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ORIGINAL ARTICLE

Paediatric kidney transplantation in small children – a single centre experience

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Summary

Kidney transplantation (KTx) remains a challenging procedure in small children. This study presents our centre results. From 1983 to 2004, 40 of 442 paediatric KTx were performed in children with a body weight <11 kg. Median body weight was 9.2 kg (range: 7.2–10.9), median age was 2.7 years (range: 0.9–5.9). Preoperative dialysis was performed in 87.5%. In 24 cases (60%) grafts came from cadaveric (CAD) and in 16 cases (40%) from living related donors (LRD). Median donor age of CAD was 8 years (range: 1–40). The overall 1-, 5-, 10-, 15-year patient survival was 93%, 90%, 90% and 87% respectively. The overall 1-, 5-, 10-, 15-year graft survival was 90%, 80%, 66% and 56% respectively. There was no significant difference in survival of CAD or LRD grafts. Median follow-up was 13.7 years. Initial graft function rate was 100% for LRD and 79% for CAD. The relative glomerular filtration rate (GFR) showed no statistical difference between CAD and LRD. Main reasons for graft loss were chronic transplant nephropathy. Paediatric KTx is the treatment of choice even in very small children. Living donor KTx is the preferable donor source in terms of primary graft function and timing to transplantation.

Introduction

Kidney transplantation (KTx) is the treatment of choice for children with end-stage renal disease (ESRD) [1–3]. Children with well-functioning graft have a better quality of life, improved cognitive development and near normal growth in comparison with dialysis [4,5]. Furthermore, KTx is more cost-effective than dialysis [6]. Despite advances in improved immunosuppressive regimes [7–10], surgical technique and peri- and postoperative management over the last decade [1,11–13], KTx remains a challenging procedure in small children. The aim of this paper is to present our centre results with paediatric KTx in very small children weighing <11 kg.

Patients and methods

Recipients

From 1968 to 2004, a total of 4448 KTxs including 545 paediatric kidney transplants (12%) were performed at our centre. With the introduction of cyclosporine graft survival rates increased dramatically. Therefore, only CsA or Tacrolimus-treated patients were included. Patients with combined transplantations were excluded.

In the period between 1 January 1983 and 31 December 2004, 442 paediatric KTxs were performed, of which 40 children (9%) had a body weight of <11 kg at the time of transplantation. Data from this cohort with primary KTx were followed for peri- and postoperative complications and for long-term results. There were 25 males and 15 females. Median age of the recipients was 2.7 years (range: 0.9–5.9). The median body weight at the time of transplantation was 9.2 kg (range: 7.2–10.9). Most frequent underlying diseases for renal failure were obstructive uropathy (22%), hypoplasia (25%) and nephrosclerosis (15%). Dialysis was necessary in 35 cases (87.5%), in most cases peritoneal dialysis (91%) was performed. In five cases renal transplantation could be performed pre-emptively (12.5%; Table 1).

Table 1. Recipients characteristics with paediatric kidney transplantation (KTx).

Recipients characteristics	No. of patients ($n = 40$)
Median age (years)	2.7 (range: 0.9–5.9)
Median body weight (kg)	9.2 (range:7.2–10.9)
Gender (male/female)	25/15
Underlying kidney diseases	
Obstructive uropathy	9 (22)
Dys-/hypoplasia	10 (25)
Congenital nephrosclerosis	6 (15)
Polycystic kidney disease	5 (12)
Focal segmental glomerulosclerosis	4 (10)
Acute Renal Failure	1 (2.5)
Hemolytic uremic syndrome	3 (7)
Diverse	2 (5)
Total	40 (100)
Preoperative dialysis	35 (87.5)
Peritoneal dialysis	32 (91)
Pre-emptive transplantation	5 (12.5)

Parenthesis values are given as percentage.

Donors

In 24 cases, the source of grafts was from CAD (60%) and in 16 cases from LRD (40%). The median age of CAD was 8 years, ranging from 1 to 40 years. In most cases donor grafts were from paediatric donors aged between 2 and 12 years (54%), in three cases (12.5%) of donors younger than 1 year and in two cases (8%) the donors were adolescents aged between 13 and 16 years. Only six donor kidneys (25%) were from donors older than 16 years. The median age of LRD was 32 years, ranging from 26 to 36 years. For LRD parental donation was used exclusively. The median cold ischaemic time (CIT) was 19 h (range: 2 h 48 min–45 h 10 min) for all grafts. The median CIT for cadaveric donor organs was 23 h 40 min (range: 16 h 30 min–45 h 10 min) and for living donation 4 h (range: 2 h 48 min–6 h 20 min).

Surgical technique

Before 1993, allografts were transplanted transperitoneal ($n = 15$) and since 1993 extraperitoneal ($n = 25$). In cases of the transperitoneal approach, a midline incision was used, the right hemicolon was mobilized, the graft was placed to the right retroperitoneal space. For vascular anastomoses, the recipient's aorta and distal caval vein was used. The extraperitoneal approach was achieved via a curved pararectal skin incision. The right side was preferred, because of the direct venous drainage to the distal caval vein. The peritoneum was mobilized from the psoas muscle and from the retrohepatic area. Distal aorta and distal inferior caval vein were sparingly freed. The renal donor artery was placed in end/side technique to the distal aorta between the inferior mesenteric artery and iliaca bifurcation by running suture technique. The renal vein was anastomosed to the distal caval vein in the same technique and to avoid kinking shortened when necessary. Variant vascular anatomy was observed in 11 cases (27.5%). Separately sequential artery anastomosis was the preferred technique in cases of multiple arteries. The ureter was anastomosed to the bladder using uretero-cystoneostomy with antireflux technique without stenting according to a modified Lich Gregoir. The extravesical anastomosis is performed with 6–0 PDS running absorbable suture. In two cases reconstructive surgery of the bladder was necessary. Primary wound closure was aimed for. However, to avoid the risk of graft compression because of size mismatch of the graft and the small recipient situs wound closure was performed using an absorbable mesh with secondary skin closure ($n = 1$). Simultaneous nephrectomy of the native kidney or appendectomy was performed when indicated. The peritoneal dialysis catheter was maintained and removed secondarily when graft function was stable. Median operation time was 3 h 5 min (range: 2–6 h 45 min) and 3 h 15 min (range: 2 h 45 min–4 h 10 min) for the transperitoneal and 2 h 45 min (range: 2–6 h 45 min) for the extraperitoneal approach.

Immunosuppression

Most of the children received dual immunosuppression with Cya/steroids, 10 patients received basiliximab with two single doses of 10 mg on days 0 and 4. There were four patients with triple immunosuppression with mycophenolate mofetil (1.2 g/m^2/day). No child received azathioprine, one patient with hyperoxaluria received tacrolimus.

Acute rejections

There were 10 patients with at least one rejection. Four of them had two rejection episodes and two patients had three rejection episodes. Rejections were treated with steroid bolus therapy and in the patients with three rejections mycophenclate mofetil (MMF) was added. No antibody therapy was used for rejection therapy. Five graft losses occurred in the rejection group.

Statistical analysis

Statistical analysis for patient and graft survival was calculated using Kaplan–Meier method. For comparison of subgroups log-rank or Wilcoxon tests were used. The student *t*-test was used for comparison of the relative glomerular filtration rate. *P*-values <0.05 were considered statistically significant.

Results

Patient and graft survival

The overall patient survival at 1-, 5-, 10 and 15 years was 93%, 90%, 90% and 87% respectively. The 1-, 5-, 10 and 15 years graft survival was 90%, 80%, 66% and 55% respectively (Fig. 1). The graft survival rate at 1-, 5-, 10 and 15 years was 94%, 87%, 69% and 63% in the LRD group versus 92%, 73%, 68% and 68% in the CAD group, showing no statistical difference between the groups (Fig. 2). Differentiating between the donor ages in the CAD group in grafts from donors ≤12 and >12 years also showed no statistical difference (data not shown).

Cause of death

Six patients died between 0.1 and 17.9 years after transplantation. Causes of death were pulmonary haemorrhage (1), metabolic dysregulation (1) and sepsis (1). Three infants died of unknown causes. Two of the six death occurred despite graft function (Table 2).

Cause of graft loss

Seventeen graft losses occurred between day 1 and 11.3 years after transplantation. The most frequent cause of graft loss was CTN (70%) in 12 cases (0.4–11.3 years post-transplantation). Almost 80% of the recipients develop hypertension and require antihypertensive medication to normalize the blood pressure. CTN was diagnosed clinically

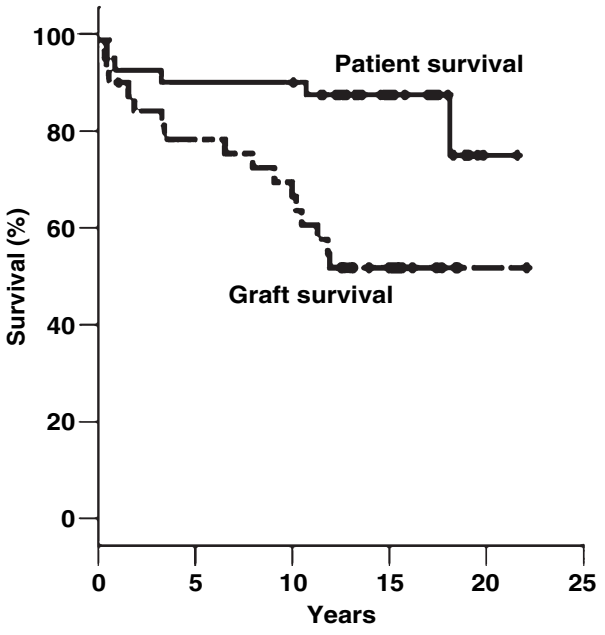

Figure 1 Overall patient and graft survival for children with first paediatric kidney transplantation (KTx) weighing <11 kg ($n = 40$).

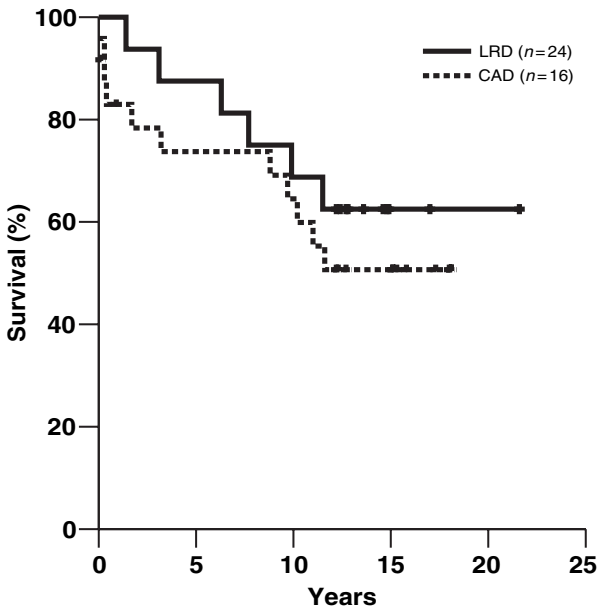

Figure 2 Comparison of graft survival from living related donors (LRD) kidney donors ($n = 24$) versus cadaveric (CAD) kidney donor grafts ($n = 16$). Graft survival showed no statistical difference ($P = 0.43$).

Table 2. Results.

Characteristics	
Median follow-up (years)	13.7
Graft function [*n* (%)]	
PGF	35 (87)
DGF	3 (8)
NGF	2 (5)
PGF-LRD	100
Total deaths and causes of deaths [*n* (%)]	6 (15)
Unknown	3
Pulmonary bleeding	1
Metabolic dysregulation	1
Sepsis	1
Graft loss and causes of graft loss [*n* (%)]	17 (42.5)
CTN	12
Thrombosis	2
HUS	1
Sepsis	1
Unknown	1
Postoperative complications [*n* (%)]	13 (33)
Thrombosis	2
Urine leakage	2
Ureter stenosis	2
Reflux	1
Wound infection	3
Threatening graft compression	1

PSR, patient survival rate; GSR, graft survival rate; PGF, primary graft function; DGF, delayed graft function; NGF, no graft function; CTN, chronic transplant nephropathy; HUS, haemolytic syndrome; LRD, living related donors.

and not biopsy-confirmed. Two grafts were lost because of vascular thrombosis on the day of surgery. One graft was lost due to sepsis 0.3 years, one due to haemolytic syndrome, 1.4 years and another one due to unknown causes 7.6 years post-transplant (Table 2).

Graft function

Initial graft function was observed in 35 grafts (87%), delayed graft function in three grafts (8%) and non-function was apparent in two cases with graft thrombosis. All LRD grafts showed primary function. CAD grafts from donors ≤12 vs. >12 years of age showed no difference in terms of primary function.

Relative glomerular filtration rate (GFR)

The relative glomerular filtration rate (GFR) corrected to body surface area was calculated from serum creatinine and body height, according to Schwartz *et al.* [14], a formula that enables an estimation of GFR in children with good accuracy. The relative GFR showed no statistical difference between the CAD and LRD group 3 years after transplantation (Fig. 3).

Postoperative complications

Postoperative complications occurred in 13 cases (33%), vascular thrombosis in two cases on the day of transplantation. Despite immediate re-operation, the grafts were lost. The donors of the two thrombosed grafts were aged 1 and 7 years. The kidney of the 7-year-old donor had two arteries on one patch; the other one had a single vascular anatomy. There were no cases of en-bloc donor KTx. Ureter complications were seen in five cases (13%). There were two leakages, two stenoses and one reflux. The cases with stenosis and leaks occurred in the early postoperative period and could be repaired surgically without negative influence in the follow-up. The reflux was re-operated 1 year after transplantation, the graft is still functioning well without signs of urinary tract infections. Of these five cases of complications three occurred in the CAD group, which were associated with a prolonged cold ischemic time of >20 h (21, 22 and 26). Three cases of wound infections with secondary wound healing were observed. One case of graft compression could be timely rescued without consequence for the graft. A mesh graft was used for secondary wound closure.

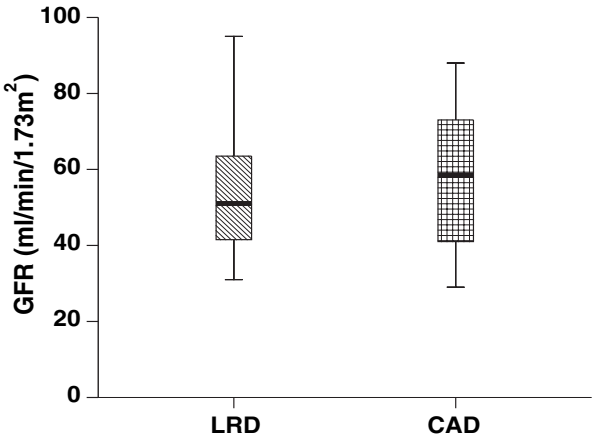

Figure 3 Comparison of the relative glomerular filtration rate (GFR) from living related donors (LRD) kidney donors ($n = 12$) versus cadaveric (CAD) kidney donor grafts ($n = 16$) 3 years post-transplantation. GFR showed no statistical difference ($P = 0.74$ in *t*-test).

Viral infections

Severe CMV infections and graft loss because of CMV or Epstein-Barr virus (EBV) did not occur. In the past, we used CMV prophylaxis in high-risk patients with seropositive donors and seronegative recipients. Nowadays, we perform a pre-emptive therapy in cases of positive pp65 viraemia.

Discussion

Despite improvements in dialysis therapy in children over the last years, KTx is still considered as the preferable therapy for children with ESRD. Meanwhile refined surgical techniques, improved immunosuppressive protocols and peri-operative management have made KTx a safe procedure [1,2,15]. However, especially in very small children KTx can be a challenging procedure with a higher risk of peri-operative complications and poorer outcome [16]. There are known factors, such as centre experience, surgical technique, recipient weight, donor age and graft source, which may contribute to different graft survival rates.

Previous publication showed that results of paediatric renal transplantations were better when performed in experienced paediatric transplant centres [17]. For decades our centre has a continuous paediatric kidney transplant program but even here the number of patients weighing <11 kg is small. Although it is known that the risk of early graft failure because of surgical complications is higher in smaller children [13]. According to current policy paediatric renal recipients have to weigh at least 6 kg with a minimum age of 6 months. The reason for this requirement is not based on the technical aspect, but the difficulties arising from specifically tailored immunosuppression for such small children.

Refined surgical technique graft loss due to of surgical complications has become a rare occurrence. Initially

graft compression was one of the major concerns when considering the extraperitoneal approach, which is of particularly important when using an adult kidney in these small patients. In a study published earlier, it could been shown that there was no difference in initial graft function, graft survival and surgical complications regarding both techniques [1]. However, it is our opinion that the extraperitoneal approach offers different advantages. It avoids the risk of bowel complications such as postoperative bowel atony and adhesions and there are no risks of peritonitis. In addition extraperitoneal placement maintains the possibility of peritoneal dialysis.

Postoperative complications were mainly caused by ureter complications. Urological complications are associated with significant morbidity in renal transplantation. Factors influencing the success of the neoureterocystostomy include not only the anastomotic technique but also the vascular supply of the donor ureter. Review of the urological complications revealed that all donor kidneys had a single renal artery. However, more complications were observed in CAD group (3), which were associated with a prolonged cold ischemic time. This might have been a negative influence in the ureter blood supply and could be a possible explanation for the higher rate of urological complications. Studies have shown that stents decrease the rate of ureter complications in paediatrics and adults [18,19], but other studies could not show any advantages of prophylactic ureter stenting [20] and there are insufficient valid data for these patients. The use of stents may be indicated in selected cases with technical difficulties regarding the anastomosis or when there is a vascular compromise to the ureter blood supply. Donor age might be another factor influencing graft outcome. In this study both cases of graft thrombosis occurred with grafts from donors aged 1 and 7 years, but both in the early period.

In previous studies, it was shown that kidneys from paediatric donors had a decreased graft survival rate caused by infections and technical problems compared with organs from adult donors [21,22]. Graft loss was seen mainly in donor organs from paediatric donors <5 years of age [23]. However, when eliminating this subgroup graft survival rate was comparable with adult donors. The actual NAPRTCS report demonstrates that the poor outcome of very young donors occurred predominantly in the age group 1–2 years [24]. Based on earlier experience our policy was not to use organs from donors younger than 5 years. With improved technique and experience this policy has been changed as short-term results were comparable. However, over the last years there is growing evidence, that long-term results in graft function are better in children receiving paediatric donor grafts than adult donor grafts [25]. Paediatric donor organs are able to adapt the GFR with growth of the recipient, whereas adult donor grafts do not because of initial down regulation of the nephrons and following nephron cicatrisation. This was also shown in a matched pair analysis performed by one of our co-authors from the Eurotransplant (ET) community [26]. These circumstances changed our initial reluctance to accept paediatric donor organs.

A further clinical problem, which can be observed in small children with extreme donor/recipient size discrepancy, is severe cardiovascular stress. As this can lead to chronic cardiac insufficiency this is another valid argument to be considered when allocating organs. The fact that in children paediatric donor organs perform better than adult organs should be considered in the Eurotransplant kidney allocation system, a system, which has already been implemented in various countries outside the ET community.

Comparing paediatric KTx to alternative best medical renal replacement therapy, the early and long-term risks of the transplantation have to be discussed carefully. With modern immunosuppression rejection episodes are no longer the main issue, but severe infections remain a clinical problem [27] indicating the risk of chronic overimmunosuppression. Therefore, particular attention to tailored immunosuppressive regimens and hypertension are mandatory for excellent long-term results. In the long-term follow-up the most frequent cause for graft loss was CTN. Almost all of the recipients develop hypertension and require antihypertensive medication to normalize the blood pressure. Hypertension is one and probably the main risk factor for CTN. Long standing hypertension is also the risk factor for increased mortality after transplantation [28]. Nowadays the leading causes of death with functioning graft are cardiovascular events [29]. In contrast to adolescents non-compliance is more likely to be a lesser factor for chronic graft failure in these small children just as chronic underimmunosuppression because of careful outpatient control and good compliance by the parents.

In contrary to KTx, it has been shown that dialysis demonstrates poorer weight gain, retarded growth and psychomotor development [2]. Long lasting dialysis had a 15 times higher risk of cerebrovascular death compared with those living long with a good functioning renal allograft [30]. Furthermore, life-threatening infections remain also a major problem with dialysis [31].

In conclusion, paediatric KTx is the treatment of choice even in very small children despite the operative risk and side effects of long-term immunosuppression. The extraperitoneal approach with vascular anastomosis to the distal aorta and caval vein is our preferred technique. Using this technique with interposition of a mesh graft for wound closure, graft compression with vascular

thrombosis can be avoided. Living donor KTx is the preferable donor source in terms of graft function and timing to transplantation. KTx should be considered early to allow children an almost normal physical, mental and social development.

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