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Applicability of Enhanced Recovery Program for Advanced Liver Surgery

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Abstract
Background Enhanced recovery programs (ERPs) have been developed in various surgical fields and have been shown to accelerate postoperative recovery without increasing the incidence of adverse events. Whether ERP can be safely applied to patients undergoing complex liver surgery with a risk of liver failure remains unclear.
Methods We created an ERP by rearranging our conventional postoperative treatments and applied this program to patients undergoing major hepatectomy between 2008 and 2013. The ERP elements included greater perioperative education, individualized postoperative fluid therapy, and early mobilization. The success of the ERP was evaluated on postoperative day (POD) 6 based on the criterion of independence from continuous medical intervention with the exception of an abdominal drainage tube. Adherence to each item in the ERP was evaluated, and risk factors for delayed accomplishment were analyzed.
Results Altogether, 200 patients were included, and 165 patients (82.5 %) completed the ERP. Multivariate analyses showed that (1) an age of 65 years or older and (2) a red blood cell transfusion were independent risk factors for delayed accomplishment. The performance of thoracotomy or choledocojejunostomy did not significantly affect accomplishment of the ERP. Oral intake starting on POD 1 was achieved in 179 patients (89.5 %), and termination of intravenous drip infusions on POD 5 was feasible in 72.5 %.
Conclusions An ERP for major hepatectomy was completed in more than 80 % of the patients. Earlier bowel movement can be challenged. The liquid in–out balance should be adjusted on an individual basis, rather than uniformly, especially for patients over 65 years of age or who required a red blood cell transfusion.

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Introduction

Liver resection continues to be the main curative treatment for primary and secondary hepatic malignancies despite several percutaneous interventions that have been developed. Patients who have undergone liver resection are at risk of not only surgical stress but postresectional liver failure as well. Liver resection is also associated with a high rate of postoperative complications (around 30 %) [1–3].

Over the last 2 decades, traditional postoperative treatments, including prolonged bed rest, have been reconsidered, and perioperative pathways aimed at earlier mobilization after surgery—so-called fast-track pathways or enhanced recovery programs (ERPs)—have been developed [4, 5]. Most of these pathways contribute to a shortened hospital stay and reduce hospital costs without having a negative impact on the surgical outcome [6]. In 2011, the Enhanced Recovery After Surgery (ERAS) Society published guidelines, and the creation of ERPs in the fields of cardiovascular and colon surgery began to spread to include surgical procedures in other fields [7, 8]. Now, such programs are facing the challenge of being implemented for highly invasive surgery, such as esophagogastrectomy [9] and hepatectomy [8, 10–13].

Liver resections can range from limited resection in a normal liver to hemihepatectomy in damaged liver. The reconstruction of the portal or hepatic vein and a choledocojejunostomy are also sometimes required. Considering these variations, whether a single ERP is both safe and feasible for all patients undergoing a liver resection remains unclear.

We modified our traditional perioperative program, which had enabled a zero-mortality rate after liver resection, after considering the main elements of ERAS [14]. This modified program was then applied as an ERP for patients undergoing open liver resection. The aim of the present study was to evaluate the practicality and feasibility of our ERP, especially for patients undergoing major hepatectomy.

Methods

Major hepatectomy was defined as the resection of three or more Couinaud's segments of the liver. All consecutive patients who underwent a major hepatectomy at the Japanese Red Cross Medical Center between April 2008 and March 2013 were included in the study. Patients who underwent concomitant resection of gastrointestinal and/or colorectal tracts were excluded. The demographic and clinicopathologic data were collected from a prospectively maintained database and medical records.

Enhanced recovery program for advanced liver surgery

Preoperative care

Patients who were to undergo a major hepatectomy received a checklist and an information booklet about the preoperative guidance. The booklet described the method used for respiratory rehabilitation, daily medical events after admission, daily mobilization goals, and nutritional goals after the operation. If desired, the patients received counseling by trained nurses and a psychotherapist. One day before the surgery, the patients ingested magnesium citrate and a sennoside as a bowel preparation. The nil-by-mouth condition was observed from 10 p.m. (2200 h) onward. No premedication was given. On the day of surgery, a thoracic epidural catheter was placed between levels Th10 and Th6 in all patients except those with a platelet count of <80,000/mm^3. From the beginning of the operation, patients received 0.125 % levobupivacaine via the epidural catheter. After surgery, levobupivacaine mixed with morphine or fentanyl was continuously infused at a rate of 4–6 ml/h using a patient-control analgesia (PCA) system. Patients in whom the epidural catheter was not applied received a continuous intravenous infusion of fentanyl and regular oral intake of nonsteroidal inflammatory drugs (NSAIDs). Normothermia was maintained during surgery using a forced-air warming blanket and by monitoring the deep body temperature. Intermittent pneumatic leg compression devices were also applied.

Table 1 Summary of the enhanced recovery program for advanced liver resection

Before admission	At the time of operation decision, patient is informed of preoperative respiratory rehabilitation program
	Counseling is added if necessary
After admission	At the time of admission, fast-track rehabilitation program is discussed with patient
	Central venous line is inserted the day before surgery
	Oral intake is allowed until 12 hours before operation
Day of Surgery	Thoracic epidural catheter (Th6–Th10 level) is placed with continuous infusion of bupivacaine 0.125 % with fentanyl at a rate of 4–6 ml/h until day 5, plus intravenous NSAIDs. If an epidural catheter is contraindicated, patient-controlled analgesia with morphine is applied plus intravenous NSAIDs
	Intravenous fluid administration (glucose 0.05 g/kg/h, hydroelectrolytic solution with amino acid 45 ml/kg/day) is started
	Urine and ascites volumes and electrolytes are measured
	Body temperature is maintained with a body-warming device
	Elastic stockings and intermittent pneumatic compression machine are used
POD 1	Nasogastric tube is removed when drainage of the discharge is <200 ml
	Patient is mobilized out of bed for >1 h
	Intravenous fluid administration is continued (glucose 0.10 g/kg/h, hydroelectrolytic solution with amino acid 45 ml/kg/day)
	Oral fluid intake is initiated
POD 2	Enhanced mobilization is started (>2 h out of bed)
	Chest drain is removed (if daily amount of discharge is <200 ml)
	Intravenous fluid administration continues (glucose 0.15 g/kg/h, hydroelectrolytic solution with amino acid 45 ml/kg/day)
POD 3	Solid food intake is initiated
	Intravenous fluid administration continues (glucose 0.20 g/kg/h, hydroelectrolytic solution with amino acid 45 ml/kg/day)
POD 4	Diet is increased on a daily basis
	Intravenous fluid administration continues (glucose 0.10 g/kg/h, hydroelectrolytic solution with amino acid 20 ml/kg/day)
POD 5	Epidural catheter is removed
	Intravenous fluid administration is discontinued. Central venous line is removed
POD 6	Accomplishment criteria are assessed

NSAIDs nonsteroidal antiinflammatory drugs, *POD* postoperative day

Table 2 Summary of elements in an enhanced recovery after surgery program included in previous studies

Parameter	van Dam [8]	Koea [10]	Hendry [11]	Lin [12]	Jones [13]	Present study
Year of study	2008	2009	2010	2011	2013	–
No. of patients	61	50	34	56	46	200
Major resection	54 %	42 %	ND	34%	46 %	100 %
Counseling	Yes	–	Yes	Yes	–	Yes
No premed.	Yes	Yes	Yes	Yes	Yes	Yes
Thromboembolic Rx	Yes	Yes	Yes	–	Yes	Yes
No bowel prep.	Yes	–	Yes	Yes	Yes	–
No drain	Yes	–	Yes	Yes	Yes	–
Epidural analgesia	Yes	Yes	Yes	Yes	Yes	Yes
Fluid restriction	Yes	Yes	Yes	Yes	Yes	Yes
Hypothermia prevention	Yes	–	Yes	Yes	Yes	Yes
NG tube removal	0	0	0	–	0	1
Oral intake (POD)						
Fluid	0	1	1	–	0	1
Solids	1	1	1	1	0	3
Out of bed (POD)	1	1	1	1	1	1
Laxatives	Yes	–	Yes	–	Yes	Yes
Urinary catheter removal (POD)	3	1	3	–	2	4

Rx prophylaxis, *premed.* premedication, *prep* preparation, *POD* postoperative day, *NG* nasal gastric, *ND* no data

Surgical technique

Hepatectomy was performed using a J-shaped incision. A thoracotomy through the ninth intercostal space was added if the resection segments included S7 and S8. Liver transection was performed using the Pean fracture method under an intermittent Pringle maneuver [15]. At least one closed-type drainage tube was routinely placed on the raw surface of the liver. The intraoperative infusion was controlled so the result of the following formula [16] would be 4–6 ml/kg/h.

$$(\text{Infusion volume} - \text{amount of blood loss})(\text{ml})/\text{body weight (kg)}/\text{anesthesia time (hour)}$$

Postoperative care

The nasogastric tube was removed, at the latest, by the morning of postoperative day (POD) 1, and liquid oral intake was immediately resumed. An out-of-bed program aimed at walking was applied on the same day. Solid foods were resumed, at the latest, on POD 3. The amount of urine and drainage tube discharge were measured regularly, and the urine electrolytes were monitored for the purpose of controlling the intravenous drip under a favorable in–out water balance and to prevent excess administration of potassium (Table 1). The characteristics of our ERP and a comparison to previously reported ERPs for liver surgery are shown in Table 2.

Criteria for accomplishing ERP

The accomplishment of ERP was judged on the morning of POD 6 using the following criteria: normal or decreasing serum bilirubin level, absence of fever (<37.5 °C for >48 h), adequate pain control with oral analgesics only, ability to consume water and solid foods without requiring intravenous fluids, and adequate mobilization independently or at the preoperative level. The evaluation was made not only by the liver surgeons in charge of the patient but also by independent assessors, including co-medical staff members.

Assessment of accomplishment and adherence to program

The rate of accomplishment of the ERP on POD 6 and the reasons for nonaccomplishment were investigated. Among the ERP items, adherence (i.e., accomplishment on the standard date) to the following items were assessed: removal of nasogastric tube by POD 1; walking by POD 1; removal of thoracic tube by POD 2; oral intake by POD 3; removal of urinary catheter by POD 4; removal of epidural catheter by POD 5; and termination of intravenous hyperalimentation by POD 5.

Risk factors analysis of delayed accomplishment

Between the group who accomplished the ERP and those who could not accomplish the ERP by POD 6, preoperative

Table 3 Clinical characteristics of patients who underwent the enhanced recovery program

Characteristic	Accomplished group ($n = 165$)	Delayed group ($n = 35$)	p
Age (years)	62 (33–89)	69 (25–83)	0.052
Sex (M/F)	97/68	20/15	0.858
BMI (kg/m^2)	21.7 (13.3–2.3)	22.0 (15.4–26.6)	0.858
Preoperative data			
ASA (1/2/3)	33/107/16	6/21/8	0.125
ICGR15 (%)	8.4 (4.5–38.4)	9.9 (2.1–30.6)	0.712
PVE	53 (32 %)	15 (43 %)	0.223
Diagnosis			
HCC	47 (28 %)	8 (23 %)	0.742
Metastases	71 (43 %)	14 (40 %)	0.498
Others	47 (28 %)	13 (37 %)	0.310
Benign disease	11 (7 %)	3 (8 %)	0.688
Operative procedure			
Thoracotomy	128 (78 %)	32 (91 %)	0.063
Repeat hepatectomy	13 (8 %)	4 (11 %)	0.494
Right hepatectomy	81 (49 %)	20 (57 %)	0.3861
Multiple resections	56 (34 %)	15 (43 %)	0.321
No. of resections	1 (1–33)	1 (1–14)	0.256
Hepaticojejunostomy	29 (18 %)	10 (29 %)	0.140
Operation time (min)	512 (264–1252)	670 (315–1112)	0.0003
Blood loss (g)	935 (100–5160)	1510 (245–5200)	0.0003
RBC transfusion	21 (13 %)	14 (40 %)	0.0001

BMI body mass index, *ASA* American Society of Anesthesiologists, *ICGR15* indocyanine green retention at 15 min, *PVE* pulmonary vein embolism, *HCC* hepatocellular carcinoma, *RBC* red blood cells

factors [age, sex, American Society of Anesthesiologists (ASA) score, indocyanine green retention at 15 min (ICGR15) value, and portal vein embolization] and operative factors (amount of blood loss, operation time, red blood cell transfusion, thoracotomy, and choledocojejunostomy) were analyzed to identify risk factors for delayed recovery after surgery.

Statistical analysis

The statistical analysis was performed using JMP software (SAS Institute, Cary, NC, USA). The median and ranges of continuous parameters were compared using the Mann-Whitney U test. Categoric parameters were compared using the Pearson χ^2 test or the Fisher exact test, as appropriate. A two-group comparison was performed. Univariate and multivariate analyses were performed using the logistic regression method. Variables with $p < 0.20$ in a univariate analysis were entered into the multivariate analysis. The results were considered statistically significant when $p < 0.05$.

Results

During the study period, a total of 821 patients required liver resection at our institution. Of these patients, 221 underwent major hepatectomy. In all, 15 of these patients simultaneously underwent pancreaticoduodenectomy, 4 colectomy, and 2 partial resection of the duodenum and were excluded from the study. Thus, 200 patients were included in the present study. The patients' characteristics are shown in Table 3.

Assessment of accomplishment of the program

In all, 165 patients (82.5 %) accomplished the ERP by POD 6. The reasons for delayed accomplishment in the remaining 35 patients were as follows: ascites ($n = 16$), delayed gastric emptying (DGE) ($n = 5$), insufficiency of oral intake ($n = 4$), small-bowel obstruction ($n = 2$), pneumonia ($n = 2$); re-laparotomy ($n = 2$), pancreatitis ($n = 1$), spinal infarction ($n = 1$), urethrorrhagia ($n = 1$), hematochezia ($n = 1$).

Assessment of adherence to individual items

The nasogastric tube was removed, and fluid intake was started immediately in 184 patients (92.0 %) on the operative day or POD 1. Overall, 181 patients (89.5 %) were able to consume solid food by POD 3. The epidural catheter was placed and used for pain control until POD 5 in 80.0 % of the patients. The urinary catheter had been removed by POD 4 in 147 patients (73.5 %), and the central venous catheter had been removed and the drip infusion had been completed by POD 5 in 145 patients (72.5 %) (Fig. 1).

Risk factor analysis for delayed accomplishment

The results of univariate and multivariate risk analyses for delayed accomplishment of ERP are shown in Table 4. In the univariate analysis, patient age, amount of blood loss, operative time, and red blood cell transfusion were significantly associated with delayed accomplishment of the ERP. In the multivariate analysis, red blood cell transfusion [$p = 0.007$; odds ratio (OR) 5.47; 95 % confidence interval (CI) 2.45−12.21] and an age of $\geq$65 years ($p = 0.004$; OR 3.48; 95 % CI 1.48−8.7) were revealed as independent factors for delayed recovery after a major hepatectomy.

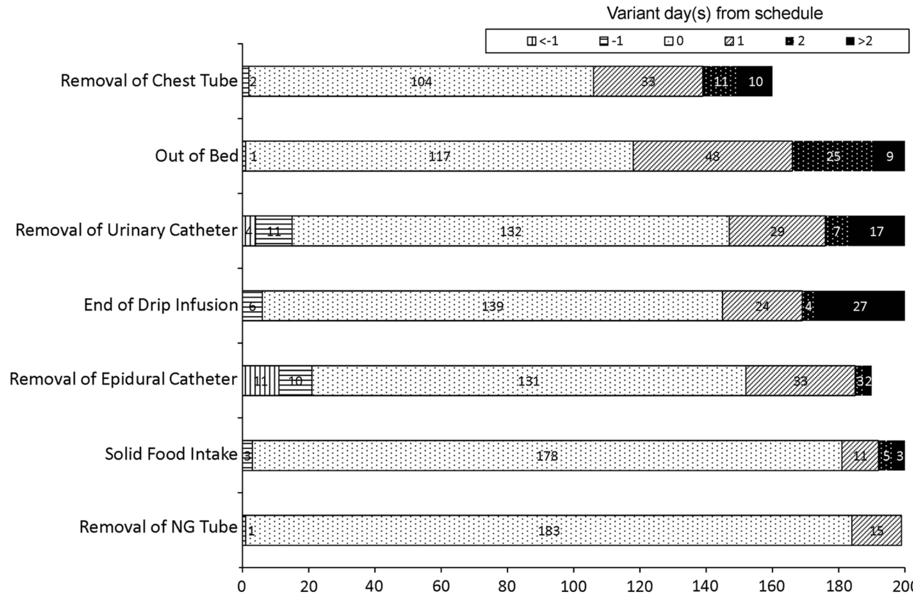

Fig. 1 Adherence of individual items in the enhanced recovery program. Each *bar* shows the variance from the postoperative day that was scheduled in the program. *Numbers* in the *bars* show the number of the patients who received each treatment on that day

Discussion

In our study, 82.5 % of the patients who underwent a major hepatectomy were able to accomplish the ERP by POD 6. The risk factors for delayed recovery after surgery were identified as (1) age >65 years and (2) red blood cell transfusion. Thoracotomy, choledocojejunostomy, or preoperative portal venous embolization had little impact on the patients' postoperative recovery.

In recent years, a zero-mortality rate after liver resection has been achieved at several high-volume centers [1, 2, 17]. The procedure for liver resection and the perioperative care of patients undergoing this procedure can thus be regarded as having a high rate of successful completion. However, there is no guarantee that the quality of a zero-mortality liver resection protocol can be maintained even after radical renovation of the perioperative care. If the only benefits of applying an ERP for an invasive hepatectomy procedure are reductions in the length of the hospital stay and medical expenses, the risk to the patient might be unacceptable. In the present study, we considered what can be changed safely and what should not be changed radically in terms of perioperative care. Based on these judgments, we created a program that incorporates earlier removal of catheters and aggressive mobilization of the body and bowels at an earlier stage, with some items being omitted in a gradual manner.

Several articles have been published comparing ERP with traditional perioperative care for patients undergoing liver resection [10, 11, 13]. Koea et al. [10] showed that the benefits of ERP include earlier resumption of meals and shortened hospital stay. Jones et al. [13] added an objective analysis using an questionnaire for patients and showed that a higher postoperative quality of life score was achieved among the ERP group. However, a randomized control trial for ERP cannot be performed using a double-blind method, and the feasibility of treating patients undergoing liver resection in two different ways at a single institution seems questionable. It is also difficult to extinguish biases in judgments of effectiveness and decisions regarding hospital discharge completely. In general, the study populations in the above-mentioned articles were around 50 for each arm, and a major hepatectomy was performed in fewer than half of them. Statistically, the studies did not have sufficient power to conclude that ERP was not inferior to traditional perioperative care with regard to morbidity and mortality after liver resection. Therefore, it might be too early to conclude that traditional perioperative care can be modified to enable an earlier recovery fashion.

The length of the hospital stay (LoS) is one of the most important factors of an ERP. Under the Japanese insurance system, the mean LoS after liver resection is more than 20 days, and it cannot be denied that social and familial factors affect this duration. We evaluated the accomplishment of the ERP criteria on POD 6, rather than the LoS. However, our criteria can be regarded as the conditions required for discharge in Western countries except for the continued use of drainage tubes.

In the present study, we did not adopt a "no drain" policy, although adverse effects of the routine use of drainage tubes have been demonstrated since the 1990s [18–20], including prohibition of early mobilization and a risk of surgical-site infection [21, 22]. Further study is

Table 4 Multivariate analysis of risk factors associated with delayed accomplishment of the enhanced recovery program

Variable	No.	Delayed No.	Univariate analysis		Multivariate analysis	
			p	OR (95 % CI)	*p*	OR (95 % CI)
Age (years)						
≥65	90	22 (24.4 %)	0.019	2.41 (1.14–5.12)	0.004	3.48 (1.48–8.7)
<65	110	13 (11.8 %)				
BMI (kg/m^2)						
≥25	24	4 (16.7 %)	0.908	1.07 (0.51–2.24)		
<25	176	31 (17.6 %)				
Thoracotomy						
Yes	160	32 (20 %)	0.063	3.08 (0.89–0.64)	0.721	1.27 (0.37–5.91)
No	40	3 (7.5 %)				
Hepaticojejunostomy						
Yes	39	10 (25.6 %)	0.15	1.88 (0.81–4.33)	0.596	1.34 (0.45–3.97)
No	161	25 15.5 %)				
Operation time (h)						
≥10	78	22 (28.2 %)	0.0014	3.29 (1.54–7.03)	0.146	2.1 (0.77–5.81)
<10	122	13 (10.7 %)				
Blood loss						
≥1200 g	87	25 (28.7 %)	0.0002	4.15 (1.87–9.23)	0.055	2.55 (0.98–6.85)
<1200 g	113	10 (8.8 %)				
RBC transfusion						
No	162	19 (11.7 %)	<0.0001	5.47 (2.45–12.21)	0.007	5.47 (2.45–12.21)
Yes	38	16				

needed to clarify the criteria for selecting patients who can undergo an early and quick removal of drainage tubes and for those who do not require a drainage tube.

The adherence ratio for removing the nasogastric tube and the commencement of fluid and solid food oral intake was more than 90 %. An earlier recovery program promoting gastrointestinal peristalsis can thus be adopted. In a randomized control study, Pessaux et al. [23] insisted that there was no clinical advantage to using a nasogastric tube. However, in their study, 12 % of the patients required reinsertion of a nasogastric tube. In our cohort, DGE and small bowel obstruction occurred in seven patients (3.5 %), but these complications became apparent 3 days or more after surgery. Nasogastric tubes can be removed just after surgery. However, because the mean operation time was more than 10 h and most of the operations were completed after suppertime, commencing oral intake on POD 0 was not practical.

More than 70 % of the patients were able to get out of bed and walk on POD 1. Promoting a step-by step rehabilitation program and preoperative patient education can contribute to greater adherence to this item. In contrast, we found low adherence to removal of the chest tube and continuous intravenous drip infusion, which were associated with fluid balance problems. Even though we strictly controlled the fluid volume and electrolytes, some patients with impaired liver function and massive postoperative discharge of pleural effusion and/or ascites required adequate fluid compensation. Some patients required a drip infusion because of a decreased appetite and oral intake. For patients who are >65 years of age and who require an intraoperative red blood cell transfusion, ERP should not be mandatory and the in–out balance control and drip infusion should not be ended prematurely. Other programs should be developed for such patients.

A limitation of this study is that only subjects with relatively good liver function were eligible to undergo major hepatectomy. Whether our ERP is applicable to patients with impaired liver function or liver cirrhosis who are scheduled to undergo segmentectomy, instead of major hepatectomy, remains unclear.

Conclusions

In the present study, we applied the ERP for patients who underwent major hepatectomy. More than 80 % of these patients accomplished the program and achieved almost enough recovery for discharge by POD 6. The remaining 20 % of the patients required additional fluid therapy.

When planning a liver resection, a variety of liver functions, operative procedures, and remnant liver volumes must be considered. Instead of applying a single perioperative program for all liver resections, various ERPs should be developed and selected according to the extent of the liver resection and each patient's condition.

Conflict of interest None

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