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Enhanced Recovery in Liver Transplantation: A Feasibility Study

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Abstract

Background Enhanced Recovery After Surgery (ERAS) programmes after surgery are effective in reducing length of stay, functional recovery and complication rates in liver surgery (LS) with the indirect advantage of reducing hospitalisation costs. Preoperative comorbidities, challenging surgical procedures and complex post-operative management are the points that liver transplantation (LT) shares with LS. Nevertheless, there is little evidence regarding the feasibility and safety of ERAS programmes in LT.

Methods We designed a pilot, small-scale, feasibility study to assess the impact on hospital stay, protocol compliance and safety of an ERAS programme tailored for LT. The ERAS arm was compared with a 1:2 match paired control arm with similar characteristics. All patients with MELD <25 were included. A dedicated LT-tailored protocol was derived from publications on ERAS liver surgery.

Results Ten patients were included in the Fast-Trans arm. It was observed a 47% reduction of the total LOS, as compared to the control arm: 9.5 (9.0–10.5) days versus 18.0 (14.3–24.3) days, respectively, $p < 0.001$. The protocol achieved 72.9% compliance. No differences were observed in terms of post-operative complications or readmission rates after discharge between the two arms. Overall, it was observed a reduction of length of stay in ICU and surgical ward in the Fast-Trans arm compared with the control arm.

Conclusion Considered the main points in common between LS and LT, this small-scale study suggests that the application of an ERAS programme tailored to the LT setting is feasible. Further testing will be appropriate to generalise these findings.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00268-018-4747-y) contains supplementary material, which is available to authorized users.

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Introduction

The Enhanced Recovery After Surgery (ERAS) programme is an evidence based, multimodal approach that aims to optimise perioperative management [1], to attenuate the response to surgical stress and improve recovery, decrease post-operative complications and hospital length of stay (LOS) [2, 3]. Major liver surgery is still affected by 3–5% mortality and 17–56% morbidity rate [4, 5], especially among frail patients: the management of pulmonary, renal and septic complications [4–6] including liver dysfunction require surgical, critical care and hepatology expertise, thus further complicating the patient's path. ERAS programmes are increasingly being applied to complex surgical procedures [7, 8], including liver surgery [9]: their implementation is associated with a 30–50% reduction in LOS, a 0.66 [95%IC:0.49–0.88] relative risk of perioperative complications, and reduced hospitalisation costs [10–14].

Preoperative comorbidities, challenging surgical procedures and complex post-operative management are the points that liver transplantation (LT) shares with liver surgery. Moreover, in Europe and Asia both the procedures are performed by the same hepato-pancreatic-biliary (HPB) surgical team. Considered a well-standardised and life-saving treatment for end-stage liver disease (ESLD) [15], LT remains an expensive and resource-intensive therapeutic intervention [16–18]: besides the surgical aspect [19, 20], ESLD complications [17] and post-operative immunosuppression [21] are responsible for 6–10% death rate within the first month [22] and 2–40% all-confounded morbidity [19–21, 23]. Although, in some selected cases, LT can be considered no more technically complex than major liver surgery, especially in low-MELD patients, with small HCC and compensated cirrhosis.

To date, some evidence exists on isolated items of ERAS programme tested on ESLD patients undergoing LT, as early extubation [24–26] or rapid recovery [27]. One single study recently reported the use of a 13-items enhanced recovery protocol in LT setting [28]. Despite, no firm conclusion can be driven on the basis of these publications.

Considered the main points in common between complex liver surgery and LT, including the same HPB surgical team, we decided to realise an adaptation, prospective small-scale *feasibility study* [29] focusing on the changing programme contents, to determine whether the use of an ERAS programme tailored to the LT setting, will be appropriate for further testing.

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Methods

Study design

The study was designed as a prospective single-arm, open-label, feasibility study of an ERAS programme adapted for LT (Fast-Trans programme).

The local Ethics Committee approved this study in July 2016 (ID RCB: 2016-A00676-45). All LT procedures were performed by the Liver Transplant Department, Hôpital Pitié-Salpêtrière, Paris, France.

All patients listed for LT underwent an extensive workup before their inscription, including oncologic staging in case of primary liver cancer, and among others cardiovascular, metabolic and nutritional status exploration. This latter was assessed either by measurement of the total psoas area at the 3rd lumbar vertebra [30] either through BMI [31]. Neither routine preoperative nutritional support [32, 33] nor adapted physical activity [34] is usually scheduled.

Patients were screened by one of the Authors (RB) in the outpatient consultation setting. If already on waiting list, patients were informed of the ongoing protocol and proposed to participate during the regular follow-up consultation. Alternatively, patients could be informed during the final outpatient consultation before subscribing to be listed, or during the pre-transplantation workup hospitalisation.

Reporting of this study followed the STROBE checklist for observational studies (supplementary material).

Study population (Fast-Trans arm)

Between August 2016 and May 2017, all patients receiving deceased-donor full-size grafts after circulatory death (DCD) or brain death (DBD), which matched the inclusion criteria, were eligible for enrolment in this study. In our institution, DCD grafts are considered exclusively in case of Maastricht III category (controlled cardiac arrest). All patients were informed of the study and gave their written consent to participate in it.

- Inclusion criteria
  Recipients participating in the study had to be 18 years old or older, with a MELD score <25 and provide their written informed consent before an organ was offered to them.

- Exclusion criteria
  Candidate recipients listed for multiple organ transplants, patients with fulminant liver failure, retransplantation, split or living donor LT, or MELD >26 were excluded from the study.
- Intraoperative exclusion criteria
  Complicated and technically demanding procedure from a surgical point of view.
  Blood transfusion >6 Red Blood Cell Units (RBC), indicative of a complex procedure.

Control population (control arm)

The Fast-Trans arm was compared with a match paired control arm having similar characteristics. To achieve a well-matched homogeneous control arm of adequate size, we included LT performed in 2015–2016 in the same centre and by the same team.

As for the Fast-Trans arm, were excluded recipients with a MELD score >26, cases of retransplantation, multi-organ transplantation, fulminant hepatic failure and split LT. Each patient in the Fast-Trans arm was matched retrospectively with two controls (1:2 ratio), based on a stepwise method (Fig. 1):

- Recipient's MELD score.
- Recipient's BMI ± 2 kg/m^2 (one recipient exception ± 6).
- Recipient's age ± 5 years (one recipient exception + 8/− 6).
- Recipient's gender.

Primary objective and endpoint

The primary objective of our study was to assess the impact of an ERAS programme in the LT setting on post-operative outcomes, evaluated from the total hospital stay.

Secondary objectives and endpoints

The secondary objectives of our study were:

- Clinical tolerance, evaluated in terms of the compliance with the items in the protocol.
- Post-operative outcomes, evaluated from the time to functional recovery, stays in the ICU, surgical ward and hepatology ward.
- Safety, assessed from the rates of readmission (0–30 days) after discharge, 90-day post-operative complications and 90-day mortality.

Procedures and protocol

No ERAS protocol goal-oriented specifically designed for LT is available in the literature. For this reason, we developed a modified protocol based on the evidence available on ERAS and liver surgery [9, 25, 35–39], which was specifically tailored for LT and its associated clinical pathway (Table 1).

Discharge criteria

Functional recovery was based on seven criteria that focused on both the patient and graft, defined as follows:

Patient-centred criteria:

- Adequate pain control with oral analgesics,
- Independently mobile,
- Tolerance of solid foods,
- No intravenous fluids.

Graft-centred criteria:

- Normal or declining levels of total bilirubin (TB), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and a normal prothrombin time (PT) or at least 80% of the normal value,
- Good compliance with the immunosuppressive regimen, no immunosuppression-induced adverse effects (e.g., renal failure, tacrolimus overdose),
- Normal Doppler ultrasound findings.

When all of these seven criteria were met, we considered a patient to have functionally recovered. It is medically justified to discharge patients if they meet the criteria for a full functional recovery and are willing to go home [37].

Follow-up

No dedicated ERAS nurse coordination was available at the time of the study, and the adherence to the protocol was followed by two of the authors (RB and AM). After discharge, the liver transplantation coordination (four nurses specially trained and dedicated to LT) managed the follow-up schedule after the hospital discharge. A detailed list of outpatient consultation is offered to the LT patient, with a surgeon, a hepatologist and an anaesthetist. Before each consultation liver biology and liver echodoppler US is organised. During the first month after LT patients are seen every week, during the second month every 2 weeks, and later every month, for the first year.

The discharge was organised at home or care-home depending on familial, social and logistic environment of the patient.

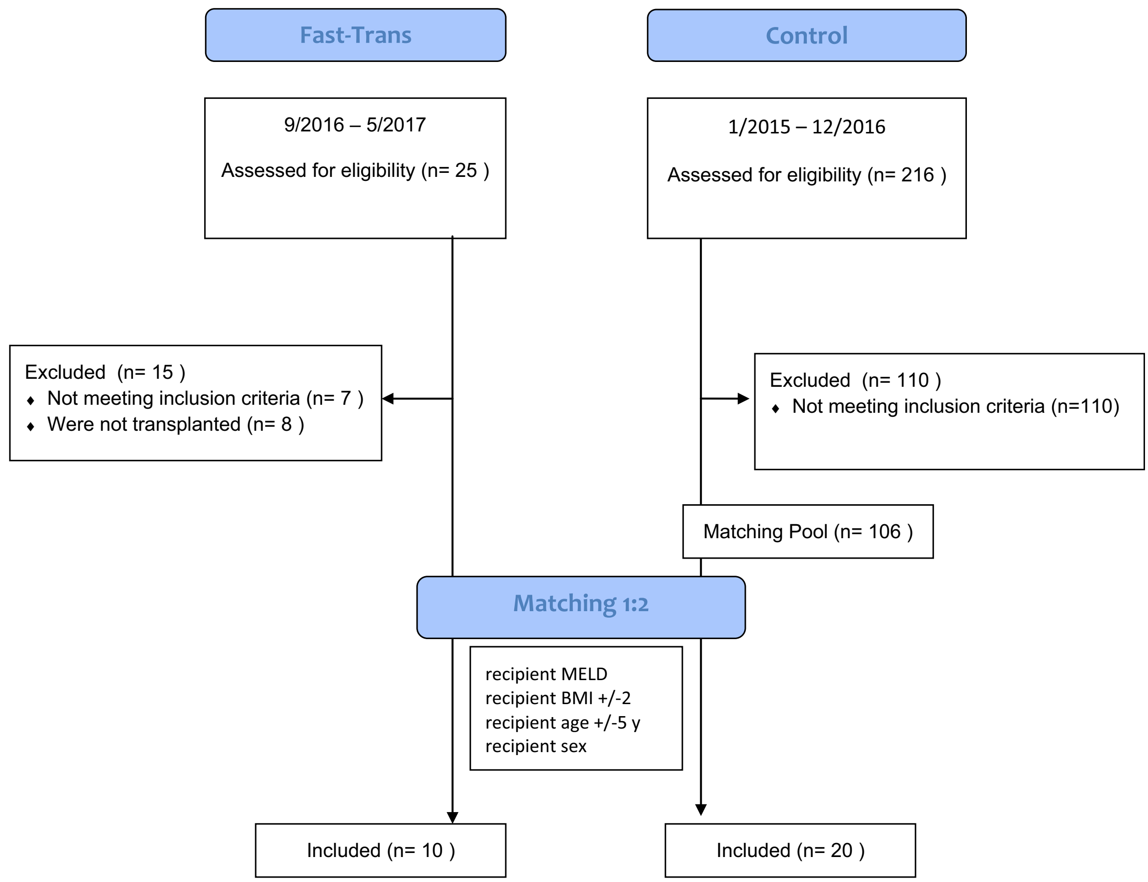

Fig. 1 Flow diagram of patient selection, and inclusion

Data collection and management

Baseline data (gender, age, body mass index, diabetes, underlying liver disease, presence of cancer and previous treatments) determined from the patient's medical history and physical examination, serum laboratory tests and appropriate preoperative workups were collected. Intraoperative data were also obtained on the donor (DCD/DBD, cause of death, graft weight, preservation solution) and recipient (duration of surgery, blood transfusion, cold ischaemia time, technical details on vascular anastomosis). Post-operative data (length of stay in the ICU and ward, complications) were also recorded, including compliance with each item of the protocol. Preoperative and intraoperative data were extracted directly at the end of LT or from the operative report and anaesthesiology monitoring report. Post-operative items were daily recorded in a dedicated form for each patient by two of the Authors (RB and AM): directly bedside or from digital ICU and ward records.

All data were collected in a prospectively maintained database dedicated to LT, declared to the *Commission Nationale de l'Informatiques et des Libertés* (French Data Protection Authority; CNIL No. 1929196).

In case of missing data in either the paper or digital files, the worst-case scenario data imputation was considered. In particular for functional recovery, given the retrospective nature of the control arm, the number of days from LT to discharge (LOS) were imputed to the number of days from LT to functional recovery, in the control arm.

Statistical analyses

The sample size calculation was based on primary outcome and endpoint (total hospital stay expressed in days). In our 2014–2015 LT cohort, the mean hospital stay of a subgroup of patients meeting the same inclusion criteria of this study was of 25 days $\pm$ 9. Based on the only study published in the literature observing a 36% reduction of the hospital stay in the experimental group [28], we expected a decrease of 35% in the Fast-Trans arm compared to the control arm. With a power of 80%, alpha error of 5%, and a 1:2 matching design, we calculated that 27 patients needed to be enrolled: 9 in the experimental arm and 18 in the control

Table 1 Experimental "Fast-Trans" protocol items

N	Preoperative	
1	Outpatient counselling and information	Regarding the procedure, recovery programme, discharge criteria and immunosuppressive regimen
2	Preoperative carbohydrate loading	Using a special high-carbohydrate drink. Because it is not possible to determine the exact timing of anaesthesia induction, the carbohydrate load is administered when the patient is admitted to the ward and waiting to go to the OR
3	Absence of pre-anaesthetic medication (anxiolytic)	Long-acting anxiolytic drugs are avoided
Intraoperative		
4	Antimicrobial prophylaxis and skin preparation	Intravenous antibiotics are administered before the skin incision and less than 1 h before LT. Post-operative "prophylactic" antibiotics are not recommended
5	Prevention of intraoperative hypothermia	Normothermia should be maintained during LT by means of a warmed IV fluids and an upper-lower body air-warming device
6	Incision	The choice of incision is at the surgeon's discretion; either an inverted L or J shaped incision. A Mercedes-type incision should be avoided because of the higher risk of incisional hernia
7	Adapted IV filling	Guided by trans-oesophageal intraoperative US, or using a Swan Ganz catheter
8	Temporary portocaval anastomosis	The use of a temporary PCS during OLT improves hemodynamic status, reduces intraoperative transfusion requirements, and preserves renal function during and after OLT
9	No prophylactic nasogastric intubation	Prophylactic nasogastric intubation increases the risk of pulmonary complications after hepatectomy. Its routine use is not indicated
10	No prophylactic abdominal drainage	The evidence available is not conclusive
11	Prevention of post-operative nausea and vomiting	A multimodal approach to PONV should be used. Patients should receive PONV prophylaxis with two anti-emetic drugs: ondansetron 4 mg IV and droperidol 0.625–1.25 mg IV
12	Antithrombotic prophylaxis and/or anti-aggregation	If PLT >50,000. Can be started intraoperatively if two arterial anastomoses or if the patient is considered to be at risk
13	Early extubation (<6 h after the end of LT)	According to extubation criteria
Post-operative		
14	Early mobilisation (POD1)	2 h at least on a chair, or four times a day
15	Patient-controlled analgesia	Morphine 5 mg/ml (150 mg in 30 ml). Patient-controlled dose: 1—3 mg. Lockout: 8–15 min. 4 h limit: 30–70 mg.
		PCA should be initiated after an initial bolus dose of 5–20 mg morphine (2–3 mg every 5 min up to 20 mg) to attain adequate plasma morphine concentrations. Doses should be reduced in patients aged over 70 years, and in those with severely compromised physical status
16	Gastric probe removal POD1	
17	Clear liquid per os POD1	
18	Enteral feeding per os POD1	Normal food intake should be started from day 1 after surgery
19	Stop IV fluids POD1	The central catheter is removed when leaving the ICU
20	*Per os* analgesia (POD2)	Nefopam: 20 mg/4—6 h
		Tramadol: 100 mg/12 h
		Morphine sulphate: 10 mg/4—6 h
21	Abdominal drain removal POD 2	If output less than 500 ml/day
22	Urinary probe removal POD2	
23	Stop IV analgesia POD3	
24	Independent mobilisation POD3	Can tolerate >6 h on a chair and/or walk three times a day
25	Daily revision of discharge criteria	When all eight are met, the patient is considered to have functionally recovered
26	Audit	

POD post-operative day, *IV* intravenous, *ICU* intensive care unit, *LT* liver transplantation, *PONV* post-operative nausea and vomiting

arm. Anticipating 10% dropout, 30 patients were enrolled in the study.

Categorical variables were reported in terms of percentages while continuous variables were summarised using median and 25–75% values. Pearson's Chi-squared or Fisher's exact tests were used (as appropriate) for categorical variables and the Mann-U Whitney test for continuous variables. A p value <0.05 (two-tailed) was deemed to be significant. All analyses were performed using SPSS software, version 22.0 for Windows (SPSS Inc., Chicago, IL).

Results

Between September 2016 and May 2017, 76 LT was performed. Twenty-five patients were screened and included in the protocol, and 17 were transplanted: seven were subsequently excluded from the protocol and the remaining ten (13.1%) were considered for this analysis. These ten patients in the Fast-Trans arm were then matched 1:2 with 20 control patients who received standard care (Fig. 1). The matching variables (MELD, BMI, age and gender) were identical in both arms (Table 2).

Patient and donor characteristics

No differences were observed among the indications for LT in the two arms, except for a higher rate of Hepatocellular Carcinoma (HCC) ($n = 9$, 90% vs. $n = 9$, 45% respectively, $p = 0.024$), previous surgery ($n = 9$, 90% vs. $n = 10$, 50% respectively, $p = 0.049$) and an older donor age (78.8 (60.1–89.3) vs. 52.4 (46.0–83.6) years, respectively, $p = 0.005$) in the Fast-Trans arm than in the Control arm (Table 2).

Preoperative and intraoperative characteristics

The pre- and intraoperative characteristics of the patients are summarised in Table 2.

Some marked differences were observed between the two arms regarding specific elements of the protocol, such as preoperative information and carbohydrate drink loading, but only in the Fast-Trans arm. Patients in this arm were also extubated earlier (2.0 (0.0–2.0) versus 7.5 (4.5–13.0) hours respectively, $p = 0.001$), and fewer of them required an abdominal drain ($n = 5$, 50% vs. $n = 19$, 95%, respectively, $p = 0.002$) at the end of LT than in the control arm. No differences were observed in terms of the duration of surgery, cold ischaemia time or blood transfusions. No episodes of primary non-function (PNF) or early allograft dysfunction (EAD) were observed.

Post-operative characteristics

Patients in the Fast-Trans arm resumed *per os* analgesia (3 (1.0–4.0) vs. 4.5 (2.7–6.3) days, respectively, $p = 0.017$) and solid food intake (2 (1.0–2.0) vs. 4 (3.0–5.5) days, respectively, $p = 0.000$) sooner after surgery. Similarly, central venous catheters (2 days (2.0–5.0) vs. 6 days (4.5–7.8) respectively, p <0.001), gastric probes (0 (0.0–0.5) vs. 2 (1.0–4.3) days, respectively, $p = 0.000$), urinary probes (1 (1.0–2.5) vs. 6 (2.7–7.8) days, respectively, $p = 0.000$) and abdominal drains (1 (0.0–2.5) vs. 4 (2.0–5.3) days, respectively, $p = 0.012$) were also removed earlier than in the control arm (Table 3).

Primary outcome

In the Fast-Trans arm, it was observed a 47% reduction of the total length of stay, as compared to the control arm: 9.5 (9.0–10.5) days versus 18.0 (14.3–24.3) days, respectively, p <0.001 (Table 4).

Secondary outcome

- Overall, the observed compliance with the protocol was of 72.9% in the Fast-Trans arm (Fig. 2).
- The post-operative outcomes in the Fast-Trans arm versus the control arm, evaluated from the time to functional recovery, was of 7.5 (6.0–7.0) versus 18 (14.3–24.3) days (p <0.001), stays in the ICU 3 (2.0–4.0) versus 4.5 (3.0–8.3) days ($p = 0.005$) and surgical ward 1.5 (0.0–2.0) versus 6 (0.0–8.3) days ($p = 0.01$). In the hepatology ward, the time to functional recovery observed was of 6 (5.0–6.0) versus 7 (6.0–11.5) days ($p = 0.53$) (Table 4).
- No differences were observed in terms of post-operative complications ($n = 5$, 50% vs. $n = 16$, 80%, $p = 0.08$) and 30 days readmission rates after discharge ($n = 3$, 30% vs. $n = 4$, 20%, $p = 0.07$) (Table 4) in the Fast-Trans arm versus control, respectively. Post-operative mortality was nil in both arms.

Discussion

Enhanced Recovery After Surgery (ERAS) programmes are increasingly implemented in all fields of surgery, resulting in lower hospital stay, post-operative complications rate and hospitalisation costs [3, 13, 14, 40, 41].

LT is one of the more complex, expensive and resource-intensive therapeutic intervention that modern medicine has to offer [15, 16], and its considerable morbidity rate, heightens concern towards the financial climate of LT [16, 22]. Although in some selected case LT is no more complex than liver surgery, with short duration of surgical procedure, low transfusion rate, no abdominal drainage, early extubation and short hospital stay [8, 24–26, 42, 43].

Table 2 Patient and donors demography and preoperative characteristics

	Control	Fast-Trans	
Total *n* = 30	*n* = 20	*n* = 10	*p*
Male (%)	17 (85)	8 (80)	1
Age, Y	58.2 (52.6–65.3)	60.1 (52.5–66.1)	0.74
BMI (Kg/m^2)	23.6 (20.3–26.2)	24.6 (20.0–32.8)	0.85
BMI >35 (%)	2 (10)	1 (10)	1
ASA Score			1
2	13 (65)	7 (70)	
3	7 (35)	3 (30)	
MELD Score	7 (6–9)	7 (6–10)	0.81
Liver Disease (%)			
Alcohol	9 (45)	7 (70)	0.26
Viral cirrhosis	10 (50)	7 (70)	0.44
HBV	4 (20)	2 (20)	1
HCV	8 (40)	6 (60)	0.44
Metabolic syndrome	4 (20)	2 (20)	1
Biliary disease	3 (15)	0	0.53
HCC	9 (45)	9 (90)	0.024
Post-medical/surgical history (%)			
Tabagism	11 (55)	5 (50)	1
Ischaemic Heart disease	1 (5)	0	1
Previous surgery	10 (50)	9 (90)	0.049
Preoperative ascites	5 (25)	1 (10)	0.63
Donor characteristics			
Age, Y	52.4 (46.0–83.6)	78.8 (60.1–89.3)	0.005
BMI (Kg/m^2)	24.6 (21.1–32.0)	25.8 (22.7–34.7)	0.52
Graft detail			0.43
DBD	17 (85)	10 (100)	
DCD	2 (10)	0	
Domino	1 (5)	0	
Graft Weight (gr)	1405.0 (1080.0–1919.8)	1355.0 (934.5–2033.5)	0.78
Preservation solution			0.039
Celsior®	0	1 (10)	
IGL-1®	7 (35)	2 (20)	
Scot-15®	10 (50)	2 (20)	
Custodiol®	3 (15)	2 (20)	

Categorical variables are reported using percentages; continuous variables are summarised using median and 25–75% percentiles

BMI body mass index, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *MELD* model for end-stage liver disease, *HCC* hepatocellular carcinoma, *DBD* donation after brain death, *DCD* donation after cardiac death

Our centre performed every year more than 180 liver procedures, for primary liver cancer or liver metastasis [44–48], and the same HPB surgical team realise yearly more than 100 LT [49, 50].

Despite the malnutrition high prevalence in cirrhosis [17], ERAS recommendations for liver surgery are equally fit for these patients that may require an hepatectomy for liver cancer, later followed by LT. Sarcopenia, moreover, is the common negative point affecting outcomes in liver surgery and LT as well [17]. Nevertheless, given the main points in common between liver surgery and transplantation, including the same HPB surgical team, we decided to test the feasibility of a tailored ERAS programme on a small selected series of "easy" LT.

This being said, surgeons, intensivists and hepatologists showed some reluctance in changes such as the no-drain

Table 3 Preoperative and intraoperative characteristics

	Control	Fast-Trans	*p*
Total *n* = 30	*n* = 20	*n* = 10	
Preoperative information	0	10 (100)	0.001
Preoperative carbohydrates drink	0	5 (50)	0.002
Premedication	0	1 (10)	0.33
Balanced IV anaesthesia	20 (100)	10 (100)	NS
Hypothermic prevention	20 (100)	10 (100)	NS
Antibiotic therapy	20 (100)	10 (100)	NS
Surgical procedure			
Incision			0.078
Inverted J shaped	9 (45)	7 (70)	
Inverted L shaped	11 (55)	2 (20)	
Mercedes	0	1 (10)	
Ascites (ml)	0 (0.0–75.0)	0 (0.0–275.0)	0.95
Caval anastomosis			0.44
Piggyback	18 (90)	10 (100)	
Cava replacement	2 (10)	0	
Temporary portocaval anastomosis	17 (85)	10 (100)	0.53
Biliary anastomosis			0.54
Bilio-biliary anastomosis (%)	18 (90)	10 (100)	
Hepaticojejunostomy	2 (10)	0	
Biliary drainage			0.26
Internal	3 (15)	4 (40)	
Kehr	1 (5)	0	
Abdominal drain	19 (95)	5 (50)	0.002
Cold ischaemia (h)	6.1 (5.2–8.7)	6.6 (6.1–7.9)	0.62
Surgery duration (h)	6.7 (5.7–8.2)	6.0 (5.9–8.4)	0.21
Blood transfusion, patients	9 (45)	6 (60)	0.7
Blood transfusion, No. RBC	0 (0–4)	1 (0.5–3)	0.91
Intraoperative fluid filling	4000 (2875–4250)	4500 (3500–9250)	0.32
Early extubation <6 h (h)	7 (35)	9 (90)	0.007
Early extubation (h)	7.5 (4.5–13.0)	2.0 (0.0–2.0)	0.001
PONV	1 (5)	9 (90)	0.000

Categorical variables are reported using percentages; continuous variables are summarised using median and 25–75% percentiles

IV intravenous, *RBC* red blood cells, *PONV* post-operative nausea and vomiting

policy, rapid extubation and enteral feeding, as well as deperfusion and early mobilisation, despite published literature on focused elements of ERAS programme in LT.

Mandell and coll [26], showed—in 3 years—a 96% increase in the early extubation rate after LT, and triage directly to the surgical ward without ICU up to 82%, without compromising patient safety. Another study by Maffei et al. [51] showed that the introduction of an early intensive rehabilitation programme in the ICU after LT enabled patients to sit up sooner and resume intestinal transit earlier than patients in the control group.

All these studies focused on isolated elements of ERAS programmes: even if results are satisfactory, no single element but rather the combination of them in a structured protocol determines the outcome. [35, 52]. In this line, a different approach has been initiated by Rao and coll. [28], with a 13-points perioperative protocol in LT, with a significant reduction in ICU and total hospital stay in the experimental arm.

The principles of ERAS have been adopted by most specialties, producing their own specific protocols, with the generic pre-, intra- and post-operative elements adapted to some specialty specific and evidence-based interventions

Table 4 Post-operative characteristics, morbidity

	Control	Fast-Trans	*p*
Total $n = 30$	$n = 20$	$n = 10$	
Antiplatelet treatment	13 (65)	8 (80)	0.67
Opioid-based patient-controlled analgesia	1 (5)	2 (20)	0.251
Oral analgesia (pod)	4.5 (2.7–6.3)	3 (1.0–4.0)	0.017
Solid food (pod)	4 (3.0–5.5)	2 (1.0–2.0)	0.000
CVC removal (days)	6 (4.5–7.8)	2 (2.0–5.0)	0.000
Gastric probe removal (days)	2 (1.0–4.3)	0 (0.0–0.5)	0.000
Urinary probe removal (days)	6 (2.7–7.8)	1 (1.0–2.5)	0.000
Abdominal drain removal (days)	4 (2.0–5.3)	1 (0.0–2.5)	0.012
Hospital stay			
ICU (days)	4.5 (3.0–8.3)	3 (2.0–4.0)	0.005
Surgical ward (days)	6 (0.0–8.3)	1.5 (0.0–2.0)	0.01
Hepatology ward (days)	7 (6.0–11.5)	6 (5.0–6.0)	0.53
Time to functional recovery (days)	18 (14.3–24.3)	7.5 (6.0–7.0)	0.000
Total Length of stay (days)	18 (14.3–24.3)	9.5 (9.0–10.5)	0.000
Post-operative complications			
Clavien–Dindo			0.09
I	3 (15)	1 (10)	
II	11 (55)	4 (40)	
III	3 (15)	0	
Complications	16 (80)	5 (50)	0.08
Acute graft rejection	1 (5)	0	
Acute hyperglycaemia	1 (5)	0	
Acute renal failure	5 (25)	0	
Acute urinary retention	1 (5)	1 (10)	
Bile fistula	1 (5)	0	
Cardiac arrhythmia	1 (5)	0	
Confusion	1 (5)	0	
Early arterial stenosis	0	1 (10)	
Mild sepsis	3 (15)	0	
Nausea	0	1 (10)	
Peptic ulcer	1 (5)	0	
Surgical site haematoma	1 (5)	2 (20)	
Rehospitalisation <30d	4 (20)	3 (30)	0.07
Bile duct stenosis	2 (10)	1 (10)	
Impaired general condition	1 (5)	1 (10)	
Anaemia	1 (5)	0	
Haematuria	0	1 (10)	
Death	0	0	NS

Categorical variables are reported using percentages; continuous variables are summarised using median and 25–75% percentiles

POD post-operative day, *CVC* central venous catheter, *ICU* intensive care unit

[53]: in LT these are represented by the simultaneous care required by the complex interface between both patient and graft. Despite, the protocol of the aforementioned study by Rao and coll [28], lacks of specific interventions relevant for liver transplantation or graft care For this reason, and in the absence of stronger level of evidence a new, dedicated, multimodal protocol of care patient and graft centred relying on published data from liver surgery and transplantation, was designed. The same should be said for the detailed list of discharge criteria, involving both aspects of

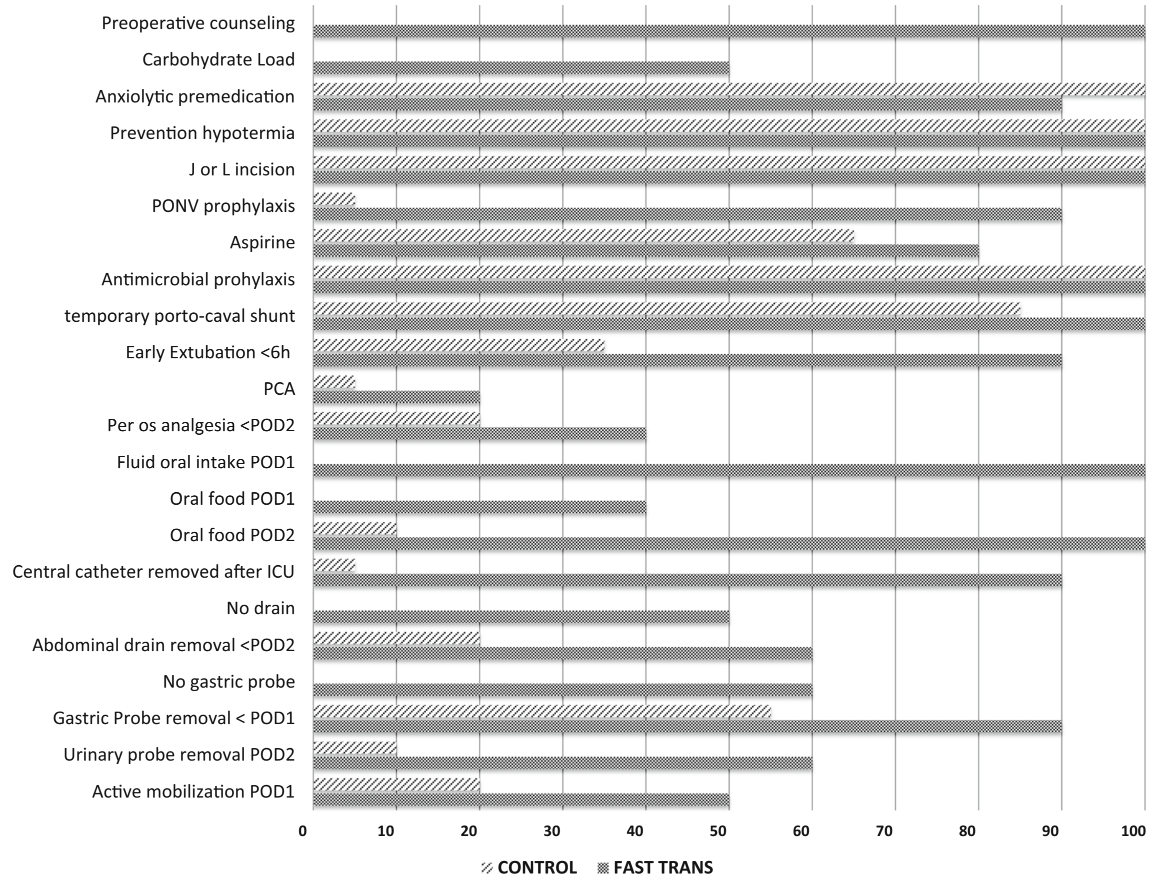

Fig. 2 Protocol items' compliance

treatment (patient-related and graft-related), to more precisely assess the "functional recovery" than simply borrow a checklist tailored for liver surgery [9].

In this way, we could observe a 47% reduction of the total length of stay in the experimental arm when compared to standard care. Only half of the patients in the experimental arm required an abdominal drain, and compared to the control arm, this was removed earlier. Extubation, CVC, gastric and urinary probe were removed earlier in the experimental group compared to the control one, as well. The compliance to the protocol items was as high as 72.9% (Fig. 2), comparable to that observed during previous ERAS programmes [40, 41]. Moreover, similar rates of early readmission and post-operative complications in both arms were observed in both groups: these results are even more interesting when considering the older donor's age and the higher rate of previous surgery in the Fast-Trans arm when compared to the control arm.

Interestingly, no difference in time of surgery nor in transfusion rate was observed in the two arms, supporting the idea that perioperative care, more than surgery in itself, is associated with better outcomes.

This study had several limitations: first, due to safety concerns, the inclusion and exclusion criteria for the Fast-Trans arm resulted in stringent selection. In particular, MELD score <25 and transfusion of less than 6 RBC units cut-offs, were decided after common discussions with the surgical and anaesthesiology medical staff, despite the existing literature [26], to minimise any risk towards patients. The counterpart is that patients involved represented no more than 10% of our yearly cohort. Moreover, we can understand that in centres where the HPB and transplant team are not the same, some concerns about feasibility of this approach could be argued.

Second, in the absence of a dedicated nurse coordinator, the ERAS protocol was led and monitored by surgeons and intensivists, and thus less efficiently than by a trained and dedicated coordinator.

Unlike digestive or pancreatic surgery [3, 7, 11], the effect-size of ERAS on the reduction of complications rate in liver surgery is little, and often limited to Clavien–Dindo grade I [10, 54, 55]. One of the reasons can be related to the considerable inherent morbidity of liver surgery, which is even higher in liver transplantation, given the ESLD morbidity and the immunosuppressive regimen. Not surprisingly, no difference in complication rate was observed in this study, given the limited sample size and because the study was not designed for that purpose. Besides, the observed reduction in LoS can be explained by the active stimulation of patients since the end of LT, for bedside mobilisation, early feeding and drains removal in the experimental group. Finally, the single-centre design of this study precluded any further generalisation of our findings.

Conclusion

In conclusion, the specificity and innovative nature of our study were to focus on simultaneous care of the patient and liver graft: the largest part of the ERAS guidelines for liver surgery items could be transposed to the LT clinical pathway with a dedicated, *patient- and graft-centred* protocol and discharge checklist. Our data suggest that its application would be feasible, but the generalisation of these findings warrants further larger, prospective, randomised clinical trials using the same or a similar protocol, with broader patient's inclusion criteria.

Author contributions OS, OL, AM and RB conceived and wrote the manuscript. All Authors were in charge of patients, revised and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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