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Nickolas Mitrou
Western University

Shahid Aquil
Western University

Marie Dion
Western University

Vivian McAlister
Western University

Alp Sener
Western University

See next page for additional authors

Authors
Nickolas Mitrou, Shahid Aquil, Marie Dion, Vivian McAlister, Alp Sener, and Patrick P. Luke

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ORIGINAL ARTICLE

Transplantation of pediatric renal allografts from donors less than 10 kg

Nicholas Mitrou[1] | **Shahid Aquil**[1,2,3] | **Marie Dion**[1,2] | **Vivian McAlister**[1,2,3] | **Alp Sener**[1,2,3] | **Patrick P. Luke**[1,2,3]

[1]Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

[2]Department of Surgery, Western University, London, ON, Canada

[3]Multi Organ Transplant Program, Western University, London, ON, Canada

Correspondence
Patrick Luke
Email: patrick.luke@lhsc.on.ca

Present address
Nicholas Mitrou and Shahid Aquil, London Health Sciences Centre University Hospital, Western University, Windermere Road, London, Ontario, Canada

Alp Sener, Department of Surgery, Western University, University Hospital, London, Ontario, Canada

Few transplant programs use kidneys from donors with body weight (BW) < 10 kg. We hypothesized that pediatric en bloc transplants from donors with BW < 10 kg would provide similar transplant outcomes to larger grafts. All pediatric en bloc renal transplants performed at our center between 2001 and 2017 were reviewed (N = 28). Data were stratified by smaller (donor BW < 10 kg; n = 11) or larger donors (BW > 10 kg; n = 17). Renal volume was assessed during follow-up with ultrasound. Demographic characteristics were similar between the 2 groups of recipients. After mean follow-up of 44 months (smaller donors) and 124 months (larger donors), graft and patient outcomes were similar between groups. Serum creatinine at 1, 3, and 5 years was no different between groups. At 1 day posttransplant, mean total renal volume in the smaller donors was 28 ± 9 mm^3 vs 45 ± 12 mm^3 ($P < .01$). By 3 weeks, it was 53 ± 19 mm^3 (smaller donors) versus 73 ± 19 mm^3 (larger donors) (P = NS). Complication rates were similar between both groups with 1 case of venous thrombosis in the smaller group. With experience, outcomes are equivalent to those from larger pediatric donors.

KEYWORDS
clinical research/practice, deceased, donors and donation, kidney transplantation/nephrology, organ acceptance, organ procurement and allocation, surgical technique, urology

1 | INTRODUCTION

There is an increasing discrepancy between the number of patients waiting for kidney transplants and the number of available donors. Importantly, from 1997 to 2014, the number of patients on dialysis has increased substantially while the rate of transplant has been stagnant.[1] This discrepancy has led to potential recipients spending an increasingly longer waiting time on dialysis. In addition to increasing morbidity and mortality, increased wait time on dialysis is a strong risk factor for worse posttransplant outcomes.[2,3] Therefore, it is critical to increase the size of the renal donor pool to improve patient outcomes.

One strategy is to transplant pediatric donor kidneys into adult recipients. Because the kidneys are small, there is increased risk of thrombosis rates.[4,5] For this reason, en bloc transplant of both donor kidneys have been performed to allow vascular anastomosis between the larger aorta and vena cava of pediatric kidneys in the recipient vasculature.[6] However, pediatric donor kidneys are less likely to be used than are adult kidneys given the complexity of back table reconstruction and potential for posttransplant complications.

Within the pediatric donor population, there is an inverse relationship between the body weight (BW) of donors and the rate of organ discards.[7,8] The smallest donors are far less likely to actually be used than are larger pediatric donors. Specifically, Pelletier et al [7] showed that the rate of organ discard in pediatric donors increases substantially when BW is < 10 kg, a finding that was confirmed by Maluf et al.[8] The main deterrent from using these kidneys is the high theoretical risk of thrombosis and functional capacity.[4,5]

Abbreviations: BW, body weight; BMI, body mass index; DCD, donation after cardiac death; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; GN, glomerulonephritis; HD, hemodialysis; NDD, donation after neurologic determination of death; PCKD, polycystic kidney disease; PD, peritoneal dialysis; RRT, renal replacement therapy.

However, pediatric en bloc kidneys have been shown to provide long-term renal outcomes similar to adult single kidneys, although there remains a paucity of data regarding the smallest donors weighing < 10 kg.[4,6,9-12] Because these donors provide an important potential graft resource, it is important to assess the function and complications of using such small donor kidneys.

We tested the hypothesis that kidneys from these very small donors (weight < 10 kg) were equivalent in terms of patient and graft survival to pediatric transplants from donors > 10 kg.

2 | METHODS

2.1 | Study population

All pediatric en bloc transplants performed at our center between 2001 and July 2017 were retrospectively analyzed. There were 28 transplants, and these were divided into a small group, from donors with BW < 10 kg, and a large group containing donors with BW > 10 kg. All donors in the small group were also < 8 months old. This study was approved by the Office of Research Ethics at Western University.

2.2 | Transplant

Pediatric en bloc transplant was performed using previously described techniques.[13] Accordingly, the immunosuppression administered was in accordance to that described in the aforementioned publication. All recipients received an intraoperative intravenous dose of 5000 IU heparin, followed by a postoperative taper of heparin infusion as previously described by our group in the prevention of thrombosis in pancreas transplant recipients.[14] Anastomosis was specifically targeted to the external iliac artery and vein. Briefly, patients were induced with Thymoglobulin (Sanofi, Lyon, France) in all patients except 1 from the large group, in whom basiliximab (Novartis, Basel, Switzerland) was used. Maintenance immunotherapy included tacrolimus, prednisone, and mycophenylate mofetil in all patients.

2.3 | Renal function

Serum creatinine was evaluated in all patients during follow-up. We used serum creatinine as an index of renal function. We did not calculate estimated glomerular filtration rate (GFR) because the equations for this estimate assume that serum creatinine is at steady state, but serum creatinine changes rapidly posttransplant, thus violating this assumption and invalidating the standard equations for calculating eGFR in this context. Terminal GFR was calculated in donors before explant by using the CKD-EPI equation.[15]

2.4 | Survival

Patient and graft survival rates were compared between the small and large groups. Kaplan-Meier curves were generated to show both patient survival and graft survival.

2.5 | Renal growth assessment

Renal volume was calculated according to Equation 1 by using ultrasound images.

$$V = \frac{4}{3}\pi r_x r_y r_z \quad (1)$$

where r_x, r_y, and r_z are the radii of each kidney measured in 3 planes. Individual kidney volume was assessed, and both grafts were included when both were measured. Therefore, reported mean volumes represent the volume of a single kidney, not the combined volume of the en bloc graft. Volume was compared between the small and large groups at time intervals posttransplant.

2.6 | Statistical analysis

Between-group comparisons were made using the Wilcoxon rank sum test. Groups were compared over time by using 2-way mixed-models ANOVA with planned comparisons. This was done to allow specific comparison between the 2 groups at different time points and to minimize the number of statistical comparisons being made. Data are shown as mean ± SD. Data analysis was performed on Matlab r2016b (The Mathworks, Natick, MA), and statistical analyses were performed using SPSS (IBM, Armonk, NY).

3 | RESULTS

3.1 | Study population

Demographic characteristics of the recipients are presented in Table 1. There were few significant differences in demographic characteristics between recipients of grafts from the groups of large or small donors (Table 1). One difference was that recipients in the large group were more likely to have received pretransplant peritoneal dialysis (62.6% vs 36.4%). In addition, there was significantly longer mean follow-up time in the large group (44 months vs 124 months, $P = .0024$). This was a result of the late introduction of small pediatric en bloc transplant to our transplant program, rather than a difference in survival.

Demographic characteristics of the donors are presented in Table 2. There were no sex differences between the groups of donors. Terminal GFR was not significantly different between the groups. Donation after cardiac death (DCD) and donation after neurologic determination of death (NDD) types of donation were used in both the large and small groups. In the large group, 3 of 17 were DCD, while in the small group, 3 of 11 were DCD (P = NS).

All transplants were performed with similar techniques by 3 surgeons. There were no differences in warm or cold ischemic times between the groups. Ureteral reconstruction was performed using a Wallace technique in all patients except for 5 patients who received grafts from the smallest donors. Instead, ureteral reconstruction was performed by transplanting both ureters along with a patch of bladder trigone.[16] This technique enabled more robust anastomosis of the very small ureters in these donors, although it should be noted

TABLE 1 Recipient characteristics

Recipient characteristic	Donor BW < 10 kg (n = 11)	Donor BW > 10 kg (n = 17)	*P*-value
Sex, % male	36	35	.98
Age, y	46 ± 14	48 ± 17	.89
BMI, kg/m^2	24 ± 6	27 ± 5	.33
First transplant, %	82.7	89.2	—
RRT time, wk	28 ± 19	25 ± 27	.84
Predialysis, %	9.1	5.6	—
HD, %	72.7	58.8	—
PD, %	36.4	63.6	—
Primary renal disease, %			
Diabetes	0	18.2	—
Hypertension	9.1	36.4	—
IgA nephropathy	9.1	9.1	—
PCKD	9.1	9.1	—
FSGS	27.3	0	—
GN	36.4	45.5	—
Obstructive	0	18.2	—
Other	0	18.2	—
Total follow-up time, mo	44 ± 40	124 ± 55	<.003

BW, body weight; BMI, body mass index; RRT, renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; PCKD, polycystic kidney disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis.

TABLE 2 Donor characteristics

Characteristic	Donor BW < 10 kg (n = 11)	Donor BW > 10 kg (n = 17)	*P*-value
Sex, % male	55	47	.72
Age, wk	6.3 ± 1.6	23.8 ± 10.4	<10^{-4}
BW, kg	4.3 ± 3.4	14.0 ± 2.6	<10^{-4}
GFR, mL/min	25.4 ± 9.9	35.1 ± 21.1	.14
Warm ischemia time, min	7.3 ± 12.9	5.3 ± 12.1	.65
Cold ischemia time, min	900 ± 600	1200 ± 500	.24

BW, body weight; GFR, glomerular filtration rate.
Warm ischemia time is listed for donation after cardiac death cases.

that in the initial report[16] there were potentials for complications such as necrosis of the bladder patch.

3.2 | Renal function

Renal function was assessed based on serum creatinine and is presented in Figure 1. In both the large and the small groups, there was a rapid decline in serum creatinine in the first weeks after transplant. By approximately 1 month posttransplant, serum creatinine had normalized in both groups. There were no significant differences in serum creatinine between the groups.

3.3 | Survival

Patient survival was 100% in both the small group and the large group in the first 34 months posttransplant. Long-term survival was 100% in the small group at a maximal follow-up of 108 months, whereas it was 82.4% in the large group at a maximal follow-up of 196 months.

3.4 | Renal volume

At the time of transplant, grafts from the small group were significantly smaller than the grafts from the large group (Figure 2). The small group mean volume was 28 ± 9 mm^3, and the large group volume was 45 ± 12 mm^3 (P < .01). This size difference continued for the first 2 weeks posttransplant, but the difference was abrogated by the third week posttransplant. At this point, the small group had a mean volume of 53 ± 19 mm^3 and the large group had a volume of 73 ± 19 mm^3 (P = NS). The grafts in all patients grew at similar rates and achieved volumes that were not different between the groups. By 1 year posttransplant, the small group's mean renal volume was 88 ± 44 mm^3 while the large group's was 93 ± 52 mm^3 (P = NS).

4 | COMPLICATIONS

Summary statistics of complications and outcomes of the transplants are presented in Table 3. Complications in each group were classified according to the Clavien-Dindo classification system.[17,18] In the small group, there were 3 Clavien II complications in the small group,

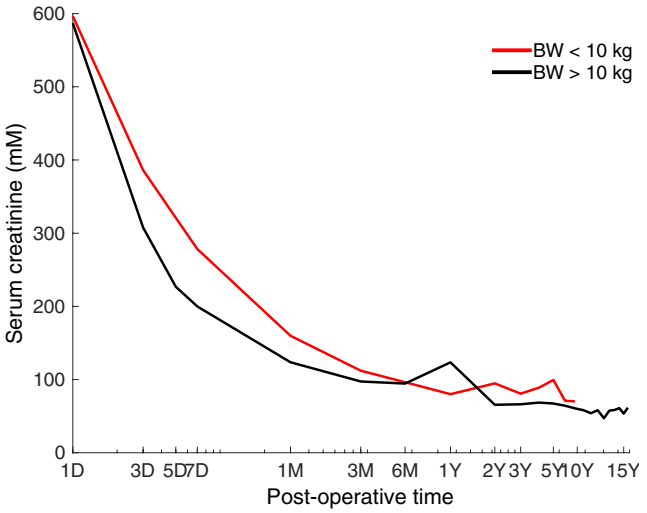

FIGURE 1 Serum creatinine in recipients of transplants from donors in the large (black) and small (red) groups. Serum creatinine declined rapidly in both groups during the first year posttransplant, and there were no significant differences between the groups. Note that the *x*-axis is logarithmic [Color figure can be viewed at wileyonlinelibrary.com]

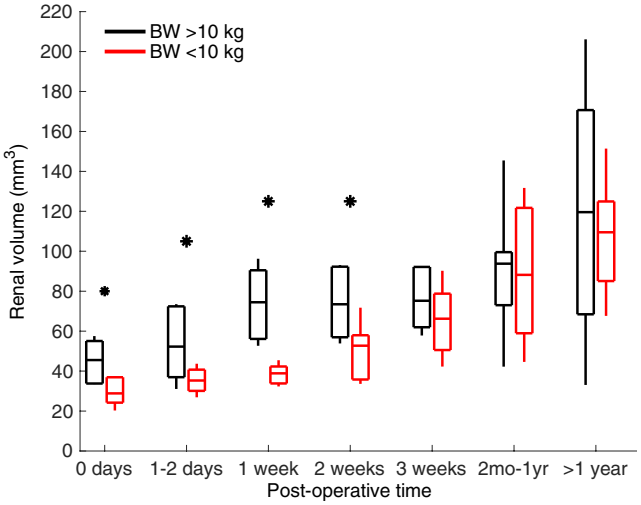

FIGURE 2 Renal volume in patients with grafts from the large (black) donors and small (red) donors. Renal volume was lower in the small group for the first 2 weeks posttransplant, but by 3 weeks the small grafts had grown so that their volume was no different from those in the large group [Color figure can be viewed at wileyonlinelibrary.com]

which included heparinization for thrombus in 1 patient, ureteric obstruction in 1 patient, early T cell–mediated rejection in 1 patient, and hydronephrosis in 1 patient. In the large group, there were 2 Clavien II complications, including a rejection episode and sepsis. In the small group, there were 3 patients in whom reoperation was performed (Clavien IIIb) for clot evacuation, ureteral reimplant, and graft nephrectomy, respectively. In the large group, no patients required reoperation.

Afterward, there were 3 deaths with function in the large group while there were no deaths in the small group (Figure 3). One patient

TABLE 3 Posttransplant complications and graft losses

Complication or loss, no. of patients	Donor BW < 10 kg (n = 11)	Donor BW > 10 kg (n = 17)
Delayed graft function	5	4
Rejection	1	1
Thrombus	1	0
Hydronephrosis	1	0
Recurrence of primary disease	0	1
Ureteral complication	2	0
Infection	0	1
Posttransplant dialysis required	5	3
Patient death with intact graft	0	3

in the large group and 2 patients in the small group underwent graft nephrectomy for either rejection or rejection-related complications. This resulted in a death-censored graft survival of 81.8% versus 94.1% (small vs large), which was not statistically significant.

5 | DISCUSSION

This study evaluated the outcomes of 28 pediatric en bloc kidney transplants using grafts from donors who weighed either < 10 kg or > 10 kg. The primary result of this study was that renal function in patients who received a pediatric en bloc kidney transplant from donors weighing < 10 kg, or who were younger than 8 months, was similar to function in those who received a pediatric transplant from

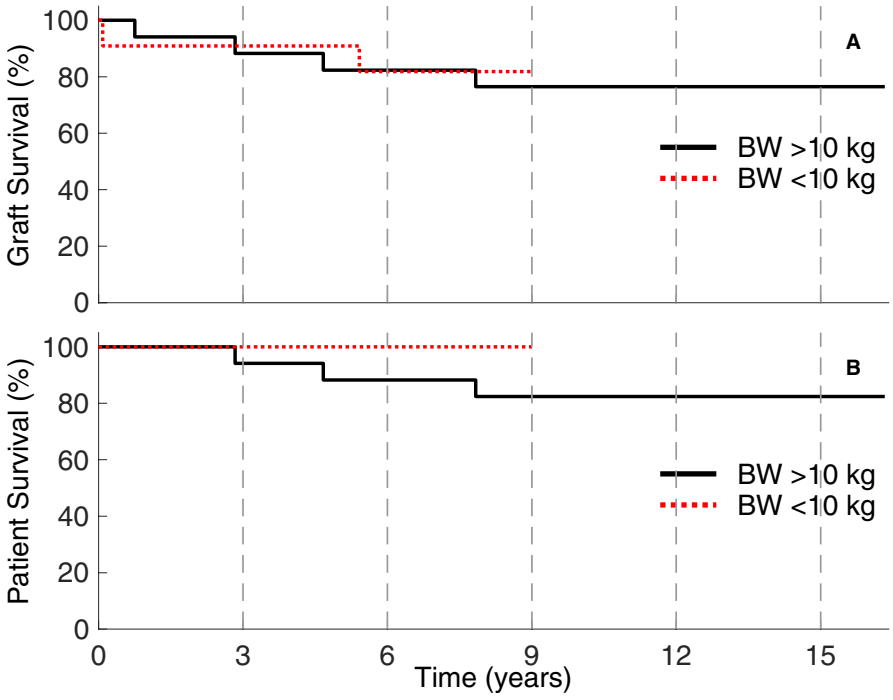

FIGURE 3 A. Graft survival in the large (black) and small (red) groups. Grafts were assigned as lost if they were removed surgically or if the recipient died with a functioning graft because in both cases the graft is no longer functional. B. Patient survival in the large (black) and small (red) groups. No patients in the small group died, while there were 3 deaths with functional grafts in the large group [Color figure can be viewed at wileyonlinelibrary.com]

larger donors. In addition, there were no significant differences in survival or in complications between grafts from the small or large groups of donors. The volume of grafts from small donors was lower than that from the large donors, but all grafts underwent rapid growth; by the third week posttransplant, the small grafts were no longer significantly smaller than the large grafts. All grafts grew substantially during the first year posttransplant.

Previous studies have consistently shown that outcomes of pediatric transplant are similar to those of adult transplant.[10,12,19,20] Indeed, Sureshkumar et al[21] reported that long-term outcomes of pediatric grafts were better than outcomes of grafts procured from living adult donors. Follow-up of pediatric transplant showed similar outcomes and renal function as adult donors up to 20 years posttransplant.[22] However, some data suggest that pediatric kidneys may still be discarded instead of potentially being transplanted.[7,8] This suggests that the use of pediatric transplants has not been optimized. Potential reasons for the high rate of organ discard include higher degree of technical difficulty compared with adult donor grafts. One example of technical difficulty is the joining of donor ureters to the recipient bladder, or ureteroneocystotomy.

Ureteroneocystotomy in very small kidney grafts carries an increased risk for complications. Therefore, in the smallest grafts, we adapted the technique to include a bladder patch from the donor. When the donor kidneys were removed, a patch of bladder trigone that includes both ureterovesicular junctions was removed so that the individual graft ureters did not have to be separately anastomosed to the recipient bladder.[16]

Our thrombosis rate with pediatric en bloc grafts was 3.5%, which is lower than the rate reported by Ana et al.[4] This rate is far higher than that reported in most adult single donor transplant series[23] and remains the main impediment in performing pediatric en bloc transplant in the majority of centers, especially with very small donors.

The single recipient who had graft thrombosis received their graft from a donor in the small group. This donor was one of the smallest donors (BW 4.0 kg). The thrombus occurred within 24 hours of transplant. The patient had decreased urine output, at which time an ultrasound was performed, which demonstrated lack of venous flow and arterial flow reversal, consistent with venous occlusion. Surgical exploration was performed, which revealed a thrombus in the donor vena cava, which prompted graft nephrectomy.

Pediatric grafts appear to grow and mature rapidly to resemble adult kidneys within the first years after transplant.[24] Interestingly, the grafts provide adequate renal function almost immediately after transplant, despite their small size. In the first days posttransplant, grafts in the small group had a mean volume of 28 ± 9 mm^3, whereas adult kidneys have been measured by magnetic resonance imaging and ex vivo water displacement to be closer to 200 mm^3.[25] Hirukawa et al[26] recently reported that glomerular volume continued to increase for at least 3.5 years posttransplant, while podocytes took approximately 3 years to mature in 1 case. Our data suggest continued growth in all grafts, in agreement with Hirukawa et al,[26] and that grafts from smaller donors undergo a rapid "catch-up" period during the first posttransplant year; the final growth capacity over years is unknown. Confidence in average renal volume measurement in each of our groups decreases as follow-up time increases. Therefore, it is possible that with a larger study population, one may unmask a hidden retained difference in renal volume between small and large kidneys. However, renal growth is theoretically asymptotic, meaning that eventually all kidneys will reach a similar maximum size and these differences, if they exist, will be abolished.

The limitations of this report include its retrospective nature and the limited size of the population. This may be addressed using a multicenter study with other centers that use donors <10 kg. It is not clear if there are lower limits to donor age. Four of our patients were 2 weeks old, and it is possible that donors younger than 2 weeks could have been used if offered to our center. As well, the use of kidneys from anencephalic donors and premature donors was not assessed.

Overall, the opportunity to provide increasing numbers of kidney transplants to patients by using ever-smaller donors is clear. The lower limit for single kidney transplant has been investigated previously,[27] but the same information is not yet clear for en bloc grafts. Recent reports demonstrating transplant of small pediatric kidneys with BW of 2.5-5 kg have outcomes similar to the outcomes reported here.[28-31] This study provides evidence that transplants with donors as young as 2 weeks old, with experience, is a potentially important method for expanding the pool of potential kidney donors.

AUTHOR CONTRIBUTIONS

N.M., M.D., and S.A. data collection, data analyzed, and wrote the manuscript; P.L. and A.S. performed transplant surgeries and posttransplant care and provided guidance in data analysis and in manuscript preparation.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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