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The influence of intraoperative blood loss on graft survival and morbidity after orthotopic liver transplantation in children

Abstract The aim of this study was to analyze the influence of intraoperative blood loss, expressed as an index of the circulating blood volume (BL), on patient and graft survival and on morbidity after primary orthotopic liver transplantation (OLT) in a series of 40 consequetive children (Mann-Whitney test, Pearson test). The influence on patient survival could not be assessed due to the low mortality. Graft survival and overall morbidity were not affected. Increased BL led only to a higher incidence of postoperative bleeding, with a subsequent higher intervention rate. In the group of children aged 3.75 years or less, significantly higher BL was found compared to the older children. In addition, prolonged intensive care unit stays and ventilator times were observed in this younger age group. The BL thus has limited repercussions on graft survival and morbidity after primary pediatric OLT.

Key words Pediatric liver transplantation · Blood loss Graft survival · Morbidity

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Introduction

Pediatric patients with end-stage liver disease or an inborn metabolic error with its primary defect in the liver will ultimately die of their disease or its secondary effects. The only way to cure these patients is to replace the liver. Long-term patient survival after orthotopic liver transplantation (OLT) is favorable, and several centers have reported 5-year patient survival of 64% to 77% [5, 6, 10, 22]. Moreover, the quality of life after OLT is good [1, 5, 11]. Therefore, OLT is an acceptable mode of treatment for children with end-stage liver disease or primary inborn metabolic errors of the liver [17].

Death after pediatric OLT occurs mainly within the first 3 to 6 months [6, 21]; the reasons vary from technical problems during organ harvesting or implantation to infection or rejection with graft failure [5, 6, 9, 14, 15, 27]. Improvement of long-term patient survival can be expected if this early patient loss can be prevented. Intraoperative blood loss (BL) is one of the factors often held responsible for early death after OLT. However, conflicting reports have been published on the relation between BL and patient and graft survival and postoperative morbidity. Several authors [2, 4, 7, 8, 12, 21, 25, 28] have confirmed a relationship between BL and postoperative mortality and morbidity and graft survival, whereas others [3, 13, 16] could not. The discrepancy may be explained by the different patient populations and the varying methods of assessment of BL in these series.

The precise impact of BL on the results of OLT remains unclear. In children, the possible effects of BL on the postoperative course may be more pronounced than in adults because of their smaller circulating blood volume. Moreover, data on the influence of BL on the postoperative course after pediatric OLT are scarce. The aim of this study was to analyze the influence of BL on early graft and patient survival and postoperative morbidity in a series of 40 consecutive primary pediatric OLTs.

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Materials and methods

Selection of recipients

From November 1982 to September 1991, 40 children with end-stage liver disease or an inborn metabolic error with its primary defect in the liver received an OLT at our institution. Selection of the patients was done according to a strict protocol [31] where the diagnosis of liver disease was confirmed and the stage and progress of the disease were determined.

Table 1 shows recipient, donor, and graft characteristics. The severity of liver disease is expressed using the Child-Pugh classification; 90% of the transplanted children were in class B or C and 10% (4 children with tyrosinemia) in class A. Of the 40 transplanted children, 23 (57.5%) had had previous upper abdominal surgery, mostly Kasai procedures for biliary atresia. In a small number of patients shunt surgery, splenectomy, or another surgical intervention for variceal bleeding had been performed.

When considered suitable for liver transplantation, the child was placed on the waiting list with an urgency grade according to the stage of the disease. Patients with recurrent hypoglycemia, hypoalbuminemia, uncorrectable clotting profile, or frequent upper gastrointestinal (GI) bleeding were hospitalized until a suitable donor liver was available. In the meantime, special care was taken to correct the patient's nutritional deficiencies as much as possible.

Donor operations

Selection of liver donors was based solely on ABO blood group compatibility (Table 1). Liver grafts were obtained from brain-dead and hemodynamically stable donors. The harvesting procedure described by Starzl et al. [24, 26] was used. Size-matched liver grafts were preferred, but when not available larger donors were accepted. The liver was reduced in size after harvesting as described by Otte et al. [18] and stored in cold preservation solution in plastic bags in a sterifoam container at 4° C until transplantation. Up to 1987, 14 grafts were perfused with Eurocollins solution (E.C.), while the University of Wisconsin solution (U.W.) was used for the other 26 grafts. The median cold ischemia times (CIT) for the grafts preserved in E.C. and U.W. were 5 and 9 h, respectively.

Table 1 Patient and transplantation variables (N = 40, all primary transplantations)

		Range
Recipient age (years)	3.4[a]	(0.33–16)
Recipient weight (kg)	13[a]	(5.7–63)
Recipient diagnosis[b]		
– Biliary atresia	20	(50%)
– Metabolic diseases	9	(22.5%)
– Cholestatic diseases	9	(22.5%)
– Acute hepatic failure	2	(5%)
Child-Pugh score of recipient		
– A (<7)	4	(10%)
– B (7–9)	14	(35%)
– C (>9)	22	(55%)
ABO blood group compatibility		
– identical	26	(65%)
– compatible	11	(27.5%)
– incompatible	3	(7.5%)
Graft type		
– full-size graft	25	(62.5%)
– reduced-size or segmental graft	15	(37.5%)

[a] Median value
[b] Number of patients

Preoperative care

Bacterial surveillance cultures were taken and the cytomegalovirus (CMV) status of the patient was determined. Infection prevention was started by selective bowel decontamination (SBD) in order to remove the gram-negative bacteria and yeasts from the GI tract as described by van der Waay and Rosman et al. [20, 32], administering three non-absorbable oral antibiotics: polymyxin E, tobramycin, and amphotericin B q.i.d. Additionally, prophylactic parenteral antibiotics (tobramycin and cefotaxim) were given and continued for 48 h postoperatively.

Recipient operations

Implantation of full-size grafts was done according to the technique described by Starzl et al. [23]. Reduced-size grafts were transplanted in orthotopic position in the same way. Segmental grafts were transplanted according to the technique reported by Ringe et al. [19]. In 25 children a full-size matched liver graft was transplanted; in the remaining 15 a reduced-size or segmental graft was used (Table 1).

In 6 children above the age of 10 years a veno-venous bypass was used. In cases of expected substantial blood loss a cell saver (Haemonetics) was used. Hepatic artery reconstruction varied depending on the quality and anatomy of the vascular supply of the recipient and the graft. Biliary reconstrction was performed in 16 cases by end-to-end choledochocholedochostomy and in 24 by end-to-side Roux-en-Y hepaticojejunostomy.

Postoperative care

The first 5 cases were treated with a conventional double immunosuppressive scheme consisting of azathioprine 2–3 mg/kg day and prednisolone in a starting dose of 4 mg/kg day, slowly tapered to a maintenance dose of 0.5–0.8 mg/kg day, and after 3 to 6 months further tapered to 0.5 mg/kg given on alternate days. In addition, cyclophosphamide 3 mg/kg day was given during the first 10 postoperative days. After May 1985, 35 patients were treated with cyclosporine A in addition to the conventional scheme in a starting dose of 4.5 mg/kg day i.v. When oral intake was possible, the i.v. dosage was converted to oral portions. Dosages were aimed at high-performance liquid chromatography (HPLC) levels of 200–250 ng/l during the first 4 weeks and 100–150 ng/l thereafter. Within this scheme, prednisolone was tapered more rapidly and to a lower level of 0.3 mg/kg day compared to the conventional scheme. Clinically evident and histologically proven rejections in the first 4 weeks after transplantation were treated with three successive i.v. bolus injections of methylprednisolone 20 mg/kg day. After this period, depending on the severity of the episodes, rejections were treated with an increase of oral prednisolone to a maximum of 4 mg/kg day for 3 days and then tapered.

Monitoring for bacterial infections was done by surveillance cultures of the oropharynx, sputum, bile, urine, and rectum three times weekly. Additionally, cultures of ascites and all discharges from wounds and drains were taken when infections were suspected. Proven bacterial infections indicated by fever, white blood cell count elevation, and positive cultures were treated according to the sensitivity pattern for the tested antibiotics. To prevent herpes simplex virus (HSV) infections, patients were given prophylaxis with oral acyclovir. Screening for CMV infection was done primarily by the determination of immediate early antigen (IeA) in plasma samples as described by van der Bij et al. [30]. Additionally, IgM and IgG levels were determined and urine and blood samples cultured. Primary treatment of proven CMV infection was done by reduction of the immunosuppression. Gancyclovir was only given when hepatitis or pneumonitis was present or the condition of the recipient did not allow delay of treatment. In case of deteriorating graft function, diagnostic tests such as ultrasound (US), cholangiograms, liver biopsy, and duplex US were performed to reveal its cause.

Patient survival, graft survival, and morbidity were assessed in 40 consecutive transplanted children with a primary graft during the 1st 6

postoperative months to analyze the influence of BL on the outcome after OTL. Graft survival was estimated by excluding all causes of graft loss leading to retransplantation and patient death irrespective of graft function. The postoperative morbidity was assessed in primarily grafted children with completed 6-month follow-up by collecting data of episodes of postoperative bleeding and rejection as well as number of infectious, GI, vascular, and biliary complications. Furthermore, data on the number of surgical interventions, days on mechanical ventilation, and total number of days in the intensive care unit (ICU) were collected. The overall morbidity was assessed by the number of postoperative complications per transplanted child.

The amount of BL was estimated by measurement of the loss via cell saver or suction devices and weighing the wet sponges. To standardize comparisons, the BL was expressed as an index of the circulating blood volume (CBV) of the child. This CBV was estimated by multiplying the body weight in kg by 80 ml per kg. The index was calculated by dividing the BL by the circulating blood volume of the child. The relationships between the indexed blood loss (IBL) and patient survival, graft survival, and morbidity were examined.

Statistical analysis (Program: SPSS)

Comparison of IBL between the variables graft survival, bacterial infections, viral infections, sepsis, vascular complications, biliary complications, GI complications, acute rejections, and incidence of postoperative bleeding episodes was calculated using the Mann-Whitney test (MW-U) for continuous variables. The values of these nominal variables were divided into two categories, mostly the presence or absence of, for example, a specific infection, a specific complication, a postoperative bleeding episode, and a failing or functioning graft. The relationship between IBL and the ICU stay, ventilator time, number of infectious complications per child, and number of complications per child was analyzed by means of Pearson's coefficient (r). A P value <0.05 was considered significant.

Results

BL ranged from 0.7 to 31.9 1 (median 4.2); the median value of the IBL was 4.045 (range 0.58–22.59) times circulating blood volume. Seven children died within 6 months after transplantation, resulting in a patient survival of 82.5%. Two children died with good functioning grafts after primary transplantation due to hyperpotassemia, with cardiac arrest at day 1 in 1 case and congestive heart failure at day 5 after OLT in the other. Five died after a retransplantation due to multiple organ failure in 3 and sepsis and decerebration in the remaining 2. In view of the study design, only the children who died after primary liver transplantation (N = 2) were taken into account for testing the relationship between IBL and patient survival. Because of this small number of children who died after primary transplantation (2 vs. 38), no reliable statistical analysis could be performed to test the relationship between IBL and patient survival.

Eight out of 40 primary grafts were lost within the 6-month study period, resulting in a graft survival of 80%. Two grafts were lost due to patient death while 6 failed: 3 by primary nonfunctioning, 2 by persistent intracellular cholestasis, and 1 by histologically proven chronic rejection. To asses the relation between IBL and early graft survival, the median IBL in the group with and without failing grafts was tested with the MW-U. No significant

difference was observed (P = 0.36) between median IBL and graft survival 6 months after transplantation.
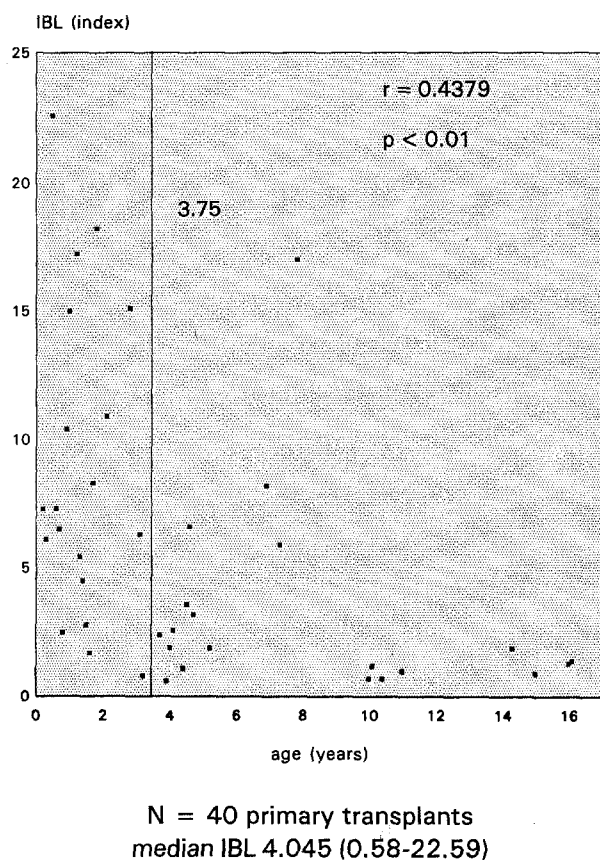
Morbidity was assessed in the 32 children who completed the 6-month study period with their primary graft. In 11 cases bacterial infections were observed, which were clinically manifest as intrahepatic abscesses or cholangitis and intra-abdominal abscesses. A total of 8 children had a septic episode based on abscesses, cholangitis, and intravascular and bladder catheters. In 10 a viral infection with CMV or Epstein-Barr virus was proven. Addition of all the registered infectious complications per patient revealed that 19 of the 32 children had at least one infectious complication (59%). No significant difference was found between the median IBL in the groups with and without a specific infection.

The vascular, biliary, and GI complications and the incidence of acute rejection were also analyzed. Vascular complications occurred in 3 children. One portal vein thrombosis was diagnosed, whereas no hepatic artery thrombosis occurred. In the remaining 2 cases an inferior vena cava syndrome was present caused by compression and torsion of the inferior vena cava. Biliary complications such as bile leakage and necrosis of the bile ducts with a patent hepatic artery occurred in 8 children. In 4 cases GI complications such as intestinal perforation and bleeding from a peptic ulcer or intestinal varices occurred. Histologically proven acute rejection was found in 18 children. Testing of the median IBL revealed no statistically significant difference between groups with and without the above-mentioned specific complications.

The incidence of postoperative bleeding episodes and subsequent reinterventions was assessed in the 40 children because it usually represents an early complication in the first days after transplantation, in contrast to the other monitored complications. A significantly higher (P = 0.01) median IBL was found in the group with postoperative bleeding (7 out of 40 children) compared to the group without bleeding. For surgical interventions (23 out of 40 children) a comparable relation to the median IBL appeared (P = 0.02). The median stay in the ICU for primarily grafted children with a follow-up of at least 6 months was 8 days (range 1–62), and the median ventilator time was 3 days (range 1–60). There was no significant correlation between the IBL and total stay in the ICU (r = 0.2515, P >0.05) or time on the ventilator (r = 0.2323, P >0.05).

Five of the 32 children with a primary liver graft and a completed study period of 6 months recovered without complications, whereas the remaining 27 had at least one complication. No significant correlation was found between IBL and number of complications per child (complication rate, r = 0.0339, P >0.05). In addition, no significant correlation was found between IBL and number of infectious complications per child (infection rate, r = 0.0593, P >0.05).

Figure 1 shows a significant correlation (P <0.01) between IBL and age of the child at the time of transplantation. In this scatterplot of IBL and age, a clear cut-off point is shown at the age of 3.75 years: the median IBL was significantly higher (MW-U, P = 0.008) in the group of

123

IBL (index)

r = 0.4379

p < 0.01

3.75

age (years)

N = 40 primary transplants
median IBL 4.045 (0.58-22.59)

Fig. 1 Correlation between blood loss index (BL) and age

children aged 3.75 years or less (N = 21/40) compared to the group of children over this age (N = 19/40). The graft survival for both age groups was, respectively, 76% (5/21) and 83% (3/19) 6 months after OLT.

The relationship between IBL and graft survival and postoperative morbidity was also tested separately for the

age groups. In both groups no significant difference was observed between the median IBL of the children with functioning or failing grafts 6 months after OLT (Table 2). Furthermore, no significant differences in median IBL were found between groups with and without the complications enumerated in Table 2 for both age groups except for a highly significant ($P = 0.003$) relationship between IBL and postoperative bleeding in the group 3.75 years of age or younger (Table 2).

No significant correlation was found between IBL and complication rate, infection rate (Table 3), ICU stay, or ventilator time in both age groups. A significantly longer median ICU stay and ventilator time was found in the group of children 3.75 years of age or younger compared to the older children (Table 4).

Discussion

In this study the relationship between BL and patient survival, graft survival, and morbidity were assessed 6 months after primary OLT. A statistically reliable analysis of the relation between BL and patient survival could not be established because of the small number of patients who died (2/40) after primary OLT. No significant relationships were demonstrated between BL and graft survival or specific or overall morbidity 6 months after primary OLT except for the incidence of postoperative bleeding with subsequently higher surgical intervention rate. Even in the group aged 3.75 years or less, with a significantly higher IBL compared to the older age group, no significant relationships were demonstrated between BL and graft survival or specific or overall morbidity 6 months after primary OLT, except for postoperative bleeding. However, the postoperative course of the younger children was more problematic, as expressed by prolonged ICU stays and ventilator times.

Table 2 Relationship of blood loss index (BL) with morbidity[a] and graft survival (N = 32)

Variable[b]	<3.75 years yes	no	P value	>3.75 years yes	no	P value
	N (BL)[c]	N (BL)		N (BL)	N (BL)	
Graft survival[d]	16 (6.36)	5 (10.91)	0.25	16 (1.87)	3 (0.88)	0.50
Infections						
– Bacterial	7 (6.14)	9 (8.29)	0.07	4 (4.22)	12 (1.59)	0.12
– Viral	4 (10.78)	12 (6.20)	0.28	6 (1.90)	10 (1.62)	0.45
– Sepsis	3 (2.39)	13 (7.32)	0.07	5 (1.37)	11 (1.94)	0.40
Vascular complication	2 (4.93)	14 (6.36)	0.69	1 (1.37)	15 (1.87)	0.75
Biliary complication	3 (6.47)	13 (6.25)	0.50	5 (1.87)	11 (1.86)	0.61
Gastrointestinal complication	2 (6.79)	14 (6.31)	0.81	2 (3.24)	14 (1.87)	0.52
Acute rejection	11 (6.14)	5 (7.32)	0.13	7 (1.37)	9 (1.94)	0.43
Postoperative bleeding episode[e]	5 (15.09)	16 (5.88)	0.003	2 (3.97)	17 (1.86)	0.43

[a] Morbidity assessed in 32 first transplants, which were observed for at least 6 months
[b] Nominal variables are dichotomised into two categories yes/no and shown as number of patients
[c] Median BL () in both categories tested with Mann-Withney U test; $P < 0.05$ considered significant
[d] Graft survival of 40 first transplants after 6 months
[e] Postoperative bleeding episodes assessed in 40 first transplants

Table 3 Correlation between blood loss index (BL) and other variables [ICU (intensive care unit) N.S. (nonsignificant)]

BL[a] Variable[d]	<3.75 years[b] r		>3.75 years[c] r	
ICU stay	0.0430	N.S.	0.0720	N.S.
Ventilator time	0.0180	N.S.	0.0180	N.S.
Infection rate	0.2688	N.S.	0.2320	N.S.
Complication rate	0.2308	N.S.	0.2210	N.S.

[a] BL as continuous variable in both age groups
[b] N = 16, first grafts, at least 6 months follow-up, children aged 3.75 years or less
[c] N = 16, first grafts, at least 6 months follow-up, children aged over 3.75 years
[d] Correlation between BL and continuous variables tested with Pearson's coefficient (r)

Table 4 Intensive care (ICU) and Ventilator support in both age groups

	Age[a] <3.75 Median (range)	Age[b] >3.75 Median (range)	P value[c]
ICU stay (days)	12 (1–24)	5.5 (1–62)	0.025
Ventilator days	8 (1–19)	2 (1–60)	0.024

[a] N = 16, first grafts, at least 6 months follow-up
[b] N = 16, first grafts, at least 6 months follow-up
[c] Mann-Whitney U test, P <0.05 considered significant

The main conclusion of this study is that BL has limited repercussions on the results of primary pediatric OLT. Increased BL leads only to a higher incidence of postoperative bleeding episodes with subsequent surgical interventions; graft survival and overall morbidity are not affected. This conclusion is in contrast to the generally demonstrated relationship between BL and outcome after OLT reported by several groups [2, 4, 7, 12, 28, 29]. Busutill et al. [4] reported significantly better 1-year graft survival and a trend toward improved long-term survival with lower BL. Bontempo et al. [2] and Stock et al. [28, 29] reported significantly better 6- and 12-month patient survival with lower BL, whereas Garcia de Silva et al. [7] concluded that the quantity of blood given during OLT is an important risk factor, and estimated a risk ratio of 1.5 for each ten units of blood given. Kirby et al. [12] reported that a high BL of more than 70 units was associated with high mortality. These series, however, were dealing mainly with mixed populations of adult and pediatric patients [4, 7, 12, 28, 29] or only adult patients [2]. Adult and pediatric patients in these mixed series are not comparable.

Pediatric OLT has special aspects including technically more demanding transplantation surgery with small vascular and biliary anastomoses, a reduced or segmental liver graft, more difficult vascular access, and a less mature immune system. Additionally, BLs during primary and secondary grafting were considered together in several publications [4, 12], but these are not comparable due to the nature and extent of these operations. Another drawback in the literature is the assessment of BL. In the majority of the mentioned studies, BL was expressed as either the number of transfused red blood cell (RBC) units or the total amount of blood products transfused including RBC units, plasma, and platelets. Excepting the series of Stock et al. [28, 29], no corrections were made in the mixed populations [4, 7, 12, 28] for body weight or surface area. Even though blood product replacement figures seem to be an objective measurement of BL, some remarks can be made. Firstly, the number of transfused RBC units will only be a partial reflection of the total blood volume lost. Secondly, in order to be a true measure of BL, transfusions have to be done in sufficient volumes to reach either preoperative hemoglobin and hematocrit levels, or prefixed levels for that particular patient. In only a few [16, 29] of the cited studies were these values stated or was a general transfusion policy described.

The mixed composition of the reported populations together with combined primary and secondary grafting and a variety of BL assessments make a reliable analysis of BL and postoperative outcome difficult. To avoid these problems, the present study was designed by choosing only pediatric patients with a primary liver graft. The absolute BL was assessed and corrected for the CBV in order to enable a comparison between individuals of different size. This seems to be the most accurate means of assessment of BL. In this study, a major impact of BL on graft survival and postoperative morbidity could not be found. However, lowering the BL still remains worthwhile in order to diminish the use of blood products and medical efforts such as reinterventions. As a consequence, the costs of OLT will decrease.

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