

ERAS in minimally invasive hepatectomy

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Open hepatectomy is associated with significant post-operative morbidity and mortality profile. The use of minimally invasive approach for hepatectomy can reduce the post-operative complication profile and total length of hospital stay. Enhanced recovery after surgery (ERAS) programs involve evidence-based multimodal care pathways designed to achieve early recovery for patients undergoing major surgery. This review will discuss the published evidence, challenges and future directions for ERAS in minimally invasive hepatectomy. (**Ann Hepatobiliary Pancreat Surg 2020;24:119-126**)

Key Words: Enhanced recovery; Minimally invasive; Hepatectomy

INTRODUCTION

Traditionally, open hepatectomy is associated with significant post-operative morbidity (15-50%) and mortality (<5%).¹⁻⁴ Post-operative complications will prolong hospital stay and patient suffering, and has a negative impact on long-term survival following hepatectomy for malignant conditions.^{5,6}

Minimally invasive surgery (MIS) for hepatectomy is now an established technique, and has become a feasible procedure for liver resections.⁷⁻¹⁰ It is important to identify patient treatments that could further improve patients' post-operative recovery and reduce complications after MIS hepatectomy.¹¹

Enhanced recovery after surgery (ERAS) programs have been shown to reduce morbidity rates and total hospital stay in colorectal surgery.¹² The aims of ERAS programs are the earlier return to normal homeostasis and functional activities by the implementation of therapies to reduce the physiological consequences of peri-operative surgical stress (Table 1).¹³ Pre-habilitation is the process of pre-operative patient optimisation with particular focus on physiotherapy, nutritional support and psychological preparation for major surgery.^{14,15}

The evidence for using ERAS in MIS hepatectomy re-

mains unclear. This review will focus on the role of ERAS within a MIS hepatectomy clinical pathway.

PUBLICATION SEARCH

A literature search of MEDLINE, PubMed, EMBASE was performed by the first author (AKYF) in August 2019 using the terminology of ERAS, enhanced recovery, liver resection, hepatectomy, fast track, enhanced rehabilitation, hepatic and hepatobiliary. The language of the literature was restricted to English.

ERAS PRINCIPLES AND OBJECTIVES

The pillars of ERAS include patient and healthcare provider engagement in shared decision-making, early enteral nutrition, goal-directed fluid therapy, avoidance of intra-abdominal drainage catheters and early post-operative mobilisation.¹⁶ In cancer surgery, rapid recovery after surgery is important to facilitate early initiation of adjuvant oncological therapies. ERAS programs can achieve this objective and potentially confer improvements in long-term cancer survival.^{17,18}

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Table 1. Mechanisms of ERAS programs in hepatectomy¹⁶

	ERAS treatment	Mechanism of action
Patient psychological preparation	Pre-habilitation	Pre-operative counselling Social support
Peri-operative hyperglycaemia and insulin resistance	Carbohydrate pre-loading	Reduce insulin resistance
Stress of prolonged fasting	Shortened duration of pre-operative fasting	Reduce insulin resistance
Post-operative pain	Aggressive pain control	Reduce inflammatory response to surgery
Prevention of post-operative ileus	Use of NSAID analgesia Early enteral nutrition	Reduce inflammatory response to surgery
Post-discharge planning	Regular assessments by surgical and nursing teams	Physical, social and psychological support

ERAS AND OPEN HEPATECTOMY

There is increasing interest and published experience describing the application of ERAS principles to hepatectomy.^{10,19,20} van Dam et al.²¹ first reported the outcomes for ERAS in open liver resection. The study concluded that there was a two-day reduction in the median hospital stay ($p < 0.001$) for patients who underwent the ERAS pathway.

ERAS programs in liver surgery can reduce complication rates by 30-60% compared to traditional post-operative care, and without an increase in re-admission rate. Several clinical trials have demonstrated the safety of ERAS combined with open hepatectomy.^{8,22,23}

Furthermore, mean duration of hospital stay and time to functional recovery can be reduced by 2.3 days^{9,10,24-28} and 2.5 days respectively.²⁹ A meta-analysis on ERAS with open hepatectomy has also reported significant reductions in post-operative complications and hospital stay.²⁷

ERAS AND MIS HEPATECTOMY

There is increasing use of minimal invasive surgical (MIS) approach to hepatectomy. MIS hepatectomy has many advantages over traditional open hepatectomy, including reduced intra-operative blood loss, hospital stay and earlier return to functional activities,³⁰⁻³² and has become standard practice for minor liver resections, especially left lateral sectionectomies.³³

The additional contribution of ERAS with MIS hepatectomy remains unclear.²¹ The combination of MIS hepatectomy with ERAS programs might have additional synergistic benefits for patients compared with MIS approach

alone.^{34,35} Laparoscopic liver resection (LLR) combined with ERAS has been shown to reduce median hospital stay by two days compared to standard LLR alone.³⁶

ERAS AND MIS HEPATECTOMY: PUBLISHED LITERATURE

There are several published studies on ERAS and MIS hepatectomy (Tables 2, 3). Stoot et al.³⁶ reported the outcomes of a pilot series of laparoscopic liver resections with and without ERAS. Thirteen patients underwent laparoscopic liver resections with ERAS and these patients had quicker return to functional recovery by two days ($p=0.04$). However, this finding was not transferred to a shorter hospital stay in the ERAS group, with similar median hospital stay between ERAS and non-ERAS groups (5 vs. 7 days, $p=0.3$).

Liang et al.³⁷ reported eighty cases of laparoscopic liver resection within an ERAS program. Median post-operative hospital stay was 6.2 days compared to 9.9 days in the conventional group ($p < 0.001$). These outcomes were similar to He et al.³⁸ who reported on eight-six cases of laparoscopic hepatectomy with ERAS: there was a reduction in post-operative hospital stay of two days ($p < 0.04$). Sánchez-Pérez et al.³⁹ did not find a statistically difference in the median post-operative hospital stay for laparoscopic liver resection with ERAS compared to standard care (2.5 vs. 3 days, $p > 0.05$).

Ratti et al.⁴⁰ compared the outcomes for MIS hepatectomy versus open hepatectomy within an ERAS program using propensity matching. Mortality was similar between the two groups, with lower morbidity in the MIS group (31.4 vs. 38.2%, $p=0.05$). Median length of hospital stay

Table 2. Published randomised clinical trials on ERAS and MIS hepatectomy

	Stoot et al. ³⁶ 2009	Sánchez-Pérez et al. ³⁹ 2012	He et al. ³⁸ 2015	Liang et al. ³⁷ 2016	Wong-Lun-Hing et al. ⁴¹ 2017
Day before surgery	Pre-surgery education Normal oral nutrition until midnight	Pre-surgery education	Pre-surgery education Avoid laxatives	Pre-surgery education No routine bowel preparation	Pre-surgery education No pre-anaesthetic medication
Day of surgery	No pre-anaesthetic medication Pre-operative oral glucose administration 2 hours before operation Mid-thoracic epidural anaesthetist and short-acting anaesthetics Avoidance of peri-operative fluid overload Non-opioid analgesia	No liquid intake 8 hours before operation Administration of anaesthetic premedication Control of intra-venous fluids Remove nasogastric tube at the end of operation No urinary catheters if operation time < 180 minutes No routine abdominal drainage Oral intake 6-8 hours after operation Mobilisation 6-8 hours after operation Analgesia: intravenous metanzol every 8 hours and intravenous paracetamol every 8 hours	Reduce fasting time to 2 hours Preoperative oral glucose administration Antibiotic prophylaxis Nausea and vomiting prophylaxis No routine nasogastric or abdominal drainage	Pre-operative oral glucose administration 2 hours before operation No routine nasogastric tube or abdominal drainage	Pre-operative oral glucose administration 2 hours before operation Mid-thoracic epidural anaesthetist and short-acting anaesthetics Avoidance of peri-operative fluid overload No routine nasogastric or abdominal drainage Restart oral intake of water/nutrition
Post-operative D0	Restart oral intake of water/nutrition <i>ad libitum</i>	Oral intake 6-8 hours after operation Mobilisation 6-8 hours after operation Analgesia: intravenous metanzol every 8 hours and intravenous paracetamol every 8 hours	Water intake 4 hours after operation Liquid diet 12 hours after operation Restrict intravenous fluid to < 2500 mls/day	Drink water 6 hours after operation Fluid restriction to < 2500 mls Patient controlled intravenous analgesia	Restart oral intake of water/nutrition
Post-operative D1	Mobilisation four times a day Cessation of intravenous fluids Patient oral fluid intake > 1500 mls Normal diet Continue portable epidural analgesia 1 g panadol every 6 hours 1 g magnesium oxide twice dailt	Drain removal within 24-48 hours Analgesia: oral administration	Removal of urinary catheter Thoracic epidural Daily review of discharge criteria	Oral nutritional supplements Mobilisation twice a day Removal of urinary catheter Reduce intravenous fluids	Mobilisation four times a day Cessation of intravenous fluids Patient oral fluid intake > 1500 mls Normal diet Removal of urinary catheter Continue portable epidural analgesia 1 g paracetamol every 6 hours Start laxatives

Table 2. Continued

	Stoot et al. ³⁶ 2009	Sánchez-Pérez et al. ³⁹ 2012	He et al. ³⁸ 2015	Liang et al. ³⁷ 2016	Wong-Lun-Hing et al. ⁴¹ 2017
Post-operative D2	Continue portable epidural analgesia Stop low dose opioids Mobilisation four times a day 1 g paracetamol every 6 hours Normal diet	Daily review of discharge criteria	Daily review of discharge criteria	Stop intravenous analgesia Start oral tramadol or celecoxib Stop intravenous fluids Mobilisation four times a day Remove abdominal drain (if any) Mobilisation Normal diet Daily review of discharge criteria	Continue portable epidural analgesia Mobilisation four times a day Stop opioids 1 g paracetamol every 6 hours Normal diet Laxatives Stop epidural analgesia or PCA Start non-steroidal anti-inflammatory drug Mobilisation Daily review of discharge criteria
Post-operative D3 (+4)	Start non-steroidal anti-inflammatory drug Stop epidural catheter Removal urinary catheter Mobilisation Normal diet Daily review of discharge criteria	Daily review of discharge criteria	Daily review of discharge criteria		

Table 3. ERAS and MIS hepatectomy: clinical outcomes of the published literature

Study	Number of patients	Type of liver resection	Primary outcome	Study result
Stoot et al. ³⁶ 2009	13 ERAS	Laparoscopic left lateral sectionectomy and minor resections	Total length of hospital stay (LOS)	Median LOS reduced in ERAS (5 vs. 7, $p > 0.05$)
Case control study	13 conventional group			
Sánchez-Pérez et al. ³⁹ 2012	26 ERAS	Laparoscopic minor resections for benign and malignant disease	LOS	Median LOS shorter in ERAS (3 vs. 2)
Case control study	17 conventional group		Readmission rate Morbidity Mortality	Readmission rate (3.8% vs. 5.8%, $p > 0.04$) Morbidity 11.5% vs. 11.8%, $p > 0.05$) Mortality (nil in both groups)
He et al. ³⁸ 2015	48 ERAS	Laparoscopic left lateral sectionectomy or wedge resection	Quality of life Length of stay	Median LOS reduced in ERAS (6 vs. 10, $p = 0.04$) QoL better in ERAS ($p = 0.04$)
Randomised control trial	38 conventional group			
Liang et al. ³⁷ 2016	80 ERAS	Laparoscopic major and minor resections	LOS Hospital expense	Median LOS reduced in ERAS (6 vs. 10, $p < 0.001$) reduced hospital costs ($p = 0.002$)
Observational study	107 comparison group			
Wong-Lun-Hing et al. ⁴¹ 2017	11 open left lateral sectionectomy	Laparoscopic versus open left lateral sectionectomy within ERAS program	Time to functional recovery	RCT stopped due to slow patient recruitment
Randomised control trial	13 laparoscopic left lateral sectionectomy			

and time to functional recovery was also shorter by two days in the MIS group ($p=0.04$). Finally, the ERAS protocol adherence rate was higher in the MIS group (83 vs. 77%), which could reflect the greater patient motivational levels in the ERAS group. The researchers also reported that the lower incidence of post-operative complications was directly related to higher rates of compliance to the ERAS pathway.

The ORANGE II (open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery after surgery programme) randomised control trial aimed to analyse the outcomes of laparoscopic versus open left lateral sectionectomy within an ERAS setting.⁴¹ The primary outcome of this RCT was the time to functional recovery. One hundred and four patients were considered eligible for the study, but only twenty-four patients underwent the study interventions (eleven patients had open surgery and thirteen had laparoscopic surgery). There was no statistically significant difference in time to functional recovery between the open and laparoscopic ERAS groups (3 vs. 3 days, $p=0.28$), and also no difference between the ERAS and control (non-ERAS) groups. The trial also reported 40% patients stayed in hospital beyond the time of functional recovery, with logistical reasons accounting for 46%. Unfortunately, the clinical trial was stopped early due to poor patient recruitment and the additional role of ERAS with minor hepatectomy could not be determined.

Yang et al.²⁶ performed a meta-analysis to evaluate the efficacy and safety of ERAS versus traditional care in laparoscopic hepatectomy. Eight studies were included in the meta-analysis, incorporating 580 patients. The ERAS group had faster return to first diet intake and flatus after surgery, reduced post-operative hospital stay and complication rates.

THE POTENTIAL PHYSIOLOGICAL BENEFITS AND CHALLENGES OF ERAS IN MIS HEPATECTOMY

Major fluid shifts can occur during hepatectomy, and patients with cirrhosis are especially sensitive to these fluid shifts. The maintenance of euvolaemia is critical for preservation of renal function and preventing ascites.³⁴ One component of an ERAS program in liver surgery is goal-directed fluid therapy, which includes treatments such as

low central venous pressure and reduced intra-operative fluid loading. This results in reduced operative blood loss, which is associated with reduced liver-specific surgical complications.⁴²⁻⁴⁵

The presence of abdominal drains after hepatectomy can inhibit early post-operative mobilisation and increase wound discomfort.⁴⁶⁻⁴⁹ Additionally, nasogastric tube placement after liver resection has been also shown to increase post-operative surgical and pulmonary complications and patient discomfort.^{50,51} These two interventions are often avoided in ERAS programs for liver resection.^{36-39,41}

The challenges of ERAS programs in liver resection are multi-fold. For major liver resections, the risk of liver failure and bile leak is increased.⁵² The liver itself might be cirrhotic, which can predispose to both post-operative ascites and haemorrhage after open hepatectomy. Conversely, in cirrhotic patients undergoing MIS liver resections, there is preservation of porto-systemic shunts with no increase in portal pressure and subsequent reduction of post-operative ascites and bleeding.⁵³ ERAS protocols might also be beneficial to cirrhotic patients by the omission of the overnight fasting and carbohydrate preloading can diminish the nutritional stress for this patient group.⁵⁴

Appropriate analgesia is an important aspect of an ERAS program. Epidural analgesia is a highly effective treatment after surgery.⁵⁵ However, in liver surgery, patients can experience transient coagulopathy and epidurals can also prolong the prothrombin time after operation.⁵⁶ Furthermore, epidural analgesia was associated with increased risk of blood transfusion without any reduction in the risk of post-operative complications or length of hospital stay.^{57,58} Presently, there are no optimal analgesia regimens for post-hepatectomy patients.²⁶

Nutrition remains a key component of the ERAS pathway to combat the catabolic phase and the increased septic risk after hepatectomy.⁵⁹ Patients undergoing hepatectomy can experience wide fluctuations in the blood glucose levels, secondary to transient insulin resistance. Hyperglycaemia can negatively impact on post-operative recovery. Pre-operative carbohydrate loading as part of ERAS program can help ameliorate the effects of transient insulin resistance and the prolonged fasting state encountered as part of traditional pre-operative care.^{60,61} However, the published literature regarding carbohydrate loading before hepatectomy is lacking.¹⁶ Nonetheless, early feeding

and rapid progression to normal diet after hepatectomy is highly encouraged.^{34,62}

Despite the evidence-based advantages of ERAS programs for major surgery, certain components of ERAS are more easily applied, as they are part of standard clinical routines, such as prophylactic antibiotic treatment and MIS approach. Other aspects of ERAS programs will require change from usual practice, including intra-operative fluid restrictive regimes, no intra-peritoneal drainage catheters and non-opioid based analgesia.⁶³ In light of the challenges in achieving strict compliance to ERAS protocols, perhaps flexibility and a tailored approach might still result in satisfactory outcomes.⁶⁴

Barriers to the initiation and establishment of ERAS programs include lack of clinical manpower and belief in the ERAS philosophies, lack of communication and collaboration between stakeholders, and an inherent resistance to change in clinical practice.⁶⁵

FUTURE DIRECTIONS FOR ERAS IN MIS HEPATECTOMY

There remains significant heterogeneity and patient case-mix in the published meta-analyses regarding ERAS and hepatectomy.²⁹ Unfortunately, future clinical studies comparing ERAS and traditional care pathways after liver resection might be considered unethical because ERAS protocols already contain evidence-based treatments that reduces surgical stress and post-operative catabolism.^{21,36}

The ERAS literature has historically reported outcomes based on length of hospital stay (LOS) and post-operative complications.⁶⁶ Some studies have highlighted the difference between readiness for discharge and actual LOS, as an issue that needs addressing in future ERAS programs.¹⁸ The difference in LOS might be more significant if these delays in hospital discharges can be avoided.³⁶

The use of patient-centred outcome measures might provide a more accurate assessment of the success of an ERAS program.¹⁷ Consistent definitions of these outcome parameters will assist in future ERAS-orientated research, whilst systematic audit and appraisal will be important for improving compliance with these outcomes measures.^{31,63,65,67}

Future research directions for ERAS and MIS hepatectomy might include the long-term data regarding the effects of ERAS on oncological outcomes. There is also

increasing utilisation of the robotic platform for MIS hepatectomy, but presently, there is no proven advantage of robotic liver resection with ERAS.⁶²

CONCLUSION

MIS hepatectomy has been shown to decrease hospital stay and post-operative complications, with faster return to baseline function when compared to open hepatectomy.

ERAS programs in MIS hepatectomy can reduce the physiological stress of hepatectomy with the combination and synergistic benefits of small wounds, less post-operative pain and analgesia requirements. There will be less post-operative ileus as a consequence of restrictive intravenous fluid regime,⁶⁸ early enteral nutrition,³⁴ reduce use of analgesia that could affect gut motility,⁶⁹ early mobilisation, avoidance of nasogastric tube⁵⁰ and abdominal drainage.⁴⁶⁻⁴⁸ The challenge for hepatobiliary surgical teams is the integration of both MIS approach and ERAS to maximise the patient benefits.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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