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Adherence to early mobilisation: Key for successful enhanced recovery after liver resection

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Abstract

Background: Enhanced Recovery After Surgery (ERAS) has been proven effective in liver surgery. Adherence to the ERAS pathway is variable. This study seeks to evaluate adherence to key components of an ERAS protocol in liver resection, and identify the components associated with successful clinical outcomes.
Method: All patients undergoing liver resections for two consecutive years were included in our ERAS pathway. Six key components of ERAS included preoperative assessment, nutrition and gastrointestinal function, postoperative analgesia, mobilisation and discharges. Successful accomplishment of ERAS was defined as hospital discharge by postop day (POD) 6. Adherences of these elements were compared between the successful and un-successful groups.
Results: During the studied period, 223 patients underwent liver resections, among which 103 had major hepatectomies. N = 147 patients (66%) were discharged within our ERAS protocol target (6 days). On multivariable analysis, sitting out of bed by POD 1 ($p < 0.03$), walking by POD 3 ($p = 0.03$), removal of urinary catheter by POD 3 ($p < 0.01$), and avoiding major complications ($p < 0.01$) were factors associated with successful completion to our ERAS protocol; whereas advanced age ($p = 0.34$) and discontinuation of PCA/epidural by POD 3 ($p = 0.50$) were not significant parameters. There was a significant difference in the length of stay ($p < 0.01$) following major and minor liver resection, of which the indications for surgery also varied significantly. There was no difference in hospital re-admission rate, and morbidity and mortality between major and minor liver resection.
Conclusions: Facilitating early mobilisation and reducing postoperative complications are keys to successful outcomes of ERAS in liver resection.

Keywords: Enhanced recovery; Liver surgery

Introduction

Enhanced Recovery After Surgery (ERAS) is a 'fast-track' recovery process that has been proven effective in liver surgery as well as a variety of clinical settings including colorectal, urological and vascular surgery.[1–5] It has been shown to be effective in reducing complications, hospital stay, and delivery cost efficiency for surgical care.[5] It focuses in utilising a multimodal recovery strategy to minimise trauma of surgery, and accelerate postoperative recovery.[6]

Uptake of ERAS in liver surgery was slower to other surgical specialties owing to concerns adopting its methods. A systematic review in 2012 identified only six studies on ERAS during hepatobiliary surgery,[7] and all of these studies were limited in terms of patient numbers.[8] More recently, larger series have been published on ERAS following hepatectomy.[2,9–11] However, despite reporting on 'consecutive hepatectomies', with the exception of Dunne et al., all these series had exclusion criteria, including biliary reconstruction, hilar cholangiocarcinoma, and advanced age.[9–11] The majority of these studies aimed

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to evaluate whether ERAS was feasible following liver surgery. A limited number of studies reported the outcomes of a true consecutive cohort of patients undergoing hepatectomy within an ERAS program.[11,12]

Having all these multimodal approaches combined into a single clinical pathway, it is difficult to fully ascertain which key components within the pathway dictate outcome. This study seeks to evaluate adherence to key components of an ERAS protocol in liver resection, and identify the components associated with successful clinical outcomes.

Materials and methods

Study cohort

We fully implemented our ERAS pathway for all patients undergoing hepatectomies in May 2010.[2] Our ERAS pathway has previously been described but is summarised in Table 1.[2]

All patients undergoing elective hepatectomy, including both laparoscopic and open surgeries, between May 2010 and June 2012 were included in our study. All data were prospectively collected. Data collected included adherence to six key elements of the ERAS protocol. These are preoperative assessment, operative factors, postoperative mobilisation, nutrition, postoperative analgesia and discharges. Operative factors include major/minor resections, type of operations and postoperative complications, which were classified according to the Dindo–Clavien classification.[13] Major complication was defined as having complications of Grade IIIb or above. Major hepatectomy is defined as liver resection for 3 or more consecutive segments.[14]

Preoperative assessment and risk stratification

Our integrated ERAS pathway commences at the hepatobiliary specialist multi-disciplinary team (sMDT) meeting, where patients are identified for surgical interventions. Postoperative social circumstances for each patient were addressed by our clinical specialist nurses prior to surgery.

Following formal preoperative assessment, an individualised perioperative care plan was developed in conjunction with the sMDT decision. This was further stratified based on a combination of anaesthetic review, and the results of Cardio-Pulmonary Exercise Test (CPET), if performed. Patients were classified as low, intermediate, or high-risk by a dedicated liver anaesthetist. This was in part subjective, but all patients with a relative oxygen uptake of <11 ml/kg/min on preoperative CPET were automatically classified as high-risk.[15] All high-risk patients were electively admitted to the critical care unit following surgery, whereas patients categorised as low risk were admitted to standard ERAS ward care. Intermediate risk patients could be admitted to the standard ERAS ward at the discretion of the specialist liver anaesthesiologist.

Table 1
Summary of ERAS pathway for liver resection.

Time point	Goals
Referral	• Discussion of referral and review of all imaging in MDT
First clinic appointment	• Patient education initiated, discussion of the full care pathway with internet video illustration • Discussion of intended operative intervention, and the associated risks and complications
Preoperative assessment	• Cardio-pulmonary exercise testing • Assessment in preoperative clinic • Review by dedicated liver anaesthetist, and discuss postop analgesia option
Day of admission	• Review of operative intervention, risks and expected outcomes. • Review of expectations of enhanced recovery
Day of surgery	• Minimise use of drains • No nasogastric tube use • Selective critical care admission post surgery • Commence oral fluid • Sit out of bed postop, if possible
Postop day 1	• Sat out of bed at least 8 h • 4 walks of 30 m or more • Respiratory physiotherapy review • Review by acute pain team • Commence full diet as tolerated • Discharge planning meeting
Postop day 2	• Maintain oral intake • If epidural in use place Fentanyl patch (25 mcg/h) at 22:00 • If PCA aim to convert to oral analgesia • Sat out of bed at least 8 h • 4 walks of 40 m or more
Postop day 3	• Removal of epidural analgesia • Discontinue supplemental oxygen if saturations within normal range. • Maintain oral intake • Sat out of bed at least 8 h • 4 walks of 60 m or more • Plan discharge
Postop day 4–6	• Maintain oral intake • Sat out of bed at least 8 h • 4 walks of 60 m or more Discharge if: • Tolerating full oral intake • Pain adequately controlled • Passing flatus and urine normally • Normal routine observations • Independently mobile and deemed safe for discharge • Patient and family happy for discharge
Day 1 post discharge	• Phone review with cancer specialist nurse (CNS)

Anaesthetic management

Patients were allowed to eat and drink until 6 h preoperatively, with clear fluids only 2 h before surgery. All patients undergoing hepatectomy had a thoracic epidural for postoperative analgesia, unless contraindicated or patient's choice (see below). Two large bore cannulas, internal jugular central venous lines, and urinary catheter were used prior to intervention. Cardiac output monitoring was used to guide fluid management and optimize organ perfusion. The pulse contour continuous cardiac output (PiCCO) was used for high-risk resections, and a bolus indicator cardiac monitor (LiDCO) for lower risk resections.

Low CVP level was achieved with a combination of thoracic epidural, fluid restriction pre- and intra-operatively, and nitrate infusion if required. All patients had prophylactic antibiotics at induction of anaesthesia using cefuroxime and metronidazole. Hypothermia was prevented by routine intra-operative monitoring and the use of an air-warming system. Calf compression stockings and devices were used intra-operatively for venous thrombotic prophylaxis. Glycaemic control was monitored throughout the operation.

Surgical procedure

A reverse L-shaped or right subcostal incision was utilised for the hepatectomy. Intra-operative ultrasound imaging was conducted to assess the suitability of the planned resection. Liver parenchyma was transected using either the Kelly-clasia technique or Cavitron Ultrasonic Surgical Aspirator, with or without intermittent inflow occlusion. Drains were not routinely used.

Postoperative analgesia

Epidural analgesia delivered using Levobupivacaine 0.1% and Fentanyl 2 mcg ml via a thoracic epidural was the standard method of postoperative pain management, unless patient preference using patient-controlled analgesia (PCA) following preoperative anaesthetic assessment. The epidural was discontinued at 8 am on the third postoperative day, with a single Fentanyl patch applied to ease the transition to oral analgesia. The specialist pain management team supported all pain management.

Perioperative care plan

Patients were admitted on the day of operation, unless precluded by clinical or social circumstances. Pathway components are illustrated in Table 1. Patients were considered eligible for discharge once they were tolerating full oral intake, adequate pain-control, passing flatus and urine, normal clinical and acceptable biochemical parameters. Patients had to be deemed independently mobile and safe for discharge by the ward staff and physiotherapist. Nurse-led discharge was incorporated within the protocol to allow an efficient and safe discharge at all times.

Accomplishment and adherence of ERAS protocol

Our ERAS pathway aims for completion (and discharge) by day 6. Non-adherence is defined by length of stay beyond the ERAS pathway. Adherence to the following specific ERAS elements were assessed: sitting out of bed by POD 1; oral diet by POD 1; walking by POD 2; removal of thoracic epidural by POD 3; removal of urinary catheter by POD 3; passing flatus by POD 5. These were selected as they were felt to represent major clinical milestones in the postoperative recovery by the clinical team.

Our primary outcome was to evaluate how adherence to these six specific ERAS elements affected the successful completion of our ERAS pathway by day 6. Secondary outcomes compared postoperative complications and hospital re-admission after discharge between the adherent and non-adherent groups.

Statistical analysis

Categorical data were presented as frequency and proportions (%) and analysed using the Pearson's chi-squared test or Fisher's exact test. Median and range were used to describe continuous data, which were compared by using the Mann−Whitney test.

Univariate analysis was performed to assess ERAS elements between the adherent and non-adherent groups. A multivariable analysis was performed to evaluate variables, which were found to be significant on univariate analysis. All statistical analyses were performed using the SigmaPlot v.12 for Windows (Systat, US), and statistical significance was taken at the 5% level.

Results

Study population

During the studied period, 223 patients underwent hepatectomy within the ERAS program, of which 167 resections were for colorectal liver metastases, 15 for benign liver disease, 27 for hilar/intra-hepatic cholangiocarcinoma, and 17 for hepatocellular carcinoma (HCC). Among the 167 patients for colorectal liver metastases, 3 had laparoscopic liver resections. Median age was 67 years (range: 28−87). Of these 223 patients, 103 (46.2%) had a major hepatectomy, and 150 (67.3%) of them were male (see Table 2).

Adherence of specific elements to ERAS protocol

One hundred and forty-seven patients (65.9%) were discharged by day 6, and classified as successfully completing the ERAS. Median length of stay (LoS) for the whole cohort was 6 days (range: 1−71).

By POD 1, 160 (72%) patients had commenced full oral diet, and 173 (77.6%) had managed to sit out of bed. N = 177 patients (79.3%) started walking with the assistance of physiotherapist by day 2. The majority of patients (n = 147, 65.9%) opted for thoracic epidural as the sole analgesic control, whereas 13.9% (n = 31) had PCA alone, and 20.2% (n = 45) required both epidural and PCA to

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Table 2
Demographic, key components and major complications (Clavien–Dindo classification: Grade IIIb or above) for ERAS compliant (LoS ≤ 6) and non-compliant groups (LoS > 6).

	Length of stay > 6 days (n = 76)	Length of stay ≤ 6 days (n = 147)	p-value
Demographics			
Male gender	49 (64.5%)	98 (66.7%)	0.858
Age ≥ 80	8	13	0.868
Preoperative assessment			
Anticipated risk (low:medium:high)	10:43:6	38:77:5	0.051
HDU admission postop	57 (75%)	88 (59.8%)	***0.036****
Anticipated early admission prior surgery	28 (36.8%)	37 (25.2%)	0.096
Nutrition and gastrointestinal function			
Commencement of oral diet > POD 1	27 (40.3%)	36 (26.3%)	0.061
Failure to passed flatus by POD 5	1	0	0.689
Type of resections			
Major hepatectomy	46 (60.5%)	55 (37.4%)	***0.002****
Postoperative analgesia			
Epidural:PCA:combined epidural and PCA	51:5:19	96:26:24	***0.040****
Epidural removal > POD 3	12 (19.4%)	11 (9.7%)	0.112
PCA removal > POD 3	6 (46.2%)	4 (11.1%)	***0.014****
Combined analgesia > POD 3	17 (25.4%)	14 (10.4%)	***0.011****
Mobilisation			
Sat out of bed > POD 1	28 (41.2%)	22 (15.7%)	***<0.001****
Walking > POD 2	27 (40.9%)	19 (13.9%)	***<0.001****
Catheter removal > POD 3	28 (45.2%)	11 (8.6%)	***<0.001****
Hospital re-admission rate after discharge	7 (9.2%)	5 (3.4%)	0.131
Reasons for hospital re-admission			
Symptomatic control (e.g. nausea and vomiting, including pain relief)	2	2	
Complications (including collection)	4	2	
Others	1	1	
Unscheduled critical care admission	7 (9.2%)	1 (0.7%)	***0.004***
Major complications (Grade IIIb or above)	16 (21.0%)	2 (13.6%)	***<0.001****
Grade IIIb	*13 (17.1%)*	*1 (13.3%)*	
	Re-intervention (7)	Bile leak with intervention (1)	
	Bile leak with intervention (5)		
Grade IVa	*2 (2.5%)*		
	Pneumonia: re-intubation (2)		
Grade IVb/V	*3 (1.3%)*		
	Multi-organ dysfunction (3)		

*Indicates statistically significant findings with $p < 0.05$.
Italic and bold italic values indicates statistically significant findings with $p < 0.05$.

achieve effective pain management. Over 86% (n = 192) of patients were successfully discontinued from either PCA or epidural or the combination of both by POD 3. Urinary catheters were removed from more than 82% (n = 184) of patients by POD 3. Only 1 patient had not established normal gut function by POD 5.

Univariate and multivariable analysis of ERAS factors for prolonged LoS

On univariate analysis specific ERAS factors associated with a LoS > 6 days included not sitting out of bed by POD 1 ($p < 0.001$), failure to establish walking at 2 days postoperatively ($p < 0.001$), failure to discontinue epidural analgesia or PCA by POD 3 ($p = 0.011$), and not having the urinary catheter removed by day 3 ($p < 0.001$).

Other factors associated with LoS > 6 days included undergoing major hepatectomy ($p = 0.002$), age ≥80 ($p = 0.029$), elective postoperative HDU admission ($p = 0.036$), and the development of Grade III and IV complications (<0.001).

On multivariable analysis, sitting out by POD 1 ($p = 0.029$), walking by POD 3 ($p = 0.033$), removal of urinary catheter by POD 3 ($p = 0.002$), and avoiding major complications ($p < 0.001$) were independent factors associated with successful compliance to our ERAS protocol; whereas elderly age ($p = 0.341$), and earlier discontinuation of PCA/epidural by day 3 ($p = 0.549$) were not significant parameters (see Table 3).

Adherence to ERAS in major and minor liver resections

Although major hepatectomy was associated with a slightly younger age group (major: minor, 63.5 vs. 69, $p < 0.03$) as compared to minor resections, more patients

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Table 3
Multi-variate analysis of variables influencing length of stay > 6 days.

Clinical variables for LoS > 6	Multi-variate analysis	Risk ratio	Confidence interval
Age	0.341	1.016	0.983−1.049
Sat out of bed by POD 1	***0.029****	2.739	1.110−6.757
Walking by POD 2	***0.033****	2.776	1.086−7.095
Removal of urinary catheter by POD 3	***0.002****	4.702	1.737−12.732
Cessation of PCA and epidural by POD 3	0.495	1.482	0.478−4.594
Major complications (Clavien−Dindo > Grade III)	***<0.001****	23.439	4.453−123.367

*Indicates statistically significant findings with $p < 0.05$.
Bold italic values indicates statistically significant findings with $p < 0.05$.

with major resections had limited overall mobility and a longer period with catheter *in situ* after surgery (Table 4). However, the extent of liver resection was not associated with increased incidence of major complication ($p = 0.515$). Major liver resection is therefore likely to be a confounding factor for poor mobilisation and delayed urinary catheter removal.

Morbidity and mortality

The overall morbidity in our cohort (Clavien−Dindo 1−5) was 35.0% (n = 78/223), with major complications (Clavien−Dindo ≥ IIIb) occurring in 19 (8.5%) patients. The overall 90-day mortality was 1.3% (n = 3/223). Two of the patients who died (re-laparotomy for small bowel ischaemia and postoperative myocardial infarction) had major resections for colorectal liver metastases and the third following resection of a hilar cholangiocarcinoma (acute fulminant liver and multiple organ failures).

Critical care admission and hospital re-admission rates

Overall postoperative HDU admission and hospital re-admission after discharge rates were 65.0% (n = 145) and 5.4% (n = 12/220, with the exclusion of the 3 deaths), respectively. There was no difference in hospital re-admission rate between the successful and non-successful groups ($p = 0.131$).

Discussion

Achieving early mobilisation and early removal of urinary catheters were key to a successful ERAS pathway and early discharge following liver surgery. This is dependent on the avoidance of postoperative complications, as would be expected logically. However, age does not preclude patients from the enrolment to ERAS following hepatectomy.

Early mobilisations by sitting the patient out of bed by POD 1, and walking by POD 2 were associated with a successful adherence to ERAS criteria. In colorectal surgery, mobilisation by POD 3 was highlighted as an independent factor associated with a successful outcome of ERAS for laparoscopic colorectal surgery.[16,17] Smart et al. further demonstrated that failure to mobilise was associated with an early deviation from the ERAS protocol in colorectal

Table 4
Demographic and key components for minor and major hepatectomies.

Type of resections	Minor resections (n = 123)	Major resections (n = 103)	p-value
Demographics			
Male gender	82 (66.7%)	68 (66%)	0.858
Median age, range	69 (28−85)	63.5 (28−87)	***0.029****
Tumour aetiology			
CRLM	105 (87.8%)	65 (63.1%)	***<0.001****
Hepatocellular carcinoma	10 (8.1%)	15 (14.6%)	
Cholangiocarcinoma	2 (1.6%)	15 (14.6%)	
Benign	6 (4.9%)	8 (7.8%)	
Median length of stay	5	6	***<0.001****
Preoperative assessment			
Planned HDU postop	62 (50.4%)	86 (83.5%)	***<0.001****
Nutrition and gastrointestinal function			
Commencement of oral diet > POD 1	28 (24.8%)	35 (37.2%)	0.074
Failure to pass flatus by POD 5	0	1	0.929
Postoperative analgesia			
Analgesia > POD 3 (including both PCA & epidural)	13 (11.9%)	19 (20.4%)	0.145
Mobilisation			
Sit out of bed > POD 1	15 (12.9%)	35 (37.2%)	***<0.001****
Walk > POD 2	12 (10.8%)	34 (36.6%)	***<0.001****
Catheter removal > POD 3	14 (13.9%)	25 (27.8%)	***0.028****
Major complications	9 (7.3%)	11 (10.7%)	0.515

*Indicates statistically significant findings with $p < 0.05$.
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surgery.[17] Our data suggest similar results following hepatectomy.

One of the most recent studies of ERAS looking at recovery after major liver surgery focused on the accomplishment of the ERAS criteria, rather than the total length of hospital stay.[18] Although there is growing awareness that LoS is not equivalent to a good final outcome measure, and that postoperative patient-reported outcome/quality of life survey might be better outcome measurements,[19] it is nevertheless a key criteria for measuring a successful ERAS programme. The majority of delayed discharges were due to social and domestic factors.[18] In this cohort, nearly a quarter of patients would have achieved the ERAS criteria, which were set out as Takamoto et al.[18] in their protocol, but were not discharged by POD 6. It is therefore our opinion that achieving ERAS criteria alone is not an adequate reflection of accomplishing successful ERAS. Our philosophy for an effective ERAS programme is that ERAS should commence at the point of the decision for surgery, at which time any potential delays after surgery are identified, and ideally rectified, prior to surgical intervention.

Delay to removal of a urinary catheter is also associated with deviation from our ERAS protocol. Similar finding was also identified in ERAS studies after colorectal surgery.[17] This delay could possibly be explained by the autonomic blockade following thoracic epidural, or other significant confounding variables such as poor mobility and the development of complications. In our ERAS protocol, the urinary catheter would not be removed as long as the thoracic epidural is *in-situ* for the concerns of developing urinary retention. However, one randomised controlled trial (RCT) demonstrated that early urinary catheter removal on POD 1 having had epidural analgesia led to a lower urinary tract infection rate, and did not increase re-catheterisation rate.[20] It might therefore be worth evaluating whether early removal of urinary catheter on POD 1 can further enhance the recovery process following liver surgery.

Advanced age and prolonged use of either epidural or PCA were associated with extended LoS in univariate analysis, but not on multivariable analysis. This finding implies that elderly age and prolonged use of epidural or PCA are confounders for other factors, such as poor mobility, but are not the key parameters for the failure of ERAS in liver surgery. Our finding is in conflict with those of Takamoto et al., who concluded that age was associated with prolonged LoS.[18] This may be due to their focus on major hepatectomy, suggesting that age is more relevant in more extensive surgery.

Major resections were associated with slower mobilisation and delay in urinary catheter removal. However, we had proportionally more patients with intrahepatic/hilar cholangiocarcinoma or hepatocellular carcinoma (HCC) underwent major hepatectomies in our cohort as compared to other studies.[9,21–23] This is likely because of our non-exclusion criteria to enrol any liver resection patients into our ERAS protocol. Despite having the same anatomical extent of resection for patients with HCC, cholangiocarcinoma and liver metastases, the patho-physiological effects vary widely among these three groups of patients. There were more underlying liver parenchymal dysfunctions in HCC and cholangiocarcinoma than liver metastases, where these patients will have better preserved liver functions prior to intervention.[21,24] This preoperative parenchymal dysfunction would potentially affect the rate of recovery, and hence ERAS outcomes.

Overall morbidity in our series was 35.0%, with major complications (Grade III or above) in 8.5%; whereas our overall mortality was 1.3%. These findings are again not dissimilar to the experience of other centres utilising ERAS in liver surgery.[21,22,24–28] This finding is lower than those treated ‘traditionally’ in other centres.[29–31] Despite the difference in recovery rate demonstrated in our cohort between major and minor hepatectomy, there were no differences in their associated morbidities. Our re-admission rate for this study is 5.4%, which is similar to other ERAS series.[21,23,27] When compared ERAS to conventional care, other studies again did not demonstrate any significant difference in their hospital re-admission rate. These findings further confirmed that ERAS is safe following liver resections.

Whilst this study is limited by its retrospective design, this series offers a true reflection of ERAS in clinical practice, without any exclusion, as opposed to its use in clinical trials or highly selected groups of patients.[9,24] The other limitation in this series is its lack of case-matching for either major or minor hepatectomy according to the underlying tumour aetiologies. This can potentially introduce bias in our data analysis.

In conclusion, ERAS should be considered as a standard of care for all patients undergoing liver resection. Old age should not be used as a de-selection criterion for enrolling patients for ERAS following hepatectomies. It is important to focus on early mobilisation and early removal of the urinary catheter, which are essential to ensure a successful ERAS program for liver resections.

Conflict of interest

None declared.

Source of funding

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Ethical approval

Ethical approval is not required for this study.

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