

# Enhanced recovery protocol after liver resection

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**Background:** Enhanced recovery protocols (ERPs) accelerate patient recovery and shorten hospital stay by optimization of perioperative care. However, experience with ERPs is still limited in liver surgery.

**Methods:** The implementation of a multimodal ERP was studied in patients who underwent open and laparoscopic liver surgery. An opioid-sparing pain treatment was chosen together with early mobilization and oral feeding, as well as restricted use of abdominal drains and catheters. Date to discharge, postoperative complications and patient satisfaction were assessed. A historical cohort of patients who underwent liver resection served as a control group.

**Results:** Some 134 liver resections (126 open, 8 laparoscopic) were performed between April 2013 and March 2014. Operations were carried out mostly for malignant liver tumours. One hundred and six (79.1 per cent) of the 134 patients were discharged by the fifth postoperative day. The median (range) postoperative hospital stay was 4 (2–11) days, compared with 6 (4–16) days for the control group ( $P < 0.001$ ). Only four patients in the ERP group were readmitted and the 30-day mortality rate was zero.

**Conclusion:** An ERP for perioperative care after liver surgery was introduced safely and effectively. Discharge within 4 days is achievable with no increase in adverse events and good patient satisfaction.

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## Introduction

Increased knowledge of perioperative changes in human physiology has resulted in implementation of multimodal rehabilitation principles for several major surgical procedures. Kehlet<sup>1</sup> described the first multimodal approach to enhance postoperative recovery and rehabilitation after major abdominal surgery in 1997. Since then, introduction of fast-track programmes or enhanced recovery protocols (ERPs) has led to a reduction in postoperative hospital stay and morbidity, and their implementation has become the mainstay of elective colorectal surgery<sup>2,3</sup>.

Liver surgery is seen as high risk. ERPs were introduced into liver surgery programmes only a few years ago. Some studies<sup>4–9</sup> have suggested that these protocols are safe and feasible after liver surgery, and that they reduce the length of hospital stay. However, experience with enhanced recovery after liver surgery is limited and protocols are lacking. Given the clear benefit of ERPs in colorectal surgery, it is difficult to justify performing large randomized and well controlled studies of such protocols for liver surgery. The

aim of this study was to assess the effect of implementation of an ERP on the length of postoperative hospital stay, morbidity and patient satisfaction in patients undergoing liver surgery.

## Methods

From April 2013, an ERP was implemented for patients who underwent liver resection at the Transplantation and Liver Surgery Unit of Helsinki University Hospital. This is a high-volume hepatobiliary unit that acts as a tertiary centre for the whole of Finland (population 5.5 million). Since 1982, more than 2000 liver operations have been performed together with over 1000 liver transplantations. The annual volume is over 150 liver resections, mostly for liver metastases from colorectal cancer.

All 19 enhanced recovery elements based on recent ERAS<sup>®</sup> Society recommendations were included in the protocol<sup>10</sup> (Table S1, supporting information). The only contraindications to use of this protocol were hilar cholangiocarcinoma or other operations in which biliary

reconstruction was necessary. All patients who underwent liver resection between 1 April 2013 and 31 March 2014 were included in the study. No extra staff were involved in implementation of the ERP compared with conventional perioperative care. All patients were informed of the protocol by the surgeon at the preoperative visit, and provided with written information.

Patients who underwent liver resection without biliary reconstruction in the unit before the implementation of the ERP served as historical controls. These patients had surgery between 15 June 2012 and 31 March 2013, and the data were collected retrospectively from the electronic medical records. At that time all patients received conventional perioperative treatment without any specific attempts to shorten the postoperative hospital stay.

### Perioperative care

Liver resections were categorized as laparoscopic (non-anatomical wedge resections, or resection of 1 or 2 segments), minor open resection (fewer than 3 segments, including multiple non-anatomical resections) or major open resection (3 or more segments). A transverse incision in the right upper quadrant extending upwards in the midline was used for open liver resections. The decision to use a drain was left to the surgeon, but the unit's policy was not to use drains<sup>11</sup>. Drains were generally removed on the first postoperative day (POD). The transfusion trigger was set individually both during and after operation at a haemoglobin level of 80–90 g/l according to the patient's co-morbidities.

All patients received a carbohydrate-rich recovery drink 2 h before the operation, together with 75–150 mg pregabalin for premedication. Anaesthesia was induced with propofol, fentanyl and rocuronium. During the procedure anaesthesia was maintained with desflurane and fentanyl boluses, or an alfentanil infusion. Rocuronium boluses were used for muscle relaxation, and either neostigmine–glycopyrronium or sugammadex for the reversal of relaxation.

For open liver surgery, the primary means of pain management was epidural block at thoracic 7–8 or 8–9 level with continuous infusion of 0.2 per cent ropivacaine with fentanyl (5–7.5 µg/ml). If epidural analgesia was contraindicated or preoperative insertion failed, a wound catheter for continuous infusion of 0.2 per cent ropivacaine was inserted by the surgeon into the preperitoneal space (under the fascia) along the upper margin of the subcostal incision before wound closure. For laparoscopic operations, conventional pain management with oral analgesics was used.

Patients were discharged to the ward after 6–8 h in the recovery room and mobilized from POD 0. Only patients with severe co-morbidities who underwent major liver resection were managed in an intensive care unit for the first night after surgery. All patients were encouraged to drink and eat from POD 0. Patients received a carbohydrate-rich recovery drink again on the evening of the day of surgery. Laxatives (mainly lactulose) were also used routinely from the day of surgery onwards.

Patients received opioid-sparing, well defined multimodal analgesia during the hospital stay. Postoperative pain was assessed regularly by means of either a visual analogue scale or a verbal rating scale. Epidural or wound catheter analgesia was used for 0–48 h after operation (from POD 0 to the morning of POD 2), and patients were weaned from invasive analgesia during POD 2. Helsinki University Hospital guidelines for the safe removal of an epidural catheter are a platelet count exceeding  $100 \times 10^9/l$  and an international normalized ratio below 1.5. Epidural and wound catheters were usually removed in the morning of POD 3. After premedication, pregabalin (50–100 mg twice daily) was continued during the hospital stay. Ibuprofen (400–800 mg three times daily) was started on the evening of operation. If ibuprofen was contraindicated, paracetamol (500–1000 mg three times daily) was used instead. Extended-release tramadol (75–150 mg twice daily) was added to the medication when the patient was being weaned off epidural or wound catheter infusion. If needed, the patient could also receive oral oxycodone (0.1–0.2 mg/kg) for severe pain. In patients with epidural analgesia, oxycodone was given only after removal of the epidural catheter. The exact doses of all analgesic drugs were left to the discretion of the anaesthetist (POD 0) or the surgeon (POD 1 and thereafter). At discharge, ibuprofen and long-acting tramadol were prescribed for use at home for pain relief for several days.

### Discharge criteria

Criteria for discharge from hospital were pain sufficiently controlled by oral analgesics, independent mobilization, eating and drinking without problems, and no untreated surgical complications. The goal of the ERP was to achieve discharge on POD 3 after a laparoscopic resection and POD 4–5 after an open liver resection, although earlier discharge was an option for all patients. Complications were recorded according to the Dindo–Clavien classification<sup>12</sup>.

**Table 1** Patient demographics and operative details

	ERP group (n = 134)	Historical controls (n = 100)	P†
Age (years)*	63 (26–86)	65 (18–84)	0.533‡
Sex ratio (F : M)	56 : 78	45 : 55	0.624
ASA fitness score*	3 (1–4)	3 (1–4)	0.708‡
I	3 (2.2)	2 (2.0)	
II	42 (31.3)	28 (28.0)	
III	78 (58.2)	63 (63.0)	
IV	11 (8.2)	7 (7.0)	
Type of surgery			0.390
Laparoscopic	8 (6.0)	10 (10.0)	
Minor open	62 (46.3)	41 (41.0)	
Major open	64 (47.8)	49 (49.0)	
Histology			0.427§
CRLM	73 (54.5)	58 (58.0)	
HCC	18 (13.4)	13 (13.0)	
pCC	8 (6.0)	5 (5.0)	
Gallbladder cancer	9 (6.7)	3 (3.0)	
Other metastases	12 (9.0)	15 (15.0)	
Benign tumour	14 (10.4)	6 (6.0)	

Values in parentheses are percentages unless indicated otherwise; \*values are median (range). ERP, enhanced recovery protocol; ASA, American Society of Anesthesiologists; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; pCC, peripheral cholangiocarcinoma. †Pearson  $\chi^2$  test, except ‡Mann–Whitney *U* test and §Fisher's exact test.

## Follow-up

Patients were contacted by telephone 3 days after discharge by a ward nurse, except for those who were discharged to a district hospital. The nurse filled out a structured questionnaire on pain, mobilization, bowel function and overall well-being, rated on a four-point scale (4, excellent; 3, good; 2, fair; 1, poor). Three months after the operation patients were seen in the outpatient clinic and the same questionnaire was completed.

## Statistical analysis

Continuous data are expressed as median (range). The groups were compared using Mann–Whitney *U* test for independent samples, Pearson  $\chi^2$  test or Fisher's exact test, as appropriate. Correlation was assessed by means of Pearson product–moment correlation coefficient.

## Results

Between 1 April 2013 and 31 March 2014, 134 liver resections were performed in 132 patients. Two patients were operated on twice during the study interval. One patient underwent a planned two-stage operation because of multiple metastases. Another patient had resection of recurrent metastasis 3 months after the first operation. As the operations were independent events, both procedures were

**Table 2** Operative details, complications and length of stay

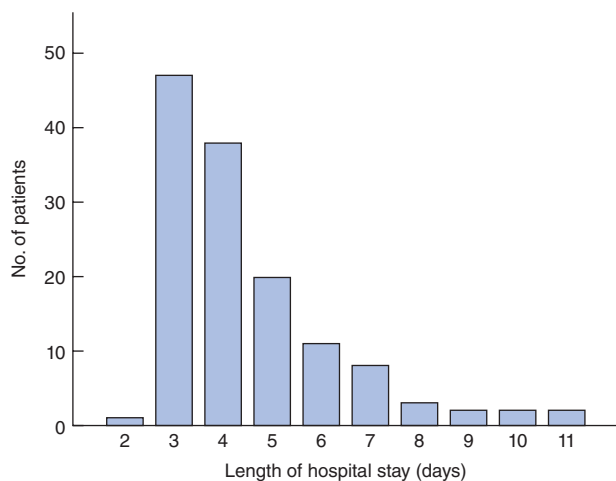
	ERP group (n = 134)	Historical controls (n = 100)	P†
Length of hospital stay (days)*	4 (2–11)	6 (4–16)	< 0.001‡
Blood loss (ml)*	500 (50–5500)	500 (100–3600)	0.645‡
Perioperative transfusion	20 (14.9)	20 (20.0)	0.829
RBC only	12 (8.9)	11 (11.0)	
Multiple blood components	8 (6.0)	9 (9.0)	
Amount of RBC transfused (units)*	2 (1–8)	3 (1–6)	0.789‡
Total no. of complications	60	99	< 0.001
Grade			
I	20 (33)	14 (14)	0.358
II	30 (50)	74 (75)	< 0.001
IIIa	4 (7)	5 (5)	
IIIb	4 (7)	3 (3)	
IVa	1 (2)	3 (3)	
IVb	1 (2)	0 (0)	
V	0 (0)	0 (0)	
Type			
Urological	19 (32)	0 (0)	< 0.001§
Pulmonary	9 (15)	13 (13)	
Cardiac	4 (7)	12 (12)	0.036§
Gastrointestinal	4 (7)	43 (43)	< 0.001§
Wound-related	2 (3)	0 (0)	
Neurological	3 (5)	10 (10)	0.043§
Other	19 (32)	21 (21)	0.470

Values in parentheses are percentages unless indicated otherwise; \*values are median (range). ERP, enhanced recovery protocol; RBC, red blood cells. †Pearson  $\chi^2$  test, except ‡Mann–Whitney *U* test and §Fisher's exact test.

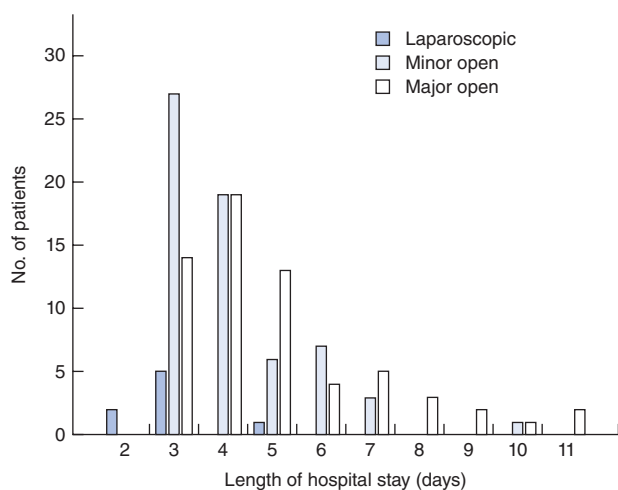
included in the analysis. Indications for liver resections, detailed demographic data and operative details for the ERP group and the historical control group of 100 patients are presented in *Table 1*.

## Analgesia

Although avoidance of premedication is an established ERP element, all patients received a single preoperative pregabalin dose to reduce the need for postoperative opioids. Epidural analgesia was used in 89 patients (66.4 per cent), wound catheter analgesia in 34 (25.4 per cent) and conventional oral analgesia in 11 (8.2 per cent). Conventional analgesia was used in all patients undergoing laparoscopic surgery, as well as in three (2.4 per cent) having open surgery. The catheter was removed on POD 2 or 3 in the vast majority of patients. In only three patients (2.2 per cent) was epidural catheter removal delayed to POD 4 owing to disturbed coagulation. The median length of hospital stay was 4 (range 3–11) days in patients with epidural



a All patients



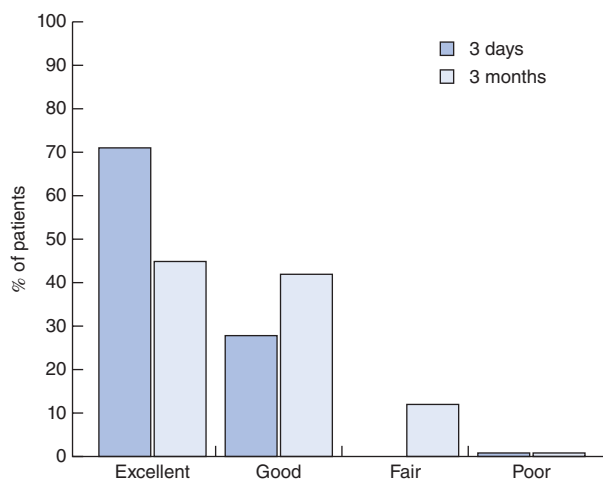
b By surgical category

**Fig. 1** Postoperative length of hospital stay for **a** all patients and **b** according to type of operation

analgesia compared with 4 (range 3–8) days in patients who received wound catheter analgesia ( $P = 0.890$ ).

The predefined multimodal analgesia was effective as 53 patients (39.6 per cent) did not receive any oxycodone for severe pain during the hospital stay. The most common deviation from the predefined multimodal analgesia was the omission of ibuprofen in 24 patients (17.9 per cent) owing to allergy, chronic kidney disease, or excessive bleeding during the operation.

The control group was comparable to the ERP group regarding the use of different types of postoperative pain management. Postoperative opioid use was more common in the control group; only 14 patients (14.0 per cent) did not receive oxycodone after surgery ( $P < 0.001$ ).



**Fig. 2** Patient satisfaction with perioperative care ascertained by interviews 3 days after discharge and 3 months after operation

### Postoperative hospital stay and readmission

The median postoperative hospital stay was 4 (2–11) days for the ERP group compared with 6 (4–16) days for the control group ( $P < 0.001$ ) (Table 2). Some 106 (79.1 per cent) of the patients in the ERP group were discharged by POD 5 (Fig. 1a). Postoperative hospital stay according to surgical approach and type of resection is shown in Fig. 1b. Some 43 per cent of the patients who underwent a minor open resection were discharged on POD 3 and 30 per cent on POD 4. Patients who underwent a major open resection stayed somewhat longer in hospital. The percentage of patients discharged to a neighbouring district hospital was significantly higher in the control group than in the ERP group: 19.0 per cent (19 patients) versus 6.0 per cent (8 patients) ( $P = 0.002$ ).

Only four patients (3.0 per cent) in the ERP group were readmitted to hospital: one patient (discharged on POD 3) owing to pain, two (both discharged on POD 5) because of raised liver enzyme levels noted at a scheduled visit to the clinic, and one (discharged on POD 3) because of fascial wound dehiscence on POD 7. The readmission rate was similar in the historical control group, in which two patients (2.0 per cent) were readmitted to the surgical ward.

### Complications

The number, severity and type of complications in each group are shown in Table 2. Some 50 patients (37.3 per cent) in the ERP group and 71 (71.0 per cent) in the control group had at least one complication ( $P < 0.001$ ). Most complications were classified as minor and had no

influence on hospital stay in the ERP group. The 30-day mortality rate was zero in both groups. Median blood loss and requirement for blood transfusion was similar in the two groups and did not correlate with postoperative complications or hospital stay (Table 2).

Median time to the first passage of stool was 3 (1–5) days in the ERP group and 4 (1–8) days in the control group ( $P < 0.001$ ). There was no difference in return to normal bowel function according to surgical approach.

### Patient satisfaction

Patient satisfaction in the ERP group is shown in Fig. 2. There was no difference in patient satisfaction between major and minor resections or laparoscopic *versus* open surgery.

### Discussion

The clear benefit of an ERP for colorectal surgery makes it almost unethical to perform randomized clinical trials for other major surgical procedures including liver surgery. Schultz and co-workers<sup>6</sup> reported a series of 100 patients who underwent liver resection followed by care according to an ERP. They reported a median length of stay of 5 days and a 6 per cent readmission rate. In that study, 32 per cent of patients underwent major liver resection, with a median length of stay of 6 days. van Dam and colleagues<sup>5</sup> recorded a median hospital stay of 6 days after open liver resection treated within an ERP. In a small Scottish series<sup>4</sup> of 12 liver resections for colorectal metastases, a median length of stay of 4 days was achieved in minor liver surgery. Recently, Jones *et al.*<sup>9</sup> reported a median stay of 4 days in patients treated within an ERP, including 46 who underwent open liver surgery with a 4 per cent readmission rate<sup>9</sup>. The present report describes the successful implementation of an ERP in a large series of 134 liver resections with a median postoperative hospital stay of 4 days and a 3.0 per cent readmission rate. Of note is that a large proportion of the patients (47.8 per cent) underwent major liver surgery.

Consistent with previous experience in colorectal surgery<sup>3</sup>, optimal pain management is one of the most important factors in optimizing postoperative recovery after liver surgery. Studies have demonstrated the efficacy of both epidural<sup>13</sup> and local wound catheter<sup>14</sup> analgesia in liver surgery. In the present protocol, the majority of patients achieved pain control with epidural or wound catheter analgesia that allowed effective mobilization early after surgery. From the authors' experience with the ERP, wound catheter analgesia seems a feasible and effective

alternative to epidural analgesia after liver surgery. As components of multimodal analgesia, both pregabalin and ibuprofen were used to reduce the need for opioids<sup>15</sup>. Indeed, almost half of the patients did not need any strong opioids after operation. This may also be because the weak opioid tramadol (extended release) was given regularly. Even in this study population consisting of the relatively old patients with major co-morbidities (American Society of Anesthesiologists (ASA) fitness grade III–IV), drugs affecting the central nervous system and ibuprofen were both well tolerated.

Rapid recovery of bowel function was associated with minimal use of opioids. Likewise, early initiation of laxatives after surgery as well as perioperative administration of carbohydrate-rich recovery drink possibly contributed to rapid bowel recovery, consistent with previous findings<sup>16</sup>.

Minor complications, including disturbance in postoperative micturition, were common, but had no influence on the length of postoperative hospital stay and overall well-being. Major complications were rare and did not seem to be associated with implementation of the ERP. This is important as complications may also have a negative influence on longer-term surgical outcomes<sup>17,18</sup>. Interestingly, ERPs may have a role in improved cancer outcomes owing to changes in a cell-mediated immunity and because patients may become fit enough more quickly for postoperative adjuvant therapy<sup>19</sup>. Although discharge was early, the readmission rate of 3.0 per cent was very low, demonstrating the safety of the protocol.

Preoperative patient information is crucial for the successful implementation of an ERP<sup>6,9</sup>. Implementation of the ERP in the present study was without any extra resources, whereas Schultz and colleagues<sup>6</sup> included a project nurse who was heavily involved in the protocol during the entire treatment process. Preoperative counselling about ERPs and exploration of patients' expectations by a specialized nurse seem important for adherence to these protocols and might lead to a further reduction in the duration of stay.

Interestingly, there was no statistical difference in length of stay between minor and major open resections. Hence it appears feasible and safe to aim for discharge from hospital 3 days after major liver surgery, including patients with a mean ASA physical status grade of III. Jones and colleagues<sup>9</sup> reported a similar length of stay but the mean ASA score of their patients was 2. Owing to the risk of acute liver failure and associated bleeding after liver surgery, patients need close monitoring for the first few days and discharge earlier than POD 3 may not be feasible, especially considering the relatively long distances between

the liver surgery unit and home, which is typical for a large country like Finland. More than half of the unit's patient population lives more than 100 km away from the liver surgery unit.

No benefit of laparoscopic surgery was seen in the present cohort. The proportion of laparoscopic procedures was less than 10 per cent, which is quite similar to that in Danish and Spanish hepatobiliary centres that use ERPs<sup>6,7</sup>. The median duration of hospital stay was 2 days after laparoscopic liver surgery in the Danish centre<sup>6</sup>, whereas it was 3 days in the Spanish centre<sup>7</sup>, as in the present study.

A shorter length of stay after major liver surgery was associated with excellent patient satisfaction, regardless of the surgical approach. Although more than half of the patients included in this study received adjuvant oncological treatments after surgery, which might have influenced their satisfaction, the majority of the patients rated their overall well-being as good or excellent at 3 months after liver surgery.

## Acknowledgements

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*Disclosure:* The authors declare no conflict of interest.

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### Supporting information

Additional supporting information may be found in the online version of this article:

**Table S1** Enhanced recovery elements (Excel document)

### Snapshot quiz

#### Snapshot quiz 15/11

**Answer:** Rectal prolapse can be treated by an abdominal or perineal approach. As it occurs mostly in elderly women, the choice depends on overall medical condition. Abdominal rectopexy (Ripstein procedure) has a recurrence rate of less than 10 per cent. Perineal rectosigmoidectomy (Alteimeier procedure) has a higher recurrence rate. Reefing of the rectal mucosa (Delorme procedure) is effective in limited prolapse but also has a high recurrence rate (around 30 per cent). Reduction of perineal hernia and closure of cul-de-sac (Moschowitz procedure) has been abandoned.