



Enhanced recovery after surgery (ERAS) program in elderly patients undergoing laparoscopic hepatectomy: a retrospective cohort study

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Background: Enhanced recovery after surgery (ERAS) has shown sufficient superiority in terms of cutting down hospital stay and costs, and reducing complications in patients undergoing laparoscopic hepatectomy (LH). However, the benefit of ERAS in elderly patients undergoing LH remains unclear, and clinical studies on this topic are still limited.

Methods: In total, 177 elderly patients (aged over 65 and underwent LH) were divided into two groups. The 107 patients in the control group received standard care, while the 70 patients in the ERAS group underwent the ERAS program after hepatectomy. The primary endpoint was the postoperative hospital stay. The secondary endpoints were resumption of oral intake, readmission rate and complications.

Results: ERAS had a positive effect on reducing length of hospital stay {6 [4–8] *vs.* 9 [7–14] days; $P < 0.001$ }. Although there was no significant reduction of overall complications in the ERAS group compared with the control group (0.500 *vs.* 0.626; $P = 0.097$), the Clavien-Dindo classification of compliances in the ERAS group was lower among the patients with complications (Grade I: 0.829 *vs.* 0.597; $P = 0.018$; Grade II: 0.143 *vs.* 0.328; $P = 0.044$), which indicated that the patients in the control group might experience more severe complications. The readmission rates remained unaffected between the two groups.

Conclusions: Consistent with younger patients, ERAS program is considered to be effective and safe, which can distinctly promote recovery after hepatectomy for elderly patients accepting LH.

Keywords: Enhanced recovery after surgery (ERAS); elderly patients; laparoscopic hepatectomy (LH)

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Introduction

Aging population takes up a vast proportion of the total population worldwide, as the consequence of the rise in human life expectancy. According to the World Population

Prospects, the total population of global world older than 65 has reached 611.90 million, accounting for 8.29% of the total population in 2015 and will reach nearly 1.5 billion in 2050, which does not necessarily mean a prolonged

healthspan but a series of health issues caused by aging (1). The enlarged hepatocytes, growing number of binucleated cells and reduction in mitochondrias are hepatic changes relating to aging, which have an impact on the liver morphology, physiology and metabolism (2). Therefore, the incidence of hepatic diseases that requires hepatectomy is fast rising in elderly patients.

Laparoscopic hepatectomy (LH) was first introduced to resect benign tumors in 1991 by Reich (3) and been further explored by numerous scholars like Wayand [1993], Azagra [1996] and Huscher [1997] (4-6). With the development and recognition of LH technology, it gradually started to involve all kinds of liver surgery even including caudate lobectomy. Although some controversy still remains, the guidelines for LH expands from local resection to major liver resections and are now very similar to those of open hepatectomy (OH). LH is not only more convenient compared to OH, such as decrease in operation time, blood loss and hospital stay, but also have less general complications and surgical complications, such as pulmonary complication, cardiac arrhythmia, renal failure, intra-abdomen bleeding, biliary leakage and subphrenic abscess (7,8). What's more, LH shows no significant differences in disease-free survival and overall survival compared with OH (9). Even though the elderly patients have lower functional reserve of the liver in comparison with the younger patients, numerous studies claimed that LH demonstrated good security and stability similar to OH even in elderly patients, suggesting that age appears less of a risk factor and would not affect the short or the long-term outcome for LH (10-12). However, as the elderly patients are suffering from more underlying diseases, less cardiopulmonary functional reserve, prolonged postoperative recovery time and compromised immunity compared with the youngsters, so it still arouses the attention of the surgeons (13).

Enhanced recovery after surgery (ERAS) is an evidence-based concept and involved in multidisciplinary perioperative care, aiming to shorten hospital length of stay and reduce complication rates in the postoperative period. ERAS fundamentally transforms traditional surgical ward care into standardized care, which emphasizes on preoperative consultations, optimizing nutrition, standardizing analgesia without the use of opioid, minimizing invasive methods to decrease electrolyte and body fluid imbalances, and promoting early mobilization (14). It develops rapidly and is applied in various surgical operations with promising results, for example, colorectal, gastric and pancreatic surgeries (15,16). In 2008, van Dam *et al.* first systematically

explore the role of ERAS program in patients undergoing liver resection (17). For it provides solid evidence of clinical safety and efficacy, then ERAS began to be implemented in many centers in hepatic surgery including laparoscopic liver resections (18). ERAS versus traditional care after laparoscopic liver resections also presented feasible and safe features in our center, but considering that the elderly are a special group, few studies have drawn a conclusion that ERAS could also benefit elderly patients underwent LH (19,20). Therefore, this study aimed to evaluate the practicability and safety of ERAS in elderly patients after LH. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tcr-19-2884>).

Methods

Patient selection

We retrospectively collected information from a cohort of patients over 65 years, who presented for LH from June 2014 to December 2017 at the Department of General Surgery, the Sir Run Run Shaw Hospital, Medical College of Zhejiang University. The inclusion criteria were as follows: (I) aged over 65; (II) underwent LH; (III) Child-Pugh class A or B liver functional status; (IV) ASA (American Society of Anesthesiologists) physical status of I to III; (V) normal coagulation function and albumin level. The exclusion criteria were listed as follows: (I) Child-Pugh class C liver functional status; (II) ASA physical status of IV or V, accompanied by severe major organ dysfunction; (III) a history of abdominal operation. A total of 70 patients followed the ERAS protocol were include as the ERAS group and 107 patients accepted conventional perioperative care were included as the control group. The two groups were consistent in age, gender, Child-Pugh classification, preoperative albumin level, disease type, basic disease, surgical procedures, and ASA physical status. Informed consent was obtained from all individual participants included in this study. Before data collection, the study protocol was evaluated and approved by the Ethical Committees for Human Subjects at Sir Run Run Shaw Hospital Affiliated to Medical College of Zhejiang University. All activities involving human participants in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 Helsinki Declaration and its later amendments or comparable ethical standards. All the patients in this study

provided written informed consent. The ID/number of ethical approval: ZJU20170724.

Clinical pathway

Preoperative care

Patients in ERAS group received respiratory function exercise and 250 mL oral carbohydrate solution two hours before surgery (diabetic take the normal saline of the same quantity in place). Patients in the control group received traditional care, including the routine care, fasting and drinking forbidden for eight hours prior to surgery. No preoperative bowel preparation or any premedication was given in both two groups.

Intraoperative care and anesthesia

Both groups had the same conventional anesthetic condition (combined intravenous and inhalation) and the application of heat preservation nursing. However, patients received extra 0.2% ropivacaine for local anesthesia around trocar incision, restriction of fluid intake (less than 2,000 mL normally), minimizing the application of abdominal cavity drainage tube according to the traumatic condition in the ERAS group. All the surgeries were performed by well-experienced surgeons in our center.

Postoperative treatment

In the ERAS group, patients are encouraged to drink less than 20 mL water six hours after the surgery. If the gastrointestinal function returned to normal with regular peristaltic sound, defecation or break wind, patients began to accept liquid diet on postoperative day (POD) 1 and semiliquid on POD 2. Patients were given nebulization besides the routine therapy with respiratory function training. The urinary catheters were removed at a day after operation, and other drainage tubes were removed as early as possible based on the drainage condition. Patients were encouraged to do more mobilization on POD 1, which helps avoiding deep venous thrombosis and ileus. Fluid infusion was strictly restricted and adjusted by clinical signs, including central venous pressure (CVP), urine output and heart rate (maintenance fluids controlled 2,000–2,500 mL/day or less on POD 1). Intravenous fluids were stopped as soon as adequate intake was achieved. Postoperative analgesia was performed by intravenous analgesic pump combined with intravenous injection of 40 mg ParecoxibNa every twelve hours. Other analgesics usually tramadol was encouraged to be given if pain control was unsatisfied. The gastric

tube was removed and the oral intake was allowed until gastrointestinal function was recovered in traditional group. There was no strict pain management and restriction of the fluid intake, and temporary administration of analgesics was permitted according to the postoperative pain. A summary table of all the clinical pathways was shown in *Table 1*.

Discharge criteria

(I) Normal temperature; (II) tolerance of solid food; (III) defecation or break wind; (IV) physical and chemical examination were normal; (V) good pain control with oral analgesia only; (VI) the basic self-care of life; (VII) all of the above and willing to be discharged.

Outcome measures

Outcome measures including duration of operation, blood loss volume, the application and the duration of postoperative of drainage tube, length of hospital stay (LOS), postoperative pain score, complications (evaluated by Clavien-Dindo classification), and 30-day readmissions were compared between the two groups respectively. The visual analogue scale (VAS) was used for self-rated health state evaluation and pain score of the patients (on a scale from 0 to 10.0), ranging from no pain to the worst pain.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median (range) while categorical variables were expressed as number (%). Correspondingly, continuous variables were compared using Student *t* test to analyze the difference while categorical variables were compared using the Chi-square test or Fisher's exact test. A *P* value of <0.05 was considered statistically significant.

Results

In total, 177 elderly patients who underwent LH were divided into two groups. The 107 patients in the control group received standard care, and the 70 patients in the ERAS group participated in the ERAS program. The patient characteristics were presented in *Table 2*, including gender, ASA grade, liver cirrhosis, and Child-Pugh classification in the two groups. There were also no significant differences in the pathological findings between

Table 1 Clinical pathway (preoperative care, intraoperative care and anesthesia, and postoperative treatment) in the two groups

Clinical pathway	For ERAS	Notion
Preoperative care	(I) Respiratory function exercise	(I) No preoperative bowel preparation or any premedication was given in both two groups
	(II) 250 mL oral carbohydrate solution two hours before surgery (diabetic take the normal saline of the same quantity in place)	(II) Fasting and drinking forbidden for eight hours prior to surgery
Intraoperative care and anesthesia	(I) Extra 0.2% ropivacaine for local anesthesia around trocar incision	(I) Both groups had the same conventional anesthetic condition (combined intravenous and inhalation) and the application of heat preservation nursing
	(II) Restriction of fluid intake (less than 2,000 mL normally)	(II) All the surgeries were performed by well-experienced surgeons in our center
	(III) Minimize the application of abdominal cavity	
Postoperative treatment	(I) Drink less than 20 mL water 6 hours after the surgery	(I) No strict pain management and restriction of the fluid intake
	(II) Accept liquid diet on POD 1 and semiliquid on POD 2 if the gastrointestinal function returned to normal with regular peristaltic sound, defecation or break wind	(II) Temporary administration of analgesics was permitted according to the postoperative pain
	(III) Give nebulization besides the routine therapy with respiratory function training	
	(IV) Remove the urinary catheters at a day after operation, and remove other drainage tubes as early as possible based on the drainage condition	
	(V) Do more mobilization on POD 1, which helps avoiding deep venous thrombosis and ileus	
	(VI) Strictly restricted fluid infusion and adjust it by clinical signs, including CVP, urine output and heart rate (maintenance fluids controlled 2,000–2,500 mL/day or less on POD 1)	
	(VII) Intravenous fluids were stopped as soon as adequate intake was achieved	
	(VIII) Postoperative analgesia was performed by intravenous analgesic pump combined with intravenous injection of 40 mg ParecoxibNa every 12 hours	
	(IX) Other analgesics usually tramadol was encouraged to be given if pain control was unsatisfied	
	(X) The gastric tube was removed and the oral intake was allowed until gastrointestinal function was recovered in traditional group	

ERAS, enhanced recovery after surgery; POD, postoperative day, CVP, central venous pressure.

the two groups (*Table 2*).

The operative details and outcomes are shown in *Table 3*. The operative time was 185 [115–240] minutes in the ERAS group and 200 [125–263] minutes in the control group ($P=0.184$). The intraoperative blood loss volume was 100 [50–300] mL in the ERAS group and 200 [100–400] in the control group ($P=0.025$), and the blood transfusion

was needed during the operation in 15 patients (ERAS group) and in 25 (control group), respectively ($P=0.763$). Nasogastric decompression tubes were used in 7 of 70 patients (ERAS group) and 15 of 107 patients (control group) ($P=0.428$). In the ERAS group, abdominal drainage tubes were used for shorter time (22/41 *vs.* 7/96 for ≤ 3 days; $P<0.001$). Oral intake was usually resumed

Table 2 Characteristics of the patients at baseline

Variables	ERAS (n=70)	Traditional care (n=107)	P*
Age (years)	69.5 (67.0–74.3)	69.0 (66.0–74.0)	0.753
Sex ratio (F:M)	23/47	32/75	0.678
Primary disease			0.904
Cirrhosis	17	25	
Hypertension	33	44	
Diabetes mellitus	15	18	
Cardiovascular disease	6	5	
Others	30	45	
Child-Pugh			0.762
A	67	100	
B	3	7	
Type of hepatectomy			0.913
≥4 segments	23	36	
<4 segments	47	71	
ASA			0.956
I	0	0	
II	58	89	
III	12	18	
ALB	38.5±4.5	39.3±4.2	0.215
Liver pathology			0.636
Hepatocellular carcinoma	41	50	
Metastatic hepatic carcinoma	5	6	
Cholangiocellular carcinoma	7	18	
Hepatolithiasis	11	21	
Hepatic hemangioma	1	2	
Others	5	10	

*, P<0.05 is considered statistically significant. ERAS, enhanced recovery after surgery; ASA, American Society of Anesthesiologists; ALB, albumin.

within six hours after surgery in the ERAS group. The median time until semiliquid diet resumption was 2 [1–2] days in the ERAS group which was a day quicker than that in the control group (P<0.001). The median hospital stay of patients in ERAS group was 6 [4–8], and 9 [7–14] in the control group (P<0.001). The readmission rates (<30 days) were similar in the ERAS and control group (1 *vs.* 4 patients, respectively; P=0.658).

Complications after LH are shown in *Table 4* and no

death was attributed to hepatectomy in two groups. The complications were evaluated using the Clavien-Dindo classification. Thirty-five of 70 patients in ERAS group had varying degrees of complications, while 67 of 107 patients in the control complained for the complications (P=0.097). However, for all patients with complications, only small proportion of patients (40 of 67 patients) in the control group were grade I complications, which was significantly lower than the ERAS group. The pain scores were used to

Table 3 Operative details and outcomes

Outcomes	ERAS (n=70)	Traditional care (n=107)	P*
Conversion to laparotomy	2	7	0.459
Operative time (min)	185 [115–240]	200 [125–263]	0.184
Blood loss (mL)	100 [50–300]	200 [100–400]	0.025
Blood transfusion (No. of patients)	15	25	0.763
Blood plasma only	3	1	0.342
Multiple blood components	12	20	0.793
Abdominal drainage tube (No. of patients)	63	103	0.171
No. of abdominal drainage tube (≥ 2)	7	45	<0.001
Duration of abdominal drainage tube (≤ 3 days)	22	7	<0.001
Nasogastric tube (No. of patients)	7	15	0.428
Semiliquid diet after surgery (d)	2 [1–2]	3 [2–5]	<0.001
Length of hospital stay (d)	6 [4–8]	9 [7–14]	<0.001
Readmission rates (<30 days)	1	4	0.658

*, P<0.05 is considered statistically significant. ERAS, enhanced recovery after surgery.

Table 4 Summary of complications

Complications	ERAS (n=70)	Traditional care (n=107)	P*
Patients with complications	35	67	0.097
Clavien-Dindo classification			
GRADE I	29	40	0.018
GRADE II	5	22	0.044
GRADE IIIa	1	3	1.000
GRADE IIIb	0	1	1.000
GRADE IVa	0	0	–
GRADE IVb	0	1	1.000
GRADE V	0	0	–

*, P<0.05 is considered statistically significant. ERAS, enhanced recovery after surgery.

evaluate the effect of analgesia (*Table 5*). On days 1, 3 and 5, the mean pain score in the ERAS group was significantly lower than that in the control group (P<0.001 on day 1 and day 3, P<0.05 on day 5).

Discussion

This study has demonstrated that ERAS program in LH for elderly patients certainly improved patients' recovery by reducing LOS and causing less complications in an

experienced center.

Since ERAS programs were first introduced by Kehlet (21) in colon surgery, recent studies have increasingly shown that ERAS programs are widely used in various surgical operations including hepatectomy, and concluded that ERAS programs manifested a significant decrease in hospital stay, costs and complications (22,23). Liang *et al.* performed a randomized controlled trial to show that LOS after laparoscopic liver resection was three days shorter in ERAS (5 *vs.* 8 days; P<0.001) as well as the less economical

Table 5 Comparison of pain scores on postoperative day 1–5 between two groups

Pain scores	ERAS (n=70)	Traditional care (n=107)	P*
POD1 (No. of patients)	68	97	0.170
VAS Score	2 [1–2]	2 [1.5–2]	0.001
No. of patients (VAS ≥4)	0	3	0.383
POD3 (No. of patients)	66	99	0.881
VAS Score	1 [1–2]	2 [1–2]	<0.001
No. of patients (VAS ≥4)	0	1	1.000
POD5 (No. of patients)	49	92	0.010
VAS Score	1 [1–1]	1 [1–2]	0.042
No. of patients (VAS ≥4)	0	1	1.000

*, P<0.05 is considered statistically significant. ERAS, enhanced recovery after surgery. VAS, visual analogue scale.

cost (China Yuan 45,413.1 *vs.* 55,794.1; P=0.006) and lower incidence rate of complications (36.2% *vs.* 55.7%; P=0.033) (19). Similar results were also reported by He *et al.*, which supported that the ERAS group was four days shorter in LOS and less expensive in comparison with the control group (24). Thus, we can draw a conclusion that the application of ERAS in LH can effectively improve prognosis and speed recovery. However, as life expectancy extends, the number of elderly people who need surgery for liver disease increases. And age is often considered a risk factor for prognosis, accompanied by high rates of complications and mortality (25–28). The ERAS protocols have a series of evidence-based care elements. The common purpose of all the elements is to reduce the bodily stress reactions caused by injury and support recovery, such as postoperative analgesia and restriction of fluid intake, which proved to have beneficial effects on the recovery. For elderly, who are always vulnerable patient with comorbidities, these reductions in the stress responses are of particular importance (29). Few studies have shown whether ERAS program is also feasible in elderly people underwent LH.

In this study, we applied the ERAS program to elderly patients (aged ≥65 years) who received LH to validate whether this concept was feasible. No significant differences were observed between two groups in the duration of operation, blood loss volume, rate of intraoperative blood transfusion, which means that ERAS does not appear to raise the risk of LH.

ERAS program requires short duration of abdominal drainage tube and early feeding time. Our patients

from ERAS group had a shorter duration of abdominal drainage tube compared with traditional group (22/41 *vs.* 7/96; ≤3/>3 days; P<0.001), which is helpful for reducing the psychological and physiological burden of the patients. Therefore, the patients are able to get out of bed early, speed up recovery of gastrointestinal function, and reduce potential infections at the same time and finally cut down the length of hospitalization. ERAS program does not require bowel preparation before surgery, which may avoid body fluid loss and electrolyte disorder inducing by bowel preparation in the conventional procedure (30). In addition, we required patients to start earlier eating moderate amount of food {2 [1–2] *vs.* 3 [2–5]; P<0.001} after the operation. It is believed that instead of bowel preparation, taking 250 mL carbohydrate solution 2 hours before surgery can eliminate the uncomfortable feelings caused by anxiety, hunger and insulin resistance (31). Early postoperative feeding was also initiated at 6 hours after surgery in order to reduce stress, energy expenditure and complications such as nausea, vomiting or enteroparalysis.

Considering that all included patients were over 65 years old, our study drew different conclusions from previous studies concerning ERAS programs (20,25). We found that no difference was observed in terms of the overall compliance (0.500 *vs.* 0.626; P=0.097). Further analysis found that ERAS group had a significant rise of grade I/II Dindo-Clavien's postoperative complications when compared with the control group. It is possible that in elderly patients, poorer physical condition might increase the possibility of complications (27). But serious accidents can be avoided in the elderly if they are benefited from the ERAS protocol.

Pain control is crucial in patients undergoing ERAS. Different from other center offering epidural anesthesia to control postoperative pain, our patients received extra 0.2% ropivacaine for local anesthesia during surgery. And a combination of patient-controlled intravenous anesthesia and intravenous parecoxib sodium (40 mg) every twelve hours was used after surgery. Consequently, complications related to epidural anesthesia can be avoided (28,30). The pain scores were lower in the ERAS group than that in the control group throughout the whole course of postoperative rehabilitation {POD 1: 2 [1–2] *vs.* 2 (1.5–2), $P=0.001$; POD 3: 1 [1–2] *vs.* 2 [1–2], $P<0.001$; POD 5: 1 [1–1] *vs.* 1 [1–2], $P=0.042$ }. Consistent with the previous studies, ERAS protocol provides good pain control which can reduce pain and stress of the elderly patients (19,20,23,31).

Due to the shorter duration of abdominal drainage tube, earlier feeding time, less serious complications and more comfortable pain control, the ERAS group had a shorter LOS than the control group {6 [4–8] *vs.* 9 [7–14] days; $P<0.001$ }. Some studies showed that ERAS programs could improve short and long-term outcomes by reducing stress, which was also observed in our study. The readmission rates between two groups remained unaffected (0.014 *vs.* 0.037; $P=0.658$). These readmission rates are considerably good to support the opinion that ERAS is a feasible and secure option for the elderly patients undergoing LH.

Nevertheless, several limitations should be mentioned. Since this is a retrospective study, reporting real-life clinical practice rather than selected trial patients might lead to potential bias. The two cohorts had limited samples included and not standardized or strictly matched, which might not summarize a solid conclusion. More high-quality, multiple-center, large-sample randomized controlled trials are required in future studies.

Conclusions

ERAS protocol is safe and feasible for elderly patients presented for LH. Elderly patients in ERAS group have less hospital stay and complications. Therefore, we hold the opinion that the ERAS program is considered to be more effective and safer, which can promote recovery than conventional care for elderly patients underwent LH.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Before data collection, the study protocol was evaluated and approved by the Ethical Committees for Human Subjects at Sir Run Run Shaw Hospital Affiliated to Medical College of Zhejiang University. All activities involving human participants in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 Helsinki Declaration and its later amendments or comparable ethical standards. All the patients in this study provided written informed consent. The ID/number of ethical approval: ZJU20170724.

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