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ORIGINAL ARTICLE

Transplantation of adult recipients by single cadaveric kidneys from pediatric donors weighing ≤25 kg can be a reliable option

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Summary

The evidence in favor of transplanting single allografts from cadaveric pediatric donors into adult recipients is equivocal. This study was performed to assess the outcome of transplantation of single kidneys from pediatric donors weighing <25 kg. Thirty-five adults transplanted by renal allografts from pediatric donors weighing <25 kg were compared with 30 matched recipients of kidneys from adult donors. Donors in study group were aged 4.2 ± 2.1 years weighing 16.0 ± 5.3 kg. In the study group, surgical complications occurred in five of 35 patients, in the control group four of 30. Serum creatinine reached nadir in 47.5 days in study group versus 30 days in controls ($P < 0.01$). Serum creatinine at 1 and 3 years were comparable in both groups. A 38.9% had proteinuria at 1 year in the study group compared with 22.7% in controls ($P = 0.36$). One-year graft survival was 91.7% in the study group versus 92.8% for controls. The surgical complications and graft survival in the study group was comparable with that of controls. The incidence of proteinuria may be more frequent, but does not appear to impact graft function. The use of single, as compared with paired, pediatric donor kidneys would allow more patients to be transplanted with equivalent results.

Introduction

The increasing disparity between demand and supply of donor kidneys available for transplantation has resulted in an expansion of the criteria used for donor selection. Although the use of kidneys from pediatric cadaveric donors for adult recipients has been suggested as a means to help alleviate this shortage, it is debated because of a reportedly higher incidence of technical complications and worse short- and long-term graft function. Kasiske *et al.* [1] cautioned that the relative size of the donor and recipient should be taken into account when choosing kidneys for transplantation. As the evidence in favor of single rather than *en bloc* paired renal transplantation from pediatric donors is rather equivocal, this study was performed to assess the outcome of transplantation of single kidney from pediatric donors weighing ≤ 25 kg, and to review the relevant literature.

Methods

In this retrospective study, the study group consisted of 35 adults who were transplanted with renal allografts from pediatric donors weighing ≤ 25 kg during the period from April 1994 to April 2004. The University Medical Center Institutional Review Board approved the study design and methodology. One patient transplanted with *en bloc* paired renal allografts was excluded from the study group. These patients were compared with 30 randomly chosen matched adult recipients of kidneys from adult donors transplanted during the same period (control group). Mean follow-up for all patients was 35.7 ± 31.25 months (14–102 months). Glomerular filtration rate was estimate using the modification of diet in renal disease (MDRD) method. STATSDIRECT software (Cheshire, UK) was used for the analysis of data. The Mann-Whitney *U*-test was used for comparing continuous

data, and the chi-square test was used for comparing categorical data in the two different groups. A *P*-value of <0.05 was considered statistically significant. Data is presented as mean ± SD.

All pediatric donor kidneys were received as a pair on intact aortic and vena caval segments. Back table inspection and splitting was carried out under sterile conditions in the operating room. The paired kidneys were separated as long as both kidneys appeared normal without surgical damage, had a single vein, and either a single artery or two arteries with ostia no more than 3 mm apart. We chose not to perform routine postperfusion biopsies because of the risk of injury to the small graft. Our center does not perform routine, protocol, biopsies.

Immunosuppression (induction and maintenance regimen) was comparable in both groups as our center uses standardized protocols. All patients received a standard steroid taper to 20 mg prednisone by postoperative day 5 and 5 mg by week 12. Mycophenolate mofetil was started at 1000 mg b.i.d., adjusted if necessary to maintain white blood cell count (WBC) >4000. Calcineurin inhibitors were started on postoperative day 1. Tacrolimus was the major component of triple drug immunosuppression in 77.7% patients of the study group in comparison with 79.3% of the control group. In the remainder of the patients of both groups the triple drug immunosuppression was based on cyclosporine.

All study patients received a 24-h infusion of low molecular weight Dextran-40 at 20 ml/h. The infusion was started in the operating room prior to reperfusion. Low dose aspirin, 81 mg/day, was began on postoperative day 1.

Our center standard protocol for blood pressure management includes calcium channel blockers (i.e. amlodipine), beta-blockers, and clonidine. All study and control patients were treated with single or combination therapy as needed. Beginning in 1999, recipients of pediatric donor kidneys were started on angiotensin converting enzyme (ACE) inhibitors during post-transplant month three if no contraindications in an attempt to minimize proteinuria. Lisinopril (10–20 mg daily) was the most commonly used medication but several others including angiotensin receptor blockers (ARB) (losartan and olmesartan) were also prescribed. No patient in the control group was prescribed an ACE or ARB.

Results

There was no difference between the groups in regards to sex, age, recipient weight, human leukocyte antigen (HLA) mismatch, panel reactive antibody (PRA), and duration of follow-up (Table 1). The causes or kidney disease are listed in Table 2. Both the groups were comparable regarding the distribution of causes of end-stage failure. Ureteral stent was used in 68.2% in study group versus 26.9% of controls ($P = 0.003$).

Donors in the study group averaged 4.2 ± 2.1 years and 16.0 ± 5.3 kg with a mean donor/recipient weight ratio of 0.24 ± 0.13. In the study group, the arterial anastomosis was carried out with an aortic patch, in all except one patient. The main arterial lumen size was 4.8 ± 2.3 mm. The size of second renal artery, when present, was 3.7 ± 0.6 mm. All patients had single renal veins. No arterial or venous extension grafts were used in any patient. Renal arteries and veins were anastomosed to the external iliac artery and vein, respectively, using fine running Prolene sutures. Table 3 lists the surgical complications occurring in each group. There was no statistical

Table 1. Comparison of demographic features in the study and control groups.

	Study group	Control group	*P*-value
Number in patients	35	30	
Men/women	18/17	18/12	NS
Age (years)	39.8 ± 14.7	43.8 ± 12.5	NS
Second transplant	1/35	4/30	NS
Recipient weight (kg)	73.6 ± 20.4	75.9 ± 26.1	NS
Body Mass Index	29.3 ± 6.7	32.4 ± 8.1	NS
HLA-A mismatch	1.4 ± 0.6	1.3 ± 0.8	NS
HLA-B mismatch	1.34 ± 0.7	1.0 ± 0.7	NS
HLA-DR mismatch	1.2 ± 0.6	1.1 ± 0.7	NS
PRA type I (peak)	14.7 ± 27.6	16.9 ± 28.6	NS
PRA type I (current)	8.3 ± 23.1	6.3 ± 19.9	NS
PRA type II (peak)	9.5 ± 18.2	12.7 ± 29.3	NS
PRA type II (current)	3.9 ± 12.2	0.7 ± 3.6	NS
Proportion of patients with induction by IL2-receptor blocker /ATG	45.7% (0 with ATG)	52.2% (2 with ATG)	NS
Ureteric Stent placement	68.2%	26.9%	0.003
Duration of follow up (months)	25.2	33.1	0.06

Table 2. Causes of renal failure

Diagnosis	Study group ($n = 35$)	Control group ($n = 30$)
Hypertension	20	16
Glomerulonephritis	1	2
Diabetes	2	3
Polycystic kidney disease	1	1
Focal segmental glomerulosclerosis	3	0
Lupus	2	2
Unknown/other	6	6

Table 3. Comparison of the surgical complications.

	Study group	Control group	*P*-value
Number in patients	35	30	NS
Hydronephrosis	1	1	NS
Hematoma	2	0	NS
Ureteric stenosis	2	1	NS
Uretero-vesical leak	0	1	NS
Fluid collection	1	1	NS
Surgical intervention required	2	2	0.99

difference in the incidence of complications or in the need for subsequent surgical intervention.

In the study group, it took a longer time for serum creatinine to reach nadir, as evident by significantly higher serum creatinine at 1 month in the study group compared with the control group (Table 4). Serum creatinine at 1 and 3 years were similar in both study and control groups (1.5 ± 0.4 and 1.3 ± 0.5 mg/dl vs. 1.7 ± 1.4 and 1.5 ± 0.4 mg/dl, respectively). In the study group the calculated glomerular filtration rate was 72.8 ± 12.1 mg/min. The graft survival at 1 year was 91.7% and 92.8%, respectively in the study and control groups. By 3 years of follow-up, five of 14 (35%) in the study group and three of 17 (18%) in the control group failed ($P = $ NS). The causes of failure in study group were: thrombotic microangiopathy ($n = 1$), sepsis due limb gangrene ($n = 1$), crescentric glomerulonephritis ($n = 1$), and steroid resistant acute rejection ($n = 2$).

All patients evaluated for rejection had a duplex ultrasound. Routine ultrasounds at specified time points were not performed. In the study group the transplant kidney size was measured on 10 ultrasounds, when rejection was suspected clinically. These ultrasounds occurred at various times ranging from 2 to 26 months post-transplant. The mean measured kidney size was 10.5 ± 2.9 by 5.0 ± 3.4 cm. No abnormal arterial or venous flow characteristics were noted. Thirty-one percent of patients in study and 16% in central group were treated for acute rejection. Biopsy proven acute rejection occurred in 29% and 16%, respectively.

Discussion

The transplantation of single (or even paired *en bloc*) pediatric donor kidneys into adults remains controversial because of concerns regarding poor short and long-term graft survival. In the immediate perioperative period technical concerns predominate. Using microvascular surgical techniques excellent vascular and ureteral anastomoses are possible. We believe that, in general, only kidneys having single arteries and veins should be split from *en bloc* pair when the donor is a small pediatric patient. We did separate three pairs with more than one renal artery, but only when certain the ostia were on satisfactory aortic patches. No kidney was lost because of thromobosis or arterial stenosis in this series. The use of Dextran in the peri- and early postoperative periods and subsequent chronic aspirin may be helpful in reducing the risk of thrombosis, but no controlled data exists to prove this hypothesis. The ureteroneocystostomy is at increased risk of technical complications, stenosis and leak, because of the small size of the ureter and tenuous blood supply. Care must be taken to avoid dissection in the hilum so that transplant ureter blood supply remains intact. In addition, the kidney must be positioned and the site of vascular anastomoses chosen to avoid any tension on the ureter. The incidence of ureteral complications was the same in the study and control groups, indicating that

Table 4. Comparison of the graft function, acute rejection and graft outcome.

	Study group	Control group	*P*-value
Number in patients	35	30	
Proportion of patients treated for ≥ 1 acute rejection	11 (31%)	5 (16%)	NS
Number of patients with biopsy proven ≥ 1 acute rejection	10 (29%)	5 (16%)	NS
Days taken for serum creatinine to reach nadir	47.5	30	<0.01
Serum creatinine at 1 week	4.9 ± 3.0	5.4 ± 4.5	NS
Serum creatinine at 3 months	2.1 ± 1.4	1.7 ± 1.9	0.009
Serum creatinine at 1 year	1.5 ± 0.4	1.7 ± 1.4	NS
Serum creatinine at 3 years	1.3 ± 0.5	1.5 ± 0.4	NS
Proportion of patients with proteinuria at 1 year	14 (40%)	7 (23%)	NS
1-year graft survival	91.7%	92.8%	NS

attention to detail and use of fine, 6-0 monofilament absorbable suture eliminates excess complications with the ureteroneocystostomy. We had a low threshold for using ureteric stents which may be responsible for lower than reported incidence of ureteric complications, although the relationship of ureteral anastomotic stenting and leak or stenosis is uncertain.

The inadequacy of pediatric donor small kidney nephron mass has been posed as having a negative impact on graft function and survival. El-Agroudy *et al.* [2] reported that low donor/recipient body weight ratio might contribute to inferior long-term renal allograft survival possibly related to hyper filtration. In the present study, recipients of pediatric donor kidneys did have a significantly slower fall in serum creatinine compared with that in the control group, which might be explained by the lower initial nephron mass. By 1 and 3 years, however, the serum creatinine was somewhat lower in the study group than in the control group. Although this was not different statistically, these findings suggest a compensatory nephron hypertrophy in the pediatric kidneys in response to the size of an adult recipient.

Sánchez-Fructuoso *et al.* [3] observed that the greater the mass, the lower the incidence of both acute and chronic rejection. In our patients, biopsy proven acute rejection was more common in the study group than the controls but the difference was not statistically significant (Table 3). In view of the relatively small sample size of this study, no definitive conclusions can be made regarding acute rejection. However, we have found that there is no correlation between donor age or donor/recipient body weight ratio to the probability of graft failure by 3 years suggesting that nephron mass in pediatric kidneys is not a limiting factor when being considered for transplantation into an adult.

Chen *et al.* [4] compared the patients who received kidney allografts from donors ranging from 26 months to 7 years old ($n = 12$) to those who had grafts from adult donors ($n = 173$). They observed that the frequency of fixed proteinuria in the first 3 years was higher in the pediatric donor group (50%) than in the adult group (28%), $P < 0.05$. In the same study, surgical complications were reported to be much higher in recipients of pediatric grafts compared with controls, including: lymphocele (50% vs. 8%), renal graft artery stenosis (33% vs. 11%), and hydronephrosis (33% vs. 9%).

In our study, we noted that the incidence of proteinuria was more common in study group, but not significantly different from the controls (Table 3). It is possible that adjusting antihypertensive management to include ace-inhibitors in our patients helped to reduce clinically significant proteinuria. The mechanism by which ace-inhibitors reduce proteinuria is by stabilizing the basement membrane [12]. Modlin *et al.* [5] reported similar findings in their report of a large single center experience of transplantation of single pediatric donor kidneys ($n = 60$; age ≤ 6 year old donors) into adults compared with a control group of 58 matched adult donors. They reported an increased incidence of proteinuria in the pediatric donor group (67% vs. 48% in controls), $P = 0.04$. However, they concluded that despite the increase in proteinuria, the long-term graft function was equivalent.

Ratner *et al.* [6] concluded that there is no advantage in adults receiving paired kidneys from cadaveric donors (≤ 5 years, $n = 12$) over those who received single pediatric allografts (≤ 5 years, $n = 10$). This supports our opinion that pediatric donor kidneys, whether single or paired, provide satisfactory renal function for adult recipients despite a significant initial disparity between renal mass and recipient body mass. We agree with Ratner *et al.* [6] that no appreciable advantage is achieved by using two pediatric kidneys for a single recipient.

Gourlay *et al.* [7] reported in their study of 83 adults who received kidneys from donors aged 5 months to 10 years that, by 1 year, the serum creatinine becomes equal ($P = 0.63$) to controls. Although the mean age and weight of the pediatric donors in this study were greater than in our series, their reported patient (and graft) survival at 1 and 3 years of 91% (77%) and 86% (68%), respectively, was comparable with the results in our patients. Pugliese *et al.* [8] reported their results in adults transplanted with kidneys from older pediatric donors ($n = 30$) with a 1-year graft survival of 76%. Jacoby *et al.* [9] followed 50 adult recipients transplanted with single kidneys from donors aged 11 to 48 months and showed 1-year allograft survival of 71.3% compared with 87.8% in their adult-to-adult controls.

Three-year graft survival in a series of 33 *en bloc* paired pediatric kidneys into adult recipients has been reported as high as 87.3% [10]. However, a survival analysis of en bloc grafts ($n = 751$) from the United Network of Organ Sharing database revealed 1- and 3-year graft survival rates of 76.3%, and 67.7%, respectively [11]. Corresponding figures for single pediatric grafts transplanted into adults for 1- and 3- year ($n = 1447$) were 72.2% and 61.1%, respectively. From the utilitarian point of view, the transplantation of a single pediatric kidney into an adult may provide a better use of a limited resource.

Graft survival and other outcome measures of transplantation are affected by various factors including technical aspects of the surgical procedure. The successful splitting of *en bloc* kidneys is dependant upon the anatomy of the donor organs. Multiple arteries or veins are considered a relative contra-indication to splitting small pediatric donor kidneys at our center. We believe the presence of small accessory vessels, even if on a common

patch, increases the risk of thrombosis. In addition, the surgeon preparing the graft must be very cautious to avoid injury to the renal pelvis and ureteral blood supply. During operation, anatomic considerations dictate the positioning of the allograft. It is critical to ensure that the kidney will not twist on the vascular pedicle. In addition, the kidney must be placed in a manner that minimizes the ureter length because of its tenuous blood supply.

In each of our cases, the kidneys were offered *en bloc* for one recipient per standard UNOS allocation methods. The recipient transplant surgeon sterilely inspected the *en bloc* donor kidney pair upon receipt in the transplant center. When it was determined by the recipient surgeon that the kidney pair could be successfully split, one kidney was offered back to UNOS for re-allocation. We believe that the current *en bloc* allocation scheme remains appropriate as the transplantability of split small pediatric donor kidneys can only be made by carefully considering all relevant factors: donor kidney anatomy, recipient characteristics, and surgeon experience. In other words, small pediatric donor kidneys should be procured *en bloc*, offered to one recipient first, and only split for two recipients when the responsible recipient transplant surgeons has determined the feasibility of splitting. All recipients were informed of the potentially increased risks associated with transplantation by a pediatric donor kidney.

We conclude that the nephron mass in pediatric kidneys is not the limiting factor when being considered for transplantation into an adult. Although the incidence of proteinuria is more frequent, surgical complications, graft function as measured by serum creatinine, and graft survival in adult recipients of single renal grafts transplanted from small pediatric donors are comparable with that of controls. Ultimately the decision to transplant pediatric donor kidneys *en bloc* or individually is dependant upon surgeon and center experience.

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