

Long-term results of paediatric kidney transplantation at the University of Heidelberg: a 35 year single-centre experience

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Abstract

Background. Kidney transplantation remains the most effective treatment for children with end-stage renal disease. We analysed data from the University of Heidelberg transplant programme to present our results on paediatric kidney transplantations over the past 35 years.

Methods. From 1967 to 2003, 354 paediatric kidney transplantations were performed at the University of Heidelberg. Data were obtained from the paediatric kidney transplantation records consisting of 291 (82%) cadaveric and 63 (18%) living donated transplants. Demographic data, family relationship of the living donors, surgical technique, immunosuppressive drugs, graft and patient survival rates were assessed.

Results. The mean age of cadaveric and living donors was 32.0 ± 17.1 and 37.6 ± 7.5 years, respectively. The family relationship of the living donors included the mother in 65% of cases, the father in 31%, and other relatives in 4%. In the last 4 years, the respective mean cold ischaemia time was 1.6 ± 0.5 h for living donated and 13.5 ± 4.1 h for cadaveric donors. The mean age of children who received kidneys from cadaveric and living donors was 11.3 ± 4.5 and 10.4 ± 4.5 years, respectively, with a male to female ratio of 57 to 43%. Overall patient survival rates were 95% after 1 year and 89% after 5 years. The patient 5 and 10 year survival rates for living donor renal transplantations were 95 and 95%, respectively. Graft survival rates improved since 1990 compared with the period prior to 1990: 82.5 vs 56.7% graft survival at 1 year and 82.5 vs 50% after 5 years ($P=0.03$). Comparing the operating technique in a subgroup of our patients that received the same immunosuppressive regimen, anastomoses with the aorta and vena cava (51%, $n=31$) were

associated with a graft survival of 86.6 and 83.3% after 1 and 5 years, whereas anastomoses with iliac vessels (49%, $n=30$) were associated with a graft survival of 55.8 and 51.6% after 1 and 5 years, respectively ($P=0.01$).

Conclusions. There has been a gradual improvement in our paediatric kidney transplantation results over time. Living donor paediatric kidney transplants have higher patient and better graft survival rates than cadaveric donor kidney transplants. Using the aorta and inferior vena cava for graft anastomosis, utilizing newer immunosuppressive drugs and implementing living kidney donation have positively affected the results of our paediatric kidney transplantations.

Keywords: cadaveric donor; cold ischaemia time; immunosuppression; living donor; paediatric kidney transplantation; surgical technique; survival rate

Introduction

Kidney transplantation is the best treatment option for patients with end-stage renal disease (ESRD), according to both quality of life and financial aspects [1–3]. The child with a well functioning graft after kidney transplantation can achieve a higher quality of life and school performance than with any dialysis therapy [4]. Kidney transplantation provides a cost-effective option in comparison to dialysis 4 years after the operation [5]. Moreover, kidney transplantation in children not only provides near normal growth and development but also reduces family problems [1,4]. The introduction of cyclosporine A (CsA) in 1983, as a potent immunosuppressive agent with less side effects compared to previous drugs, has focused more attention on paediatric kidney transplantation [6]. Many determinants play an important role in the success of paediatric kidney transplantation. Donor and recipient age, recipient

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race, cold ischaemia time, living (related and unrelated) or cadaveric donorship, HLA mismatching, and experience of the transplant centre are all factors that determine the fate of a kidney graft [1,4,7–10]. The reported graft and patient survival rates have shown improvement over the past decades. Advances in peri- and postoperative patient management, surgical techniques and immunosuppressive medications have played the most pivotal role in the constant improvement in these results [7,11]. Nevertheless, paediatric kidney transplantation has its own challenges, e.g. a more difficult surgical technique, size match problems, and side-effects of immunosuppressive therapy on growth and development of the patients [12]. Apart from these difficulties and the less available long-term results, there are some centres that have gathered experience in the field of paediatric kidney transplantation. Since living donation has become a standard and routine procedure for kidney transplantation, an increase of living donated kidney transplantation could be observed in some centres over the years [13]. Our centre has more than 35 years of experience with both cadaveric and living donor paediatric kidney transplantations. The aim of this paper is to present our results with paediatric kidney transplantation over the past decades, by reviewing different factors that might influence graft survival.

Patients and methods

Paediatric kidney transplantation at the University of Heidelberg

From 1967 to 2003, 1561 adult and 354 paediatric kidney transplants were performed at our transplant centre (Table 1). Of the paediatric kidney transplantations, defined as a recipient aged less than 18 years, 291 (82%) patients received cadaveric grafts and 63 (18%) patients received a kidney from living donors. Data from cadaveric and living donors were utilized for assessing demographic findings. Cold ischaemia time for cadaveric and living donors was evaluated. The family relationship of the living donors to the recipients was recorded. Exclusion criteria for living organ donation were the presence of cancer, renal disease or glucose intolerance, major cardiac or cerebrovascular disease not amenable to surgical correction, liver disease or alcoholism, severe pulmonary disease, and a positive T-cell crossmatch. The transplant histories of our paediatric patients were analysed for demographic data, underlying aetiology of ESRD, dialysis type and dialysis duration of the recipients. The patient and graft survival rates were analysed after 1 and 5 years in

Table 1. Overview of all kidney transplants from 1967 to 2003 at the University of Heidelberg

	Adults	Children (<18 years)	Total
Cadaveric donor	1405	291	1696
Living donor	156	63	219
Total	1561	354	1915

relation to the immunosuppressive regimen and surgical technique.

Surgical technique

Before 1990, allografts were transplanted retroperitoneally into the iliac fossa and end-to-side anastomoses were routinely performed using the iliac vessels. Since 1990, renal transplantation has been performed in a standardized technique in our department, placing the kidney extraperitoneally. Therefore, the abdomen is approached through a pararectal incision and the peritoneum is mobilized from the psoas muscle as well as from the right retrohepatic area, dissecting free the distal aorta as well as the distal inferior vena cava. Thereafter, the renal artery is anastomosed end-to-side to the aorta between the branching of the inferior mesenteric artery and the bifurcation. We shorten the renal vein as much as possible to avoid any impairment in the venous drainage as well as kinking; the vein is also anastomosed end-to-side to the distal inferior caval vein. The ureter is anastomosed to the urinary bladder using an extravesical ureteroneocystostomy after positioning a double-J catheter. Postoperatively, a complete drainage of the bladder is maintained for ~ 7 days; therefore a transurethral or a suprapubic catheter is placed into the bladder intraoperatively. Usually, the transurethral catheter is removed on the seventh day following transplantation in our department. The double-J (if inserted) as well as the Tenckhoff peritoneal dialysis catheter are removed 6 weeks following renal transplantation. In recent years the use of a double J-catheter has been discontinued and is used only in selected cases. All children received continuous infusions of heparin (100–300 IU/kg/24 h according to the individual risk factor profile) starting 1 h after surgery.

Immunosuppression

Depending on the date of kidney transplantation, the maintenance immunosuppression protocol of our department varied. There were three different time periods.

Before 1983. The immunosuppressive treatment consisted of a combination of methylprednisolone, azathioprine and monoclonal antibodies like OKT3 or antithymocyte globulin (ATG) (Fresenius, Munich, Germany) in cases of severe rejection.

Between 1983 and 1996. A combination of CsA, azathioprine and methylprednisolone was used.

Since 1996 (current protocol). A triple therapy has been instituted, consisting of CsA (initial dose: oral 500 mg/m²/day, starting 6 h postoperatively, and oral 300 mg/m²/day in two divided doses thereafter, with adjusting the individual dose according to whole blood CsA trough levels); methylprednisolone (IV 240 mg/m² intraoperatively followed by oral 48 mg/m²/day in the first week, then tapered weekly to a maintenance dose of 3.2 mg/m²/day at ~ 7 weeks following transplantation); and mycophenolate mofetil (MMF; 1200 mg/m²/day in two divided doses, starting at the first postoperative day).

Graft function

All rejection episodes were histologically confirmed according to previously published criteria [14]. Episodes of acute rejection were treated with methylprednisolone (400, 200, 200, 100 mg/m² body surface area on four consecutive days). Steroid-resistant rejection episodes were usually treated with polyclonal ATG or OKT3 after being confirmed by percutaneous biopsy; prophylactic ATG was only used in immunologically high-risk patients. Since the introduction of tacrolimus this drug was used instead of cyclosporine in steroid-resistant rejection or in immunologically high-risk recipients. In selected cases with severe calcineurin-inhibitor-related nephrotoxicity, rapamycin was used for maintenance immunosuppression instead of CsA or tacrolimus.

Statistics

Statistical analysis of survival rates was performed using the Kaplan–Meier method and compared by log-rank test. The χ^2 test was used for comparison of the survival rates, and the Fisher's exact test for comparison of surgical techniques. $P < 0.05$ was considered as being statistically significant.

Results

Donor population

The respective mean age of cadaveric and living donors was 32 ± 17.1 and 37.6 ± 7.5 years. The family relationship of the living donors included the mother in 65% of cases, the father in 31%, and other relatives in 4% (Figure 1). If the children received a graft from one of their parents, the mother (70%) was the major donor compared to the father (30%), and this proportion was the same in girls and in boys. The respective mean cold ischaemia time was 24.3 ± 4.8 h for cadaveric and 2.1 ± 1.1 h (range 1–5 h) for living donors. In the last 4 years, the cold ischaemia time at our centre dropped significantly to 13.5 ± 4.1 and 1.6 ± 0.5 h for cadaveric and living donors, respectively. In the 1967–1977 period, 33 and six children received kidneys from cadaveric and living donors, respectively. Between 1978 and 1988, the number of transplantations increased to 109 and nine; and in the 1989 to 2003 time period, 157 and 40 kidney transplantations from cadaveric and living donors were performed. These data indicate a significant increase of living-related renal transplantation in the last 14 years.

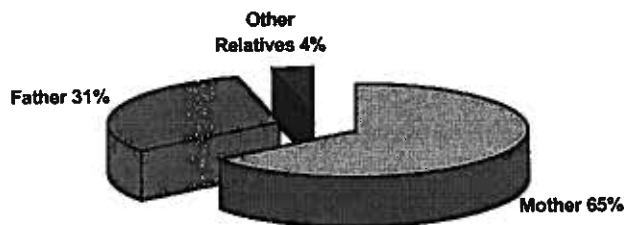


Fig. 1. Family relationship of the living donated paediatric kidney transplantations.

Recipient population

The mean age of our paediatric patients was 11.1 ± 4.5 years (range 17 months to 18 years). The mean age of children who received kidneys from cadaveric or living donors was 11.3 ± 4.5 and 10.4 ± 4.5 years, respectively. The vast majority of the children were between 6 and 15 years of age (Figure 2), with the youngest child being 17 months. Forty-three transplantations (12%) were retransplants and two children underwent a third transplantation. Male to female ratio in the patients was 57 to 43%. The primary renal disease in the recipients is listed in Table 2. Structural diseases such as renal hypo- or dysplasia and reflux or obstructive nephropathy were the most prevalent aetiologies in our paediatric patients followed by glomerulonephritis/focal-segmental glomerulosclerosis (FSGS) and nephrotic or familial syndromes. Forty-five percent of the patients who received a living donated kidney, underwent haemodialysis before renal transplantation, while 27.5% were managed with continuous ambulatory peritoneal dialysis; 27% of the patients who underwent kidney transplantation from a living-related donor were treated with preemptive transplantation. The mean time period on dialysis before renal transplantation was 21.6 months.

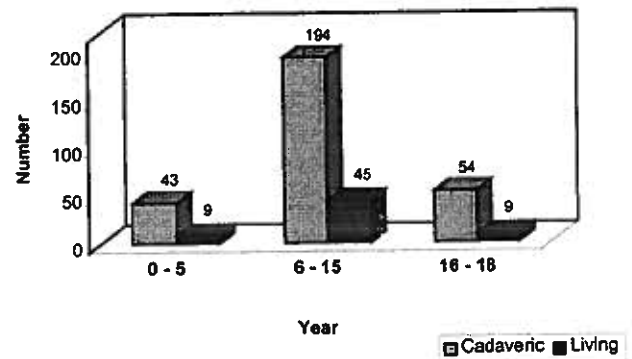


Fig. 2. Paediatric kidney transplantations ($n = 354$) at the University of Heidelberg from 1967 to 2003, according to the recipient age distribution and stratified according to cadaveric or living-related donor kidneys.

Table 2. Primary renal disease in paediatric recipients ($n = 354$) before renal transplantation

Aetiology	Percent
Structural diseases ^a	49.4
Glomerulonephritis/FSGS	30.0
Nephrotic syndrome	3.8
Familial syndromes	3.6
Cystinosis	3.2
Haemolytic uraemic syndrome	2.1
Others	7.9

FSGS, focal-segmental glomerulosclerosis. ^aRenal hypo- or dysplasia and reflux or obstructive nephropathy.

Patient and graft survival rates

The overall patient survival rates were 95% after 1 year and 89% after 5 years. The patient 5 and 10 year survival rates for living donor renal transplantations were 95 and 95%, respectively. Graft survival rates improved since 1990 compared with the period prior to 1990: 82.5 vs 56.7% graft survival at 1 year and 82.5 vs 50% after 5 years ($P=0.03$). The graft survival rates for living donor renal transplantations were 85 and 75% after 5 and 10 years, respectively. Living donated transplantations showed a better outcome compared to cadaver kidneys. The majority of chronic organ losses was caused by chronic allograft nephropathy (10.4%), and the remaining showed no aetiology (4.2%). Comparing the operating technique in a subgroup of patients without any differences in the immunosuppressive regimen, anastomoses with the aorta and vena cava (51% of transplantations, $n=31$) were associated with a graft survival of 86.6% after 1 year, whereas anastomoses with iliac vessels (49% of transplantations, $n=30$) were associated with a graft survival of 55.8% in the same time period ($P=0.01$). The survival rate after 5 years for the two aforementioned groups was 83.3 and 51.6%, respectively ($P=0.01$). Based on these decreased vascular complications, the technique using the aorta and distal vena cava has been utilized in our centre since 1990.

Discussion

Although dialysis therapy in children has shown improvement over the years, poor weight gain and retarded linear growth and psychomotor development cannot be ignored [1]. Treatment of anaemia, renal osteodystrophy and hypertension are other issues that need much attention and make a child dependent on meticulous drug therapy [1]. All of these supplemental therapeutic measures used in conjunction with dialysis are difficult to bring in line with a normal life. For avoiding these problems, kidney transplantation is the treatment of choice for children suffering from ESRD [2,4]. On the other hand, children and adolescents are constantly growing, developing and changing. Each developmental stage produces a series of medical, biological and psychological challenges that must be appropriately addressed if a truly successful graft outcome and rehabilitation are to be expected [4,7].

After establishment by Eurotransplant of new modalities of organ distribution to overcome the organ shortage for children, a greater number of grafts from cadaveric donors have been allocated to paediatric recipients, leading to preferential treatment of children [15]. This arrangement was based on the facts that HLA matching in paediatric patients was significantly poorer than in adults, and on the existing difficulties associated with maintaining dialysis access and optimizing growth in small children with end-stage renal failure [1]. Aside from the aforementioned changes in allocation of organs for children, living

donors can also help to increase the harvested organ pool for transplantation. It has been shown that the living donor is mostly a parent [13], as in our patient cohort, in which parents donated 96% of harvested living organs. Living donated kidney transplantation comprised 18% of all our paediatric transplantations. Significant differences are observed between various countries according to the rate of living donated transplantations: Nordic countries 80%, North America 60% and UK 25% [1,7]. This difference may reflect heterogeneous national programmes and various cultural beliefs as well as local conditions. Short- and long-term graft and patient survival rates are better in recipients of living donor transplants in all paediatric age groups [1,2,4,16]. Shorter cold ischaemia time, better HLA matches, lower acute rejection rates and better preoperative organ and patient preparation contribute to the better outcome in recipients of living donor kidneys [4]. The perioperative risk of the donor is a concern, but the reported mortality rate is extremely low (0.03–0.06%), and long-term follow-up of donors has not demonstrated any increased mortality or morbidity [17]. At present, we are attempting to increase the number of our living organ donations for children, in order to prevent a prolonged period of dialysis during the most critical phase of growth and development.

McDonald *et al.* [13] reported both haemodialysis and peritoneal dialysis in about one-third of the living donated kidney recipients before transplantation, with the remaining third undergoing preemptive transplantation. The report of the North American Paediatric Renal Transplant Cooperative Study (NAPRTCS) describes 13% of the cadaver donor transplants as being preemptive [16]. A report from the UK stated 20% of the transplants as being preemptive [1]. The incidence of transplantation before dialysis in our living donated patients was 27.5%, which is comparable with reported data from other groups. It has been reported that the 7 year graft survival is higher in the preemptive transplantation group than in those undergoing dialysis before transplantation [2]. Preemptive transplantation is associated with improved growth, better psychosocial development and long-term outcome. In addition, potential accesses for peritoneal and haemodialysis are preserved for later use [1].

Because paediatric renal transplant recipients may have a more intense general immunoreactivity and a higher incidence of rejection episodes than adults, some authors have suggested that they should receive more intensive immunosuppressive therapy than adults [2,18]. The 2001 report of NAPRTCS shows triple immunosuppressive therapy including prednisolone, CsA and MMF as being the most frequently used regimen [7]. Since 1996, MMF has been used instead of azathioprine as part of our triple immunosuppressive therapy. In contrast to the calcineurin inhibitors CsA and tacrolimus, MMF has no detectable effect on interleukin-2 production, but inhibits lymphocyte proliferation [19,20]. MMF therapy is associated with a better graft survival in comparison to azathioprine and

a lower rate of acute rejection episodes [21]. Moreover, it has been shown that MMF without antibody induction provides statistically similar and effective prophylaxis against acute rejection at 6 months and 1 year post-transplant in both living and cadaveric donated renal transplantation [20]. Tacrolimus, introduced into clinical practice in 1989, is a T-cell-specific immunosuppressive agent. It can be used as a primary immunosuppressive agent and as a rescue agent for either refractory acute rejection or for CsA toxicity. It is not effective for chronic renal allograft rejection [22]. Since the long-term difference in transplantation outcome for children immunosuppressed with CsA or tacrolimus is controversial, tacrolimus is not included in our immunosuppressive protocol as the first choice. Some authors reported better long-term results with tacrolimus than CsA [1,23], while some reports have not revealed this difference [4]. Hypertension, gingival hypertrophy and hirsutism are less prevalent and less severe with tacrolimus than cyclosporine. Post-transplantation lymphoproliferative disorder (PTLD) and post-transplantation glucose intolerance are more common and neurotoxicity is more severe with tacrolimus [4,23].

There are some contributing factors such as donor and recipient age, cold ischaemia time, surgical aspects and transplant centre caseloads that could influence graft survival or have resulted at least in controversial results. In previous experiences of our group, it has been shown that organs harvested from very young donors (<6 years) carry an increased risk for graft failure [9]. According to the recipient requirements, we consider a minimum weight of 8–10 kg body weight, because surgical complications increase in smaller infants. This attitude is supported by some authors, who observed a poorer short-term graft survival compared with results obtained in older children [1,8]. It has been shown that an increase of each 1 h to the cold ischaemia time causes amplifying by 4% the risk of graft failure at 3 months [1]. Maybe this phenomenon is one of the most important factors in the higher survival rate of living donor transplantations. From the surgical point of view, attention should be paid when using an adult kidney in a child. If the kidney is not disproportionately large, it is placed in the right retroperitoneum behind the caecum. Otherwise, it could be placed intraperitoneally. It is important when placing an adult kidney in a small child to rapidly transfuse 100–200 ml of blood or plasma prior to declamping to avoid severe hypotension from the shift of a large blood volume into the transplanted kidney [2]. Transplant outcome in high-volume paediatric renal transplant centres (more than 12 paediatric kidney transplants in each year) has been reported to be superior to that found in lower-volume centres [4]. According to this definition, our transplant centre has been a high-volume paediatric renal transplant centre in recent years.

The majority of our graft losses occurred in the first 6 months after transplantation, with the first 2 months reported as the critical time period for graft losses [1].

The causes of graft failure include rejection (acute and chronic), thrombosis and recurrent disease [7], with chronic rejection being the most common cause. Benfield *et al.* [7] reported a decreased prevalence of acute rejection in recent years, with a 1 year graft survival rate of 93 and 94% and an allograft half-life of 16 and 25 years for cadaveric and living donor transplantations, respectively. Our patient and graft survival rates are comparable to other high volume centres. The following factors were reported to increase the likelihood of graft thrombosis: pretransplant peritoneal dialysis, history of prior transplant, cadaveric graft from a donor <6 years of age, cadaveric allograft with a cold ischaemia time >24 h, and recipient <2 years of age [7].

We conclude that there has been a gradual improvement in our paediatric kidney transplantation results over time. Living donor paediatric kidney transplants have a higher patient and graft survival rate than cadaveric donor kidney transplants. Using aorta and inferior vena cava for graft anastomosis especially in small children and utilizing CsA as well as MMF for immunosuppression have positively affected the results of paediatric kidney transplantations in our series.

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Conflict of interest statement. None declared.

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