative nursing protocols, and clinical decision making so that they can be active participants in their care. These strategies can help alleviate negative emotions while improving patient compliance and coordination. Such consultation strategies should persist throughout the perioperative period and should continue following patient discharge. The selection of appropriate anesthesia strategies for patients undergoing hepatectomy must be made based on a comprehensive consideration of operative scope, patient coagulatory function, and patient liver function. Endotracheal intubation is used with general anesthesia in patients undergoing ERAS treatment, with composite epidural anesthesia being preferred in patients not exhibiting coagulopathy. When such an approach cannot be employed, an ultrasound-guided lower abdomen transversalis fascia plane block (TFP block) is instead conducted.

In randomized controlled studies, epidural analgesia has been associated with significant reductions in hospitalization in patients undergoing hepatectomy, while also being associated with decreased postoperative stress, reduced cardiac load, reduced postoperative intestinal paralysis, and improved protection of lung functionality Jones et al. (2013). However, there is also some evidence that epidural anaesthesia can prolong prothrombin time, resulting in potential hypotension and renal failure. The routine use of epidural anaesthesia thus remains controversial Siniscalchi et al. (2016), Jacquenod et al. (2018), and should only be employed in an individualized manner. For patients in the present study, the option to use epidural anaesthesia was carefully considered prior to surgery, and was only used in patients with normal coagulation function. Epidural anaesthesia doses were also strictly controlled, and patient blood pressure was carefully monitored during surgery to treat hypotension in a timely fashion. The use of epidural anaesthesia in the present study was associated with satisfactory outcomes and with no instances of adverse outcomes. Patients in the ERAS group exhibited lower pain scores at 24, 48, and 72 h post-surgery relative to patients in the traditional treatment group. Given that epidural anaesthesia decreases patient pain, it can also lower their anxiety and discomfort when they rise from bed. As a result, the time to getting out of bed after surgery was significantly lower among patients in the ERAS group relative to the traditional treatment group (21.29 ± 6.29h vs 56.67 ± 9.08h). Bed rest has the potential to contribute to adverse outcomes including muscle atrophy, insulin resistance, and thrombosis, and as such this more rapid resumption of activity may be highly beneficial to these patients. By controlling analgesia and anesthesia in an individualized manner, it is also possible to reduce the incidence of postoperative intestinal paralysis, and early postoperative exercise can further expedite gastrointestinal functional recovery. As such, the observed postoperative gastrointestinal function recovery time for patients in the ERAS group was significantly earlier than that of patients in the traditional treatment group (30.20 ± 5.27h vs 60.42 ± 7.8h). In our study, patients in the ERAS group experienced a postoperative hospital stay of 8.16±1.54 days and hospital costs were ¥44032±10707. Both of these parameters were significantly lower than those in the control group (10.49±3.72 days and ¥50795±10953, $P<0.05$). In the ERAS group in this study, individualized accelerated surgical programs thus played an important role in reducing patient pressure and promoting rapid recovery.

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Malnutrition is independently associated with poor outcomes in patients undergoing major surgery, and this risk factor can be mitigated through appropriate preoperative nutritional support. Patients undergoing ERAS treatment are subjected to the nutritional risk screening 2002 (NRS 2002) tool. When patients score ≥ 3 points on this risk screen, an individualized diagnostic and treatment plan is formulated and appropriate nutritional support is provided. Enteral nutrition remains the preferred treatment strategy for these patients, with parenteral nutrition being used as necessary. After a one-week intervention period, patients undergo follow-up evaluation to determine whether they can tolerate surgery. Postoperatively, patients are subjected to additional nutritional evaluation. Any patients exhibiting malnutrition or nutritional risks are subjected to individualized postoperative nutritional support treatment. Perioperative venous thromboembolism remains a common postoperative complication that can prolong hospitalization, delay patient recovery, increase the risk of mortality, and markedly increase hospitalization costs. Hepatectomy is independently associated with the risk of postoperative pulmonary embolism, and liver tumors are similarly linked to increased venous thrombosis risk Melloul et al. (2012). Both mechanical and pharmaceutical approaches can be used to lower this risk of thrombosis in patients undergoing hepatectomy, with appropriate methods being selected on an individualized basis. Basic and mechanical measures should be used to treat patients with abnormal coagulation or liver insufficiency following surgery, with basic interventions including postoperative limb movements, massage, activity's goal planning, and efforts to increase daily activity in a stepwise manner after surgery. Mechanical interventions include the wearing of anti-thromboelastic compression socks. At present, the prophylactic administration of antithrombotic therapy remains controversial. For patients in the present study, we adopted individualized plans to assess patient condition and to monitor coagulation-related indicators in real-time. For patients treated with pharmaceutical agents, low molecular weight heparin was administered 24 h post-surgery and was continually administered until patients were able to safely and freely move. In order to prevent excessive bleeding in patients that underwent epidural anesthetization, heparin was not administered until 12 h post-catheter withdrawal. Following individualized perioperative thrombosis prevention, we observed no instances of thrombosis or pulmonary embolism among patients in the ERAS treatment group. There are some limitations to the present study. Executing a double-blind study was not feasible, as the differences in perioperative care between patient groups were easily observed. In addition, this was a single-center study, and future multicenter analyses may be necessary. Finally, while individualized accelerated rehabilitation surgery protocols exhibited many advantages over control groups, such as shortening the lower costs, decreased duration of hospitalization, and better recovery, fully understanding the specific advantages of individualized ERAS and traditional ERAS will require further research. Overall, the results of the present study suggest that individualized ERAS interventions can help reduce postoperative pain, hospitalization duration, and hospitalization costs without increasing rehospitalization rates in HCC patients undergoing hepatectomy. Some prior work suggests that accelerated surgical strategies can reduce postoperative complication incidence rates Ni CY et al. (2013), Liang X et al. (2016), Ni TG et al. (2015), although other studies have failed to replicate this finding, He F et al. (2015), Rouxel et al. (2019). We did not detect any significant difference in postoperative complication incidence between patients undergoing traditional treatment and ERAS treatment. Given the potential complexities of liver cancer and the anatomy of the liver and biliary tract, we speculate that accelerated rehabilitation measures alone may not be sufficient to reduce the incidence of complications following surgical resection of this dynamic tissue in liver cancer patients. Individualized ERAS strategies can improve patient compliance and participation in clinical decision-making, but few studies have used defined compliance indicators to fully evaluate the efficacy of this approach. Future studies should thus seek to identify objective measures of patient compliance in order to robustly evaluate the utility of ERAS intervention strategies in defined surgical contexts. In summary, our findings show that individualized ERAS treatment can be safely and effectively employed in patients with liver cancer undergoing hepatectomy.

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