Liver Transplantation in Children and Impact of Intra-operative Goal Directed Therapies on Postoperative Outcome

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Short Report

Keywords: Liver Transplantation, Children, Transfusion, Outcome, Patient blood Management, Goal Directed Therapies

Posted Date: July 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-744584/v1>

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Abstract

Background: Liver transplantation is a hemorrhagic surgery with high postoperative complication rates in terms of organ dysfunction and infections. We conducted a retrospective observational monocentric study that had the objectives of determining predictors of postoperative outcome in children. In the initial cohort, 19 children underwent liver transplantation. A description of the postoperative outcomes of these patients was undertaken.

Objective: To describe intraoperative and postoperative outcomes in children undergoing liver transplantation and to propose intraoperative management implementation measures for postoperative outcome improvement.

Methods: Secondary analysis of liver transplanted patients included in the initial study.

Results: There were 19 patients who underwent liver transplantation with a median age of 31[2-154] months. Five patients had re-operations (26.3%). Fourteen (73.7%) had intraoperative and/or postoperative complications. Five (26.3%) had intraoperative hemorrhagic shock. One (5.3%) had postoperative respiratory failure, one (5.3%) had postoperative multiple organ failure, two (10.5%) had postoperative neurologic failure and five (26.3%) had cardio-circulatory failure. One (5.3%) had postoperative pulmonary sepsis, five (26.3%) had postoperative abdominal sepsis, and six (31.6%) had postoperative septicemia. Intra-operative transfusion rate was 100%. In-hospital mortality rate was 10.5% (two patients).

Conclusion:

There were multiple postoperative adverse outcome predictors. Optimal intraoperative patient management with transfusion guided by point-of-care viscoelastic devices and goal-directed fluid and hemodynamic therapy with validated parameters and tools in children is a possible pathway to upgrade postoperative evolution in pediatric liver transplantation.

Introduction

Liver transplantation is one of the most hemorrhagic surgical interventions. Postoperative complications rates in terms of organ dysfunction and infections are high due to the major characteristic of the surgery and to the critical general status of patients requiring urgent transplantation.

Intra-operative blood management and intra-operative fluid and hemodynamic monitoring are necessary for postoperative optimal outcome.

In our Hospital, liver transplantation is among interventions which are performed most of the times on an emergency basis depending on the availability of transplant grafts and patients waiting list.

We conducted earlier a retrospective observational monocentric study in our Hospital which had the objectives of determining predictors of postoperative outcome in pediatric surgical patients in neurosurgery, abdominal surgery and orthopedics (1). In this study of 594 patients, predictors of postoperative outcome were transfusion, American Society of Anesthesiologists score (ASA), emergency surgery, surgery and age. In this initial cohort, there were 19 children who underwent liver transplantation. A secondary analysis was undertaken to describe intra-operative and postoperative outcomes in these liver transplanted patients. The aim of this study was to describe intra-operative and postoperative outcomes in these patients and to suggest implementation measures for optimal intra-operative management with the aim to improve postoperative evolution in surgical pediatric patients.

Methods And Materials

Secondary analysis of liver transplantation patients included in the initial retrospective study (1).

The study was declared to the National Commission for Computer Science and Liberties (CNIL) under the registration number 2028257 v0 on the 21 February 2017 and approved by the Ethics Committee of Necker under the registration number 2017-CK-5-R1 on the 21 March 2017.

Inclusion criteria were patients under 18 years old who underwent hepatic transplantation and included in the initial retrospective study.

Exclusion criteria were patients aged more than 18 years old and patients who did not undergo hepatic transplantation included in the initial study.

Patients were included retrospectively from 1 January 2014 to the 17 May 2017.

Statistics were analyzed with XLSTAT 2020.4.1. software. Continuous variables were expressed in medians with ranges or means with standard deviations. Categorical variables were described in proportions.

In our Hospital, liver transplantation is performed according to an established protocol as described hereafter. Before surgery all patients have a trans-thoracic echocardiography, hemoglobin levels, complete blood cell count, blood coagulation analysis, plasma electrolytes, complete liver function tests, blood group, available blood products corresponding to 2–4 times whole blood volume representing 40% of packed red blood cell units, 60% of fresh frozen plasma units and 0.2U/kg of concentrated platelet units.

Induction of anesthesia is performed with sevoflurane in air-oxygen mixture. Induction of anesthesia is performed intravenously if inhalational anesthesia is contraindicated. 3 large bore peripheral intravenous lines of > 20G are inserted. Airway is secured with orotracheal intubation.

Maintenance of anesthesia is performed with sevoflurane in air-oxygen mixture, sufentanil and atracurium intravenously. All patients are monitored with bi-spectral index, central core temperature probe,

indwelling bladder catheter; one or two central venous lines inserted if peripheral intravenous catheters are not sufficient and a radial arterial catheter. Depending on patient cardiac status, hemodynamic is monitored with Flo-trac/Vigileo if weight is over 25 kg or with esophageal Cardio-Q doppler probe or with cerebral and or renal regional oxygen saturation with near infrared spectroscopy (NIRS).

Fluid therapy is managed with crystalloids containing 1L of 2.5% glucose, 2 g sodium chloride, 2 g calcium chloride at a basal infusion rate of 5–10 ml/kg/h with supplemental fluid therapy at an infusion rate of 5–30 ml/kg/h with 0.9% sodium chloride (NaCl 0.9%), albumin 5%, fresh frozen plasma, packed red blood cells, platelet units. Fluid therapy is adjusted according to central venous pressure, pulse pressure variation, hemoglobin levels, platelet levels and bleeding. The objectives are to maintain hemoglobin levels above 10 g/dL, platelet levels > 50000/ μ L, base excess 8–10 mmol/L, plasma ionized calcium levels > 1 mmol/L, glycemia between 5.5-11mmol/L, diuresis > 0.5-1ml/kg/h, prothrombin time > 30%, fibrinogen levels > 2g/L, mean arterial pressure > 55 mmHg, central venous pressure between 4–10 mmHg, pulse pressure variation between 12–15%, pH > 7 and normothermia.

All patients receive antibiotic prophylaxis with intravenous piperacillin/tazobactam or imipenem and vancomycin according to patient microbiologic status.

Tranexamic acid is administered as an intravenous bolus of 25 mg/kg followed by an intravenous infusion of 2 mg/kg/h up-to 15 minutes before the end of arterial clamping. Fibrinogen is administered if plasmatic levels are lower than 2 g/L.

Vasoactive drugs with norepinephrine or epinephrine are administered if necessary.

Immunosuppressive therapy is administered with intravenous basiliximab (simulect®) 10 mg if the weight is < 35 kg or 20 mg if the weight is > 35 kg after hepatic clamping.

Patients are transferred postoperatively sedated and intubated to the pediatric intensive care unit.

Results

Table 1 illustrates general characteristics

There were 19 patients who underwent liver transplantation with a median age of 31[2-154] months, median weight of 11.5[4.5-39] kilograms, three patients (15.8%) were ASA III and 16 (84.2%) were ASA IV. All were operated on an emergency basis. There were five patients who had reoperations (26.3%). Fourteen (73.7%) had intraoperative and/or postoperative complications. Five (26.3%) had intraoperative hemorrhagic shock. One (5.3%) had postoperative respiratory failure, one (5.3%) had postoperative multiple organ failure, two (10.5%) had postoperative neurologic failure and five (26.3%) had cardio-circulatory failure. One (5.3%) had postoperative pulmonary sepsis, five (26.3%) had postoperative abdominal sepsis and six (31.6%) had postoperative septicemia.

All patients were transfused intra-operatively. The median packed red blood cell volume was 2[1-12] units, the median fresh frozen plasma volume was 5[0-16] units and the median concentrated platelet volume was 0[0-6] units. The mean preoperative hemoglobin level was 9.8 ± 1 g/dL, and the mean postoperative hemoglobin level was 10.6 ± 1.5 g/dL. The median intraoperative crystalloid volume was 1168[130-7000] ml, and the median intraoperative colloid volume was 450[0-1700] ml.

The median length of intensive care unit stay (LOSICU) was 27[2-74] days. The median length of hospital stay (LOS) was 34[14-116] days, the median total length of hospital stay (TLOS=LOSICU+LOS) was 66[16-187] days, and the median total length of mechanical ventilation (LMV) was 4[0-39] days.

The in-hospital mortality rate was 10.5% (in two patients) (table 2). Patients with fatal outcomes had hepatic failure as a comorbidity and had intraoperative hemorrhagic shock. One patient had postoperative multiple organ failure with septicemia, and the second patient had postoperative cardio-circulatory failure with abdominal sepsis.

Table 3 illustrates co-morbidities. The majority of the patients (17, 89.5%) had hepatic failure, one patient (5.3%) had congenital heart disease and one (5.3%) had metabolic disease.

Discussion

14 patients among 19 (73.7%) had intra-operative or postoperative complications. Intra-operative hemorrhagic shock was observed in five (26.3%) patients. Liver transplantation is one of the most hemorrhagic surgical interventions. Preoperative predictors of intra-operative bleeding in hepatic transplantation have been described previously (2). All patients were transfused intra-operatively with packed red blood cells and or fresh frozen plasma and or platelet units. Transfusion with all sorts of blood product which is a necessary therapeutic in hemorrhagic surgery has been correlated with adverse postoperative outcome in terms of organ dysfunction and length of hospital and intensive care unit stays and length of mechanical ventilation in critically ill patients (1, 3, 4, 5). In children, patient blood management programs with goal directed transfusion guided with point of care viscoelastic devices have been shown to reduce intra-operative fresh frozen plasma and length of hospital stay in hemorrhagic interventions like liver transplantation (6). In our Hospital, we have not yet integrated point of care viscoelastic devices to guide transfusion in liver transplantation surgery. With existing evidence, these devices need to be integrated in patient blood management program in this surgical setting. As an improvement implementation measure a protocol with point of care device namely rotational thrombo-elastometry (ROTEM) can be integrated in patient blood management in liver transplantation as illustrated in Figs. 1 to 3. Pediatric values of ROTEM have been described previously with ROTEM delta version (7).

Hemodynamic monitoring depends on patient general status and surgery. Liver transplantation being a major surgery, hemodynamic monitoring with validated tools and parameters in children is necessary for intra-operative optimization and should be applied systematically in all patients undergoing major surgery. Pulse pressure variation and central venous pressure are not optimal parameters to guide fluid

therapy in children (8). In pediatrics, fluid therapy management in terms of fluid responsiveness is best assessed with aortic peak flow velocity variation which can be measured with echocardiography or esophageal doppler probe (Cardio-Q) (8, 9). If FloTrac/Vigileo system is used for fluid and vasoactive therapy, stroke volume variation which is determined with the arterial pressure waveform analysis, can be used to assess fluid responsiveness, however this device has not yet been validated for fluid therapy in pediatric surgical settings (10, 11). One study which included 23 patients aged from 12 to 65 years in posterior spine arthrodesis surgery showed that goal-directed therapy guided by FloTrac/Vigileo stroke volume variation decreased intra-operative bleeding and blood product requirements, postoperative pulmonary complications, intensive care unit stay and postoperative gastro-intestinal complications (12). Thus pediatric studies in surgical settings with FloTrac/Vigileo goal directed fluid and hemodynamic therapy are necessary to determine the impact of this device on postoperative outcome. Monitoring hemodynamics with validated parameters in children is mandatory for optimal intra-operative management in major pediatric surgery which has the objectives to reduce postoperative organ dysfunction. A systematic review and meta-analysis in children demonstrated that non-optimal intra-operative hemodynamic biomarkers such lactate levels, central venous mixed oxygen saturation (SVO₂), regional cerebral and renal oxygen saturation assessed by near-infrared spectroscopy (NIRS) were correlated to adverse postoperative outcome in pediatric surgical settings in terms of morbi-mortality and length of hospital stay (13). Monitoring and optimizing these biomarkers should be part of intra-operative patient management in critically ill patients and major surgery. Postoperative outcome depends on multiple predictors (1, 3, 4, 5). In this study, the rate of postoperative cardio-circulatory, neurologic, multiple organ and respiratory failure was 26.3, 10.5, 5.3 and 5.3 % respectively. The rate of postoperative septicemia, abdominal and pulmonary sepsis was 31.6, 26.3 and 5.4% respectively. In-hospital mortality rate was 10.5%. Integrating intra-operative goal directed therapy with validated tools in children is necessary to reduce postoperative adverse outcome. However, studies evidencing the impact of intra-operative goal directed fluid and hemodynamic therapy on postoperative outcome in pediatrics are still lacking therefore developing research in this field will contribute to clarify these issues in domains where a lot of questions are still unanswered (14, 15, 16, 17, 18).

Conclusion

Liver transplantation is a major surgical setting with high intra-operative transfusion rates and postoperative complications rates in terms of organ dysfunction. Postoperative adverse outcome predictors are multiple. Optimal intra-operative patient management with transfusion guided by point of care viscoelastic devices and goal directed fluid and hemodynamic therapy with validated parameters and tools in children is a possible pathway to upgrade postoperative evolution in pediatric liver transplantation.

Declarations

Conflict of Interest: The author declared no conflicts of interest.

Funding: None

Author contributions: Claudine Kumba conceptualized and designed the study and drafted the initial and final manuscript. She designed the data collection instruments, collected data, carried out initial and final analyses.

Ethics Approval: This study received approval from the Ethics Committee of Necker on 21 March 2017 under registration number 2017-CK-5-R1 and waived patient consent.

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Tables

Table 1 General characteristics of liver transplantation patients

Characteristic	N=19
Median age [range] in months	31[2-154]
Median weight [range] in kilograms	11.5[4.5-39]
ASA III n (%)	3(15.8)
ASA IV n (%)	16(84.2)
Emergency surgery n (%)	19(100)
Re-operation n (%)	5(26.3)
Patients with intra-operative and or postoperative complications (organ failure or sepsis) n (%)	14(73.7)
Intra-operative hemorrhagic shock n (%)	5(26.3)
Postoperative cardio-circulatory failure n (%)	5(26.3)
Postoperative miscellaneous n (%)	1(5.3)
Postoperative multiple organ failure n (%)	1 (5.3)
Postoperative respiratory failure n (%)	1(5.3)
Postoperative neurologic failure n (%)	2(10.5)
Postoperative abdominal sepsis n (%)	5(26.3)
Postoperative septicemia n (%)	6(31.6)
Postoperative pulmonary sepsis n (%)	1(5.3)
In-hospital mortality n (%)	2(10.5)
Transfusion n (%)	19(100)
Median packed red blood cell volume in units [range]	2[1-12]
Median fresh frozen plasma volume in units [range]	5[0-16]
Median concentrated platelet units [range]	0[0-6]
Mean preoperative hemoglobin levels $\pm$ standard deviation in g/dL	9.8 $\pm$ 1
Mean postoperative hemoglobin levels $\pm$ standard deviation in g/dL	10.6 $\pm$ 1.5
Median crystalloid volume in ml [range]	1168[130-7000]
Median colloid volume in ml [range]	450[0-1700]
Median length of intensive care unit stay in days [range]	27[2-74]
Median length of hospital stay in days [range]	34[14-116]
Median total length of hospital stay in days [range]	66[16-187]
Median total length of mechanical ventilation in days [range]	4[0-39]

Table 2 Patients with fatal outcome

	Age in months	ASA score	Co-morbidities	Intra-operative complications	Postoperative outcome	Delay of in-hospital mortality in days	Emergency	Transfusion
tation	5	4	Hepatic failure	Hemorrhagic shock	Multiple Organ Failure and Septicemia	148	Yes	Yes
tation	62	4	Hepatic Failure	Hemorrhagic shock	Cardio-circulatory failure and Abdominal Sepsis	86	Yes	Yes

Table 3 Co-morbidities

Comorbidity	Number of patients (%)
Pre-existing heart disease	1 (5.3)
Chronic liver disease	1 (5.3)
Renal failure	17 (89.5)

Figures

Figure 1

ROTEM Algorithm in children between enfant 0-24 months. CT=coagulation time in seconds, A10= clot firmness at 10 minutes, MCF =maximum clot firmness, CLI60= lysis index in % 60 minutes after CT, ML= maximum lysis in %, FFP=fresh frozen plasma, PRBC=packed red blood cells, Hb=hemoglobin

Figure 2

ROTEM Algorithm in children 2-16 years. CT=coagulation time in seconds, A10= clot firmness after 10 minutes, MCF =maximum clot firmness, CL160= lysis index in % 60 minutes after CT, ML= maximum lysis in %, FFP=fresh frozen plasma, PRBC=packed red blood cells, Hb=hemoglobin

Figure 3

ROTEM Algorithm >16 years. CT=coagulation time in seconds, A10= clot firmness at 10 minutes, MCF =maximum clot firmness, CL160= lysis index in % 60 minutes after CT, ML= maximum lysis in %, FFP=fresh frozen plasma, PRBC=packed red blood cells, Hb=hemoglobin