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Surgical aspects and outcome of combined liver and kidney transplantation in children

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Summary

In children with renal insufficiency and accompanying or underlying liver disease, combined liver and kidney transplantations (CLKT) are indicated. However, because of the rare indications, the number of paediatric CLKT is low. Our aim was to analyse CLKT in children with special regard to surgical aspects and outcome. All paediatric CLKT performed at our institution between 1998 and 2009 were retrospectively analysed. Between 1998 and 2009, 15 CLKT were performed in 14 paediatric patients (median age 8 years, range 1–16 years). The indications for CLKT were autosomal recessive polycystic kidney disease ($n = 7$), primary hyperoxaluria type 1 ($n = 7$) and retransplantation because of primary liver nonfunction ($n = 1$). In the postoperative course, six patients showed bleeding complications, thereof three patients needed operative revision for intra-abdominal bleeding. Eight of 15 patients (53%) needed dialysis. The 1- and 5-year patient survival was 100%; and 1- and 5-year graft survival was 80% for the liver and 93% for the kidney allograft. A number of different complications, especially secondary haemorrhage have to be anticipated after CLKT, requiring a timely and interdisciplinary treatment approach. With this management, our patients showed an excellent graft and patient survival.

Introduction

Since the first kidney transplantations (KTX) in the 1950s [1] and liver transplantations (LTX) in the 1960s [2], graft and patient survival has improved dramatically [3–5]. As a result, the first successful combined liver and kidney transplantation (CLKT) was performed in 1984 [6]. Renal insufficiency, because of a variety of causes, is a common problem especially in adults suffering from end-stage liver disease. Renal impairment in liver transplant patients is known to amplify the risk for both, postoperative chronic kidney disease and mortality [7,8]. Therefore, the number of CLKT in adults has shown a considerable increase over the last few years [9,10]. In addition, the introduction of the model of end-stage liver disease (MELD) for liver graft allocation has increased the allocation of organs to patients with renal insufficiency [11].

In children, on the other hand, the most common causes for CLKT are congenital diseases affecting both liver and kidney like primary hyperoxaluria type 1 (PH-1), autosomal recessive polycystic kidney disease (ARPKD) and others [10,12]. As a result of the low incidence of these diseases, CLKT in children is still a therapy performed in a very limited number of cases. As a consequence, only few data are available in the literature regarding paediatric CLKT. With increasing experience and improved outcome after isolated paediatric LTX and

KTX, a program of CLKT in children was started at our hospital in 1998. Our aim was to analyse indications and outcome of these paediatric patients.

Methods

All paediatric patients undergoing CLKT at the University Medical Centre Hamburg-Eppendorf were identified from a prospective database. Overall, 15 CLKT in 14 children were performed between 1998 and 2009. In the same time period, 407 isolated LTX and 64 isolated KTX in children were done (characteristics of these patients are given in Table 1).

The patients were analysed for donor and recipient characteristics. Special attention was given to the technical aspects of the liver and kidney transplant procedure. Intraoperative and postoperative course as well as postoperative complications, especially those related to vascular, biliary or urinary reconstruction, were monitored. Finally, graft and patient survival of the children was analysed.

Statistics

Continuous data were expressed as mean and standard deviation in case of normal distribution or otherwise as median and range. Categorical variables were expressed as number and percentage. Graft and patient survival were assessed using Kaplan–Meier survival curves. All statistics were performed using the SPSS 17.0 software for Windows (IBM, Ehningen, Germany).

Results

Recipient and donor data

Overall, 15 CLKT were performed in 14 paediatric patients (eight male patients/six female patients) between 1998 and 2009 in our hospital. Recipients had a median age of 8 years (range 1–16 years) and median weight of 17 kg (range 9–53 kg). Median follow-up was 21 months (range 1–103 months). The indications for CLKT were ARPKD and PH-1 in seven patients respectively. In addition, one child underwent liver and kidney re-transplantation because of primary nonfunctioning of the liver graft and simultaneous impaired kidney graft function because of renal artery thrombosis. Fourteen liver grafts were obtained from deceased donors. Types of graft included four whole organs, eight left lateral splits, one full left split and one right extended split. One child received a left lateral liver graft from his aunt as a living donor. All liver grafts were transplanted together with one kidney from the same deceased or living donor. Two infants received both kidneys from very young paediatric donors. Median donor age was 19 years (range 1–50 years). The median liver graft weight was 360 g (270–1200 g) and the liver graft-to-recipient weight ratio (GRWR) was 2%

Table 1. Patient characteristics (isolated kidney transplantation, isolated liver transplantation).

	Isolated KTX	Isolated LTX
Number of transplantations	64	407
Recipient age, median (range) [years]	9.5 (1–16)	1.6 (0–16)
Recipient gender (male/female)	41/23	207/200
Primary/re-transplantation	57/7	328/79
Deceased donor/living-related	49/15	308/99
Indications liver transplantation [*n*]		
Cholestatic liver disease		218
Metabolic liver disease		47
Acute hepatic failure		31
Alagille syndrome		27
Liver tumour		9
Other		75
Indications kidney transplantation [*n*]		
Congenital anomalies of kidney and urinary tract	29	
Glomerulonephritis	8	
Nephronophthisis	6	
Haemolytic uraemic syndrome	5	
Polycystic kidney disease	2	
Other	14	
Warm ischaemic time, mean [min]	41	39
Cold ischaemic time, mean [min]	777	504

KTX, kidney transplantation; LTX, liver transplantation.

(1.1–5.8%). Detailed patient and donor characteristics are given in Tables 2 and 3.

Technical aspects of the liver transplantation

Outflow reconstruction

In one out of the four patients receiving a whole liver graft, outflow reconstruction was performed using the classic technique with replacement of the inferior vena cava and two end-to-end anastomoses between donor and recipient vena cava. In the remaining three patients transplanted with a whole organ graft, and in the patient receiving a right extended graft, the liver was implanted using a modified piggy back technique with preservation of the recipient inferior vena cava and a side-to-side cavocavostomy. One child receiving a full left liver graft was also transplanted using the piggy back technique after back table-reconstruction of the remaining semicircular donor vena cava using an external iliac donor vein for replacement. All patients transplanted with a left lateral liver graft ($n = 9$, including living donation) had an end-to-side anastomosis between the donor left hepatic vein and the preserved recipient inferior vena cava. All anastomoses were performed with a running suture using Polydioxanone (PDS) 5.0 or 6.0.

Table 2. Patient characteristics (combined liver and kidney transplantation).

Number of patients	14
Number of CLKT	15
Recipient age, median (range) [years]	8 (1–16)
Recipient gender (male/female)	8/6
Recipient weight, median (range) [kg]	17 (9–53)
Liver graft weight, median (range) [g]	360 (270–1200)
GRWR, median (range) [%]	2 (1.1–5.8)
Urgency status, normal/high urgency	14/1
Primary/re-LTX	14/1
Primary/re-KTX	14/1

CLKT, combined liver and kidney transplantation; GRWR, graft-to-recipient weight ratio; KTX, kidney transplantation; LTX, liver transplantation.

Table 3. Donor characteristics (combined liver and kidney transplantation).

Donor age, median (range) [years]	19 (1–50)
Donor gender (male/female)	11/4
Donor weight, median (range) [kg]	79 (12–85)
Creatinine, mean ± standard deviation [mg/dl]	0.74 ± 0.33
Serum urea, mean ± standard deviation [mg/dl]	28 ± 15
Bilirubin total, mean ± standard deviation [mg/dl]	0.6 ± 0.3
Alanine aminotransferase, mean ± standard deviation [U/l]	86 ± 88
Aspartate aminotransferase, mean ± standard deviation [U/l]	52 ± 40
Cause of death (deceased donors), *n* (%)	
Trauma	6 (42.9)
Cerebral bleeding	4 (28.6)
Other	4 (28.6)

Portal vein reconstruction

The donor portal vein (whole organs, right extended graft and full left graft) or the left portal vein branch (left lateral grafts including the living donation graft) was anastomosed end-to-end to the recipient portal vein with a running suture by PDS 6.0.

Arterial reconstruction

Most commonly arterial anastomoses were performed between donor proper/common hepatic artery and recipient proper/common hepatic artery (two whole liver grafts, one right extended graft, one full left graft and six left lateral grafts). In two cases, arterial anastomoses were performed between donor left hepatic artery and recipient left hepatic artery (two left lateral grafts including living donation). In the remaining cases, the donor left hepatic artery (one left lateral graft) or coeliac trunk (one whole organ) was anastomosed to recipient proper hepatic artery. In one whole organ graft, the donor coeliac trunk and recipient accessory right hepatic artery were used for anastomosis. All anastomoses were performed end-to-end using interrupted PDS 6.0 or 7.0 sutures.

Biliary reconstruction

In three out of the four patients receiving a whole organ, and in the patient receiving a right extended graft, an end-to-end choledochocholedochostomy was performed. In the other patient receiving a whole organ, in the patient with full left graft and in all patients with left lateral grafts, a biliodigestive anastomosis with Roux-en-Y jejunal limb was performed. In the child receiving a left lateral graft by living donation, two biliodigestive anastomoses to the same jejunal limb were necessary. All anastomoses were performed using interrupted PDS 6.0 or 7.0 sutures.

Technical aspects of the kidney transplantation

All children received kidneys from the same donor who also donated the liver graft, including living donation. In ten cases, the left kidney, and in three cases, the right

kidney was used. In two children receiving organs from very young donors (donors 1 year of age) both kidneys from the donor were transplanted into one recipient. In the majority of cases, the donor kidney was placed extraperitoneally into the left ($n = 6$) or right ($n = 5$) iliac fossa. Otherwise, the kidney was placed into the abdominal cavity ($n = 4$).

Vein reconstruction

Donor kidney vein was transplanted end-to-side to the recipient vena cava ($n = 7$), the common iliac vein ($n = 2$) or the external iliac vein ($n = 4$) respectively. One of the children received two kidneys en-bloc. In this case, the donor vena cava segment was anastomosed side-to-side to the recipient vena cava. In the other child, the kidneys were transplanted separately with two separate anastomoses between donor kidney vein and recipient vena cava or common iliac vein respectively.

Arterial reconstruction

Arterial anastomoses were performed end-to-side between donor renal artery and the recipient aorta ($n = 7$), the common iliac artery ($n = 4$) or the external iliac artery ($n = 2$) respectively. In one child receiving an organ with two renal arteries on a native aortic patch, we performed a single end-to-side anastomoses to the recipient aorta. Analogously to the vein reconstruction in the two children receiving two kidneys, in one child the kidneys were anastomosed with a donor aortic segment en-bloc side-to-side to the recipient aorta. In the other child, two separate anastomoses were performed between donor kidney artery and recipient aorta or common iliac artery respectively.

Urinary tract reconstruction

Ureterocystoneostomy (UCNS) was performed in all patients using the technique of Gregoir-Liche. From 1998 until 2006 routine, intraoperative stenting of the vesico-ureteric anastomosis using double a J-stent was performed ($n = 8$). In both patients receiving two kidneys, two separate UCNS were performed.

All anastomoses concerning KTX were performed using PDS 6.0 running suture.

Intraoperative course

The mean cold ischaemic time was 589 ± 148 min for the liver and 840 ± 198 min for the kidney. Mean warm ischaemic time was 34 ± 10 min for the liver and 42 ± 12 min for the kidney. Patients needed a median of 2 (range 2–3) blood transfusions and 8 (range 3–28) fresh frozen plasmas. In addition, in three patients, substitution of thrombocytes was necessary.

Postoperative course

The median ICU stay was 8 days (range 5–59 days), and the duration of invasive ventilation 1.5 days (1–52 days).

All seven patients undergoing CLKT because of PH-1 were treated postoperatively by haemodialysis to reduce oxalate load to avoid kidney graft damage. In these patients, the median time at dialysis was 5 days (range 2–27 days). Only one child with CLKT for ARPKD needed haemodialysis after transplantation (8 days) because of impaired kidney graft function.

Early after CLKT liver function tests showed a steady decline with median values for total bilirubin of 2.8, 1.3, 0.7 mg/dl, for aspartate aminotransferase of 165, 40, 33 U/l and for alanine aminotransferase of 181, 72, 23 U/l at postoperative days 3, 7 and 30 respectively. Corresponding serum creatinine and urea level were 0.5, 0.5, 0.5 mg/dl and 20, 16, 25 mg/dl respectively.

In the postoperative course, six patients (40%) showed bleeding complications. Three patients with intra-abdominal bleeding (thereof two patients under dialysis treatment) underwent operative revision. In all three cases, diffuse intra-abdominal haemorrhage was shown. Two patients developed gastrointestinal bleeding. Bleeding in one child stopped after correction of the coagulation disorder. The other child underwent esophagogastroduodenoscopy, which showed bleeding from gastric ulcer that was treated successfully by endoscopic clipping. Another child, likewise under dialysis, developed a retroperitoneal haematoma after biopsy of the transplanted kidney and haematuria after suprapubic catheterization. Both problems could be treated symptomatically and by correction of the coagulation disorder.

Vascular complications were observed in three recipients after CLKT affected the liver graft in two patients and the kidney graft in one patient.

Both patients suffering from a vascular complication of the liver had a venous outflow problem diagnosed on duplex sonography. One child had received a left lateral graft from a living donor and underwent operative revision with enlargement of the venocaval anastomosis 10 days after the initial transplantation. The other child had received a left lateral graft obtained from an *ex-situ* split procedure of a deceased liver. An interventional dilatation of the anastomosis was performed 1 month after CLKT; however, the venous outflow problem persisted and the child underwent re-LTX 3 months after CLKT.

One patient with primary nonfunction of the liver developed renal artery thrombosis at the first postoperative day and underwent re-operation. A thrombectomy of the kidney graft artery was performed, followed by re-anastomosis. As a result of the primary liver graft nonfunction and the persisting impaired renal graft function, the child underwent re-CLKT.

No other vascular complications of the liver or kidney graft occurred in our patients after CLKT. Likewise no biliary or urinary tract complications were observed.

Two children experienced acute rejection of the kidney graft (in one case treated by steroid bolus therapy and in the other case by conversion of cyclosporine to tacrolimus), one child showed an acute rejection of the liver graft, and in another child acute rejection of the kidney and the liver graft was observed (both children were treated successful by steroid bolus and conversion of cyclosporine to tacrolimus).

Infectious complications were found in only two children, including a BK-viruria in one child and a systemic candida infection together with a CMV reactivation in another child.

Patient and graft survival

No patient died during follow-up. The 1-year and 5-year survival rates for the liver graft were 80%, and the 1-year and 5-year survival rates for the kidney graft 93%. As mentioned before, one child with a primary nonfunction of the liver and an impaired kidney function because of renal artery thrombosis underwent early re-CLKT on the fourth postoperative day. Unfortunately, also the second liver graft showed a primary nonfunction and therefore second re-LTX was performed 5 days later. Another child needed re-LTX after 3 months because of histological diagnosed medical-toxic liver damage and afore mentioned outflow problem of the liver graft. The mean of total bilirubin was 0.5 ± 0.3 mg/dl, and the mean of serum creatinine was 0.8 ± 0.5 mg/dl in the children with functioning graft at the last follow-up.

Kaplan–Meier survival curves of patient and graft survival following CLKT in comparison to our isolated LTX (n = 407) and KTX (n = 64) are shown in Figs 1 and 2. As a result of the low number of cases of CLKT, no statistical analysis was performed. However, graft and patient survival appears comparable or even superior compared with isolated transplantation.

Comparison of CLKT in children ≤12 kg vs. >12 kg

Overall, five CLKT were performed in five children weighting ≤12 kg (median weight 10 kg, range 9–12 kg), and the remaining 10 CLKT were performed in nine children weighting more than 12 kg (median weight 26 kg, range 17–53 kg). There was no obvious difference in the intraoperative course between children weighting ≤12 kg and children weighting >12 kg. However, because of the restricted abdominal space in the smaller infants, a temporarily abdominal wall closure was necessary in two children weighting <12 kg. The abdominal patch could be removed successfully by stepwise reduction on postoperative days 20 and 43. In the other patient group, a primary closure of the abdominal wall was possible in all children. During the postoperative course, two children (33%)

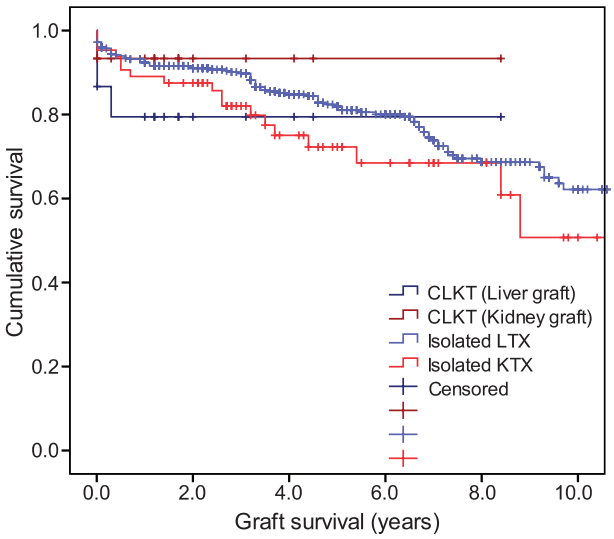

Figure 1 Graft survival following combined liver and kidney transplantation (CLKT) in comparison to isolated liver transplantation (LTX) and kidney transplantation (KTX). The figure shows the Kaplan–Meier graft survival curves for liver and kidney graft survival following CLKT in comparison to the graft survival after isolated LTX and KTX respectively.

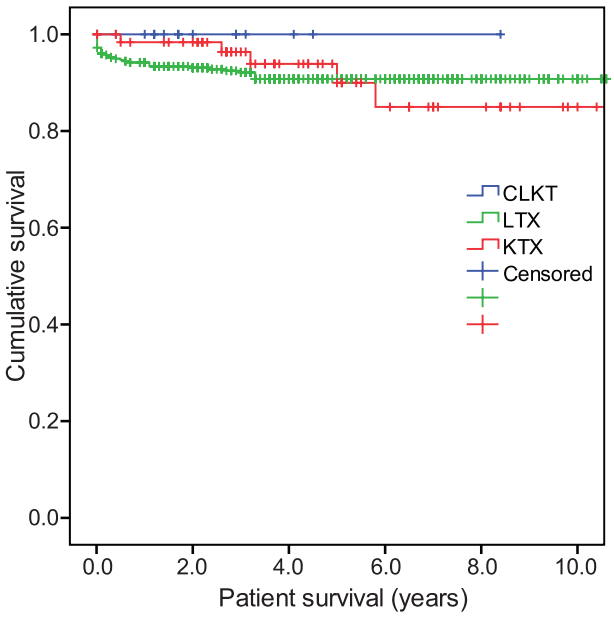

Figure 2 Patient survival following combined liver and kidney transplantation (CLKT) in comparison to isolated liver transplantation (LTX) and kidney transplantation (KTX). The figure shows the Kaplan–Meier patient survival curve for CLKT in comparison to the patient survival after isolated LTX and KTX respectively.

≤12 kg and four children (40%) >12 kg showed bleeding complications. Concerning vascular complications, one child in both groups suffered from a venous outflow problem of the liver graft. In addition, one other child >12 kg developed renal artery thrombosis. The 1- and 5-year patient survival rates were 100% in both groups. The 1- and 5-year kidney and liver graft survival rates were 100% in children weighting ≤12 kg, and 1-year and 5-year graft survival rates were 90% for the kidney and 70% for the liver grafts in the older children (>12 kg).

Discussion

In contrast to adult patients with advanced hepatic dysfunction/cirrhosis and accompanying potentially reversible [13,14] renal insufficiency, the main indications for CLKT in children are hereditary liver-based metabolic disorders resulting in an end-stage renal disease [10,12]. As a result of the rare indications in children, the number of paediatric CLKT is small and almost constant about the last decades [10,15]. Outcome data for CLKT in children are sparse. Two reviews from Sutherland *et al.* [10] and Chava *et al.* [12] analysed indications and outcomes derived from the UNOS database. Other publications relating to paediatric CLKT investigate only small patient groups with one kind of diagnosis or case reports [16–19]. Therefore, general statements about graft and patient survival are difficult. Reported 5-year patient survival rates after paediatric CLKT have shown a high variation between 50 and 100%. This is also influenced by the underlying disease [10,20–22]. In some publications, liver allograft survival after CLKT was described equal to patient survival, suggesting a death-censored liver graft survival of 100% [20,21]. Kidney allograft survival varied from 50% to 100% 5 years after transplantation [16,20,21,23]. However, the existing data predominantly regard children with PH-1. Results from CLKT in adults on the other hand suggest an equal long-term survival of liver and kidney grafts following CLKT compared with isolated organ transplantation [9].

Overall, CLKT in our paediatric patients showed an excellent graft and patient survival. Nevertheless, a number of postoperative complications have to be anticipated early after transplantation and intensive monitoring and interdisciplinary management is mandatory. Forty percent of our children showed bleeding complications after CLKT, and 27% needed operative or interventional management of haemorrhage. Spearman *et al.* [24] found bleeding complications following isolated paediatric LTX in about 5% of the cases, Sundaram *et al.* [25] showed a higher bleeding complication rate of 18%, however, regarding isolated LTX only in very young infants (≤90 days of age). The higher rate of bleeding complications in our children with CLKT might well be explained by the necessity of postoperative haemodialysis in nearly half of the infants (because of delayed kidney graft function or clearance of hyperoxaluria) and therefore accompanying anticoagulation.

Other surgical complications were rare; two patients (13%) showed liver graft outflow complications, and one child showed renal artery thrombosis (7%). No other complications of the vascular, biliary or urinary anastomoses occurred.

Multiorgan transplantation in children is still a technical challenge, especially in young children because of small-sized anatomical structures and restricted space. Reports concerning isolated LTX [26,27] or KTX [28,29] in very small children have shown good outcomes. There are few data available on the outcome of CLKT in small infants or babies. Perera *et al.* [30] showed a comparable outcome in children ≤15 kg compared with children more than 15 kg. Accordingly, subgroup analysis of the very small infants (age <3 years and weight <12 kg) in our study undergoing CLKT revealed an excellent short-term and long-term outcome (1-year and 5-year graft and patient survival rate 100%). In the postoperative course, two (33%) of the children in this study weighing <12 kg needed re-operation because of diffuse intra-abdominal haemorrhage, and one child (17%) required revision because of an outflow problem. Hence, in our study, the outcome is comparable to CLKT in our older children. As a result of the restricted space in two small infants, a temporarily abdominal wall closure was necessary and could be removed successfully by stepwise reduction.

As a result of good results even in small children, the time point of CLKT should be determined by the indication, and not by the age or weight of the recipient. Especially, in children with PH-1, early transplantation is favourable because of deposition of oxalate not only in the kidney, but also in other tissues like myocardium or retina and thereby caused damage [31]. In the few cases with early recognition of PH-1 before impairment of the kidney, even an isolated LTX could be curative [32].

In summary, despite of a number of different complications following CLKT, with a timely and interdisciplinary management, our patients with ARPKD and PH-1 showed an excellent graft and patient survival. Therefore, to improve outcome, growth and development CLKT should be suspected in all children suffering from simultaneous liver and kidney disease.

Authorship

HU: collected and analyzed data, wrote the paper. KM and NB: study design. GR: analyzed data. IK, EG and BF: collected data. FL: study design, wrote the paper.

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