En bloc kidney transplantation from infant donors younger than 10 months into pediatric recipients

Hong-yang Wang¹ | Jun Li¹ | Long-shan Liu¹ | Rong-hai Deng¹ | Qian Fu¹ | Dicken Shiu-Chung Ko² | Huan-xi Zhang¹ | Su-xiong Deng¹ | Chang-xi Wang¹,³

¹Organ Transplantation Center, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
²Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
³Guangdong Provincial Key Laboratory on Organ Donation and Transplant Immunology, Guangzhou, China

Correspondence
Chang-Xi Wang and Long-shan Liu, Organ Transplant Center, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Emails: wangchx@mail.sysu.edu.cn (CW) and liushan@mail.sysu.edu.cn (LL)

Funding information
Guangdong Provincial Key Laboratory on Organ Donation and Transplant Immunology, Grant/Award Number: 2013A061401007.

Abstract
Early graft loss and poor graft function limit the use of kidneys from infant donors. Six en bloc kidney transplantations were performed from infant donors younger than 10 months into pediatric recipients between November 2012 and September 2015 at our center. We retrospectively analyzed recipient and donor demographics, surgery procedures, complications, graft function and size, and patient and graft survival with a follow-up of 6-39 months (median 15.5 months). Donor age ranged from 1 to 10 months with weight ranging from 3.5 to 10 kg. Recipient age ranged from 10 to 16 years with weight ranging from 30 to 39 kg. One kidney was removed due to arterial thrombosis during surgery, while the other kidney of this en bloc graft remained viable. Urine leak followed by bilateral ureteral obstruction occurred in one recipient. All of the recipients showed immediate graft function. The size of the en bloc kidney increased from 4.2±0.6 cm to 7.6±0.6 cm 6 months after surgery. Patient and graft survival were both 100% at the last follow-up. Our results show that en bloc kidney transplantation from infant donors younger than 10 months into pediatric recipients is effective under the condition of experienced surgical techniques and perioperative management.

KEYWORDS
en bloc kidney transplantation, infant donors, outcome, pediatric, surgical procedures

1 | INTRODUCTION

Potential pediatric donors are underutilized for kidney transplantation.¹,² Insufficient renal mass, surgical challenge, vascular thrombosis and hyperfiltration injury are the main obstacles.³-⁷ En bloc transplantation of small pediatric kidneys can provide more renal nephrons, while increasing request for surgical techniques. Although notable surgical complications occur when en bloc pediatric kidneys are transplanted into adult recipients,⁸,⁹ the long-term allograft survival and renal function are favorable.¹⁰ There are only a few publications reporting utilization of en bloc pediatric kidneys for pediatric recipients,¹¹-¹³ and en bloc kidney transplantation from infant donors to pediatric recipients is even more rare. With development of the new organ donation and transplant system in China,¹⁴,¹⁵ accumulating pediatric donors has become a remarkable organ source of deceased kidneys. Herein, we report six consecutive cases of en bloc kidney transplantation from infant donors younger than 10 months into pediatric recipients with good outcome, and provide clinical experience and supportive evidence for utilization of small pediatric donor kidneys.

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; AUC, area under the plasma concentration time curve; CIT, cold ischemia time; DGF, delayed graft function; EC-MPS, enteric-coated mycophenolate sodium; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis; HLA MM, human leukocyte antigen mismatch; HPLC, high-performance liquid chromatography; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PD, peritoneal dialysis; PRA, panel reaction antibody; rATG, rabbit anti-human thymocyte immunoglobulin; SCr, serum creatinine; WIT, warm ischemia time.

Hong-yang Wang and Jun Li contributed equally to this work and are co-first authors.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
2 | MATERIALS AND METHODS

2.1 Study design

This is a retrospective study. Kidney transplantation from pediatric donors and for pediatric recipients in the First Affiliated Hospital of Sun Yat-sen University between November 2012 and September 2015 was included. Clinical data of en bloc kidney transplantation from infant donors into children recipients were collected and analyzed. This study was approved by the institutional ethics committee.

2.2 Data collection

The following data of donor characteristics were collected: gender, age, body weight, ABO blood type, graft size, cause of death, terminal SCr level and eGFR at procurement, CIT, and WIT of donor kidneys. The following data of recipient characteristics were collected: gender, age, body weight, ABO blood type, primary disease, dialysis treatment, SCr level and eGFR prior to transplant, PRA, and HLA MM.

Patient and graft survival were summarized. Incidence of DGF, rejection, and other complications was analyzed. Renal allograft function indicated by SCr and eGFR at 1 week, 1 month, 3 months, 6 months, and 12 months after transplantation was evaluated. Graft growth was measured by ultrasound examination at 1 week, 2 weeks, 1 month, 3 months, and 6 months after transplantation. DGF was defined when dialysis was needed within the first week post-transplant.\textsuperscript{16} Estimated GFR was calculated according to the Schwartz formula.\textsuperscript{17} After transplantation, all the patients were followed up weekly within the first month, biweekly within the next 2 months, monthly within the next 9 months, and every 2 or 3 months thereafter. No biopsy was conducted due to no evidence of clinical rejection or allograft dysfunction.

2.3 Surgical procedure of en bloc kidney transplantation

En bloc kidneys were recovered with aorta, vena cava, and bilateral ureters in continuity with bladder. The distal end of aorta and vena cava was closed inferior to renal vessels at the back table. The prepared en bloc allograft was then implanted extraperitoneally into the recipient’s right iliac fossa with a Gibson’s incision. The left and right donor kidney was respectively placed in the superior and inferior position. The proximal end of the donor aorta was preferentially anastomosed to the internal iliac artery in an end-to-end manner with continuous 7-0 polypropylene suture if the vascular caliber matched well (Figure 1A,B). Otherwise, it was anastomosed to the external iliac artery in an end-to-side manner (Figure 1C,D). The proximal end of donor vena cava was anastomosed to the external iliac vein in an end-to-side manner with continuous 7-0 polypropylene suture. When the aorta was anastomosed to external iliac artery, the arterial anastomosis was superior to the venous anastomosis to avoid compression of...
the vein (Figure 1C,D). Papaverine (15 mg) was injected intraluminally to prevent arterial vasospasm just before the arterial anastomosis completed. Grafts were placed in the target position carefully after anastomosis to prevent vessel distortion. Two ureteroneocystostomies were performed separately (Figure 1A,C) by the Lich-Gregoir technique with placement of 3.0 Fr/10 cm pediatric double pigtail ureteral stents (Cook Medical, Bloomington, IN, USA) which were removed transurethrally at 3 months after transplantation. Low molecular heparin (2000 U/d) was used for prophylactic anticoagulation in the first week after transplantation.

2.4 | Immunosuppressive regimen

rATG (1 mg/kg/d for 3 days) was used as induction therapy. Tacrolimus, MMF or EC-MPS, and prednisone were used as maintenance therapy. The trough level of tacrolimus was maintained at 6-8 ng/mL in the first 3 months, and 5-7 ng/mL thereafter. AUC of MPA was examined when renal graft function became stable. MPA concentration was examined by HPLC, and MPA-AUC0-12 hours was maintained at 30-60 mg.h/L to ensure sufficient exposure. Methylprednisolone was intravenously used at the dose of 8 mg/kg/d for 3 days. Orally prednisone was initiated at 30 mg/d, was then tapered by 5 mg/wk, and was maintained at 2.5-5 mg/d.

2.5 | Statistical analysis

Continuous variables with normal distribution were expressed as mean±SD, while continuous variables with non-normal distribution were expressed as median.

3 | RESULTS

3.1 | Demographic characteristics

Donor characteristics were summarized in Table 1. There were three males and three females, with a mean age of 4.4±3.7 months after birth and a mean body weight of 5.9±2.8 kg. Causes of death were hypoxic brain injury (n=1), congenital heart disease (n=3), traumatic brain injury (n=1), and drowning (n=1). Terminal SCr at procurement was 0.81±0.56 mg/dL. The eGFR was 60.36±36.25 mL/min/1.73 m^2. The cold and WIT of donor kidneys were 13.5±3.6 hours and 3.3±1.4 minutes, respectively.

Recipient characteristics were summarized in Table 2. There were three males and three females, with a mean age of 13.2±1.6 years, and a mean body weight of 33.9±3.6 kg. The recipient-to-donor body weight ratio was 6.6±2.5. The primary diseases were nephrotic syndrome (n=1), IgA nephropathy (n=1), ANCA-associated nephritis (n=1),
membranous nephropathy (n=1), and congenital solitary kidney (n=2). Three patients received PD and two HD. The duration of dialysis was 6.8±6.1 months. One patient underwent preemptive transplantation. PRA was negative in all recipients before surgery, and HLA MM number was 2.7±0.8.

3.2 | Transplant outcome

One unilateral kidney of an en bloc graft was removed during transplant surgery due to immediate renal artery thrombosis, while the other kidney survived and functioned well. The median follow-up time was 15.5 months with a range from 6 to 39 months. Patient and graft survival rate were 100% during the follow-up period.

There was no DGF. Graft function of the five remaining en bloc kidney transplant recipients was shown in Figure 2. The SCr decreased from 8.5±0.78 mg/dL before transplantation to 2.5±0.57, 1.2±0.33, 0.9±0.11, 0.7±0.09, and 0.7±0.10 mg/dL at 1 week, 1 month, 3 months, 6 months, and 12 months after transplantation, respectively (Figure 2A). The eGFR increased from 9.4±1.43 mL/min/1.73 m² before transplantation to 33.4±6.80, 67.9±19.10, 92.2±9.89, 110.8±14.17, and 121.4±11.43 mL/min/1.73 m² at 1 week, 1 month, 3 months, 6 months, and 12 months after transplantation, respectively (Figure 2B).

The graft function of the remaining solitary kidney transplant recipient was demonstrated separately. The SCr decreased from 5.6 mg/dL before transplantation to 2.6, 1.8, 1.3, 1.1, and 0.8 mg/dL at 1 week, 1 month, 3 months, 6 months, and 12 months after transplantation, respectively (Figure 2A). The eGFR increased from 13.3 mL/min/1.73 m² before transplantation to 28.6, 41.2, 57.7, 75.3, and 105.1 mL/min/1.73 m² at 1 week, 1 month, 3 months, 6 months, and 12 months after transplantation, respectively (Figure 2B).

3.3 | Growth of pediatric grafts

Renal graft size was routinely measured by ultrasound within the first 6 months after transplantation. The length of the en bloc kidneys was 4.2±0.6 cm at donation and increased to 5.0±0.7, 5.7±0.8, 6.7±0.6, 6.9±0.6, and 7.6±0.6 cm at 1 week, 2 weeks, 1 month, 3 months, and 6 months after transplantation, respectively (Figure 2C). The length of the solitary kidney was 5.5 cm at donation and increased to 6.6, 7.5, 7.8, 9.0, and 9.5 cm at 1 week, 2 weeks, 1 month, 3 months, and 6 months after transplant, respectively (Figure 2C).

3.4 | Complications

Mechanical injury of ureter stent caused urine leakage in one patient at 3 days after transplantation and eventually led to ureteral obstruction. The other ureter in the same patient was obstructed due to ureteral stent falling into bladder. Urine leakage was spontaneously recovered after continuously adequate drainage, and ureteral obstruction was solved by placement of new ureteral stents. There was no evidence of clinical rejection, transplant renal artery stenosis, or proteinuria during the follow-up period.

4 | DISCUSSION

This study presented clinical experience and satisfactory short-term transplant outcome of en bloc kidney transplantation from infant donors younger than 10 months into pediatric recipients, which adds supportive evidence for the utilization of small pediatric donor kidneys to children with ESRD.

Vascular thrombosis is the most common vascular complication in en bloc kidney transplantation from pediatric donors younger than 2 years old, and the reported graft loss rate is 10%-25%. Moreover, a donor age younger than 12 months is generally suggested to be a threshold for higher risk of graft thrombosis. A previous study showed three of four patients who received kidneys from donors younger than 1 year experienced graft thrombosis. In the present study, 11 kidneys from six en bloc grafts (92%, 11/12) were free of thrombosis and no en bloc allograft was lost.

Compared to the reported complicated process of vascular reconstruction, our concise method makes the back table procedure...
more easily completed in a half to one hour, so as to reduce CIT. Zhao et al. placed both graft kidneys on the very right side of the right iliac fossa. In our procedure, the two kidneys were placed straddling the iliac vessels. The left kidney was in the right iliac fossa, while the right kidney was in the space between the bladder and right pelvic wall. This procedure allows more space to place en bloc kidneys with reduced request for the length of anastomosis vessels. Salehipour et al. used proximal end of the aorta and distal end of the vena cava to anastomose to internal (or external) iliac artery and external iliac vein, respectively. However, we had to use the proximal end of the vena cava for the venous anastomosis as the distal end of the aorta and vena cava from infant donors was quite small in the diameter. It is worth mentioning the remaining donor vessels for anastomosis should be short to avoid distortion. Compared to two sets of arterial and venous anastomosis reported by Gaber et al., only one arterial and one venous anastomosis performed in implantation would shorten surgical time and reduce vascular complications. In addition, we suggest arterial anastomosis is superior to venous anastomosis to avoid compression of veins when the donor aorta is anastomosed to external iliac artery. Intra-arterial papaverine could prevent or relieve arterial vasospasm which is a common challenge encountered after reperfusion of small pediatric kidneys. Prophylactic anticoagulation was preceded to prevent thrombosis by continuous utilization of low molecular heparin (2000 U/d) in the first week after transplantation.

There are two theories of renal growth based on different physiological mechanisms: normal growth and compensatory growth, which are also respectively called “programmed growth” and “hyperfiltration-driven growth.” The mismatch in size between the donor and recipient determines the growth mode of pediatric renal grafts. Feltran et al. reported slow and gradual growth (normal growth) of pediatric kidneys when they were transplanted into pediatric recipients with approximate body weight. In this study, a remarkable compensatory growth of pediatric kidneys was observed in the first month after transplantation and it was even significant in the solitary kidney transplantation (Figure 2C), suggesting the potential compensatory function of infant kidneys. Fortunately, proteinuria indicating hyperfiltration injury was not observed during the follow-up period of 6-39 months, and blood pressure control is one of the important management to reduce hyperfiltration injury.

There are no clear criteria according to which small pediatric kidneys are transplanted as single or en bloc. Kayler et al. reported kidneys from pediatric donors weighing <10 kg were more safely transplanted as en bloc. Sureshkumar et al. reported single kidney transplantation from pediatric donors weighing <0 kg was unfavorable considering the similar graft failure risk with kidney transplantation from older donors. Borboroglu et al. believed that pediatric kidneys should be split for two recipients when the length of a kidney is more than 6 cm or the kidney is from a donor weighing more than 14 kg. In this study, all the kidneys from donors weighing <10 kg were transplanted as en bloc with acceptable vascular complications. Interestingly, it is of note the solitary kidney presented immediate graft function and sufficient compensatory effect either in kidney volume or renal function (eGFR) as shown in Figure 2. The donor age was 8 months after birth with a body weight of 8.5 kg, while the recipient age was 13 years with a body weight of 32 kg (Tables 1 and 2). With compensatory renal function and absence of hyperfiltration injury, this case suggests kidneys from pediatric donors weighing <10 kg may also be suitable for single kidney transplantation instead of en bloc kidney transplantation, with the merit of reducing surgical challenge. Further study is encouraged to prove this hypothesis.

This study has some limitations. This is a small cohort with a median follow-up period of 15.5 months. A large group of en bloc kidney transplantations from infant donors into pediatric recipients is needed to determine the transplant outcome, especially in the long-term period. Renal graft size was measured by ultrasound examination, which might affect accurate evaluation of graft growth.

In conclusion, our data suggest that en bloc kidney transplantation from infant donors younger than 10 months into pediatric recipients is effective under the condition of experienced surgical techniques and perioperative management. Further follow-up is necessary to observe the long-term outcome.

ACKNOWLEDGMENT

This study was supported by the Guangdong Provincial Key Laboratory on Organ Donation and Transplant Immunology (2013A 061401007).

AUTHORS’ CONTRIBUTIONS

Hong-yang Wang and Jun Li: Designed the research, and participated in analyzing the data and writing the manuscript; Long-shan Liu: Participated in data analysis and revision of the manuscript; Rong-hai Deng and Huan-xi Zhang: Participated in data collection and literature research; Qian Fu and Su-xiong Deng: Participated in data collection and the patients’ follow-up; Dicken Shiu-Chung Ko: Participated in writing and revision of the manuscript; Chang-xi Wang: Designed the research, wrote, and reviewed the manuscript.

REFERENCES

1. Pelletier SJ, Guidinger MK, Merion RM, et al. Recovery and utilization of deceased donor kidneys from small pediatric donors. Am J Transplant. 2006;6:1646–1652.
2. Kayler LK, Magliocca J, Fujita S, et al. Recovery factors affecting utilization of small pediatric donor kidneys. Am J Transplant. 2009;9:210–216.
3. Bresnahan BA, Mcbride MA, Cherikh WS, Hariharan S. Risk factors for renal allograft survival from pediatric cadaver donors: an analysis of United Network for Organ Sharing data. Transplantation. 2001;72:256–261.
4. Hayes JM, Steinmuller DR, Streem SB, Novick AC. The development of proteinuria and focal-segmental glomerulosclerosis in recipients of pediatric donor kidneys. Transplantation. 1991;52:813–817.
5. Thomschus O, Tittelbach-Helmrich D, Meyer S, Drognitz O, Pisarski P. Twenty-year graft survival and graft function analysis by a matched pair study between pediatric en bloc kidney and deceased adult donors grafts. Transplantation. 2009;88:920–925.
6. Sanchez-Fructuoso AI, Prats D, Perez-Contin MJ, et al. Increasing the donor pool using en bloc pediatric kidneys for transplant. Transplantation. 2003;76:1180–1184.

7. Satterthwaite R, Aswad S, Sunga V, et al. Outcome of en bloc and single kidney transplantation from very young cadaveric donors. Transplantation. 1997;63:1405–1410.

8. Bretan PJ, Fries C, Goldstein RB, et al. Immunologic and patient selection strategies for successful utilization of less than 15 kg pediatric donor kidneys—long term experiences with 40 transplants. Transplantation. 1997;63:233–237.

9. Marques M, Prats D, Sanchez-Fructuoso A, et al. Incidence of renal artery stenosis in pediatric en bloc and adult single kidney transplants. Transplantation. 2001;71:164–166.

10. Sureshkumar KK, Reddy CS, Nghiem DD, Sandroni SE, Carpenter BJ. Superiority of pediatric en bloc renal allografts over living donor kidneys: a long-term functional study. Transplantation. 2006;82:348–353.

11. Butani L, Troppmann C, Perez RV. Outcomes of children receiving en bloc renal transplants from small pediatric donors. Pediatr Transplant. 2013;17:55–58.

12. Lau KK, Berg GM, Schjoneman YG, Perez RV, Butani L. Pediatric en bloc kidney transplantation into pediatric recipients. Pediatr Transplant. 2010;14:100–104.

13. Afanetti M, Niaudet P, Niel O, Saint FM, Cochat P, Berard E. Pediatric en bloc kidney transplantation into pediatric recipients: the French experience. Pediatr Transplant. 2012;16:183–186.

14. Huang J, Millis JM, Mao Y, Millis MA, Sang X, Zhong S. A pilot programme of organ donation after cardiac death in China. Lancet. 2012;379:862–865.

15. Huang J, Mao Y, Millis JM. Government policy and organ transplantation in China. Lancet. 2008;372:1937–1938.

16. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant. 2011;11:2279–2296.

17. Schwartz GJ, Gauthier B. A simple estimate of glomerular filtration rate in adolescent boys. J Pediatr. 1985;106:522–526.

18. Zhao WY, Zhang L, Zhu YH, et al. En bloc kidneys transplanted from infant donors less than 5 kg into pediatric recipients. Transplantation. 2014;97:555–558.

19. Kayler LK, Magliocca J, Kim RD, Howard R, Schold JD. Single kidney transplantation from young pediatric donors in the United States. Am J Transplant. 2009;9:2745–2751.

20. Strey C, Grotz W, Mutz C, et al. Graft survival and graft function of pediatric en bloc kidneys in paraaortal position. Transplantation. 2002;73:1095–1099.

21. Veroux P, Giuffrida G, Cappellani A, et al. Two-as-one monolateral dual kidney transplantation. Urology. 2011;77:227–230.

22. Nghiem DD. Simultaneous double adult kidney transplantation using single arterial and venous anastomoses. Urology. 2006;67:1076–1078.

23. Salehipour M, Bahador A, Nikgehablian S, et al. En-bloc transplantation: an eligible technique for unilateral dual kidney transplantation. Int J Organ Transplant Med. 2012;3:111–114.

24. Gaber AO, Shokouh-Amiri H, Nezakatgoo N, et al. Ipsilateral placement in double-kidney transplantation. Transplantation. 2007;84:929–931.

25. Silber S, Malvin RL. Compensatory and obligatory renal growth in rats. Am J Physiol. 1974;226:242–246.

26. Malt RA. Compensatory growth of the kidney. N Engl J Med. 1969;280:1446–1459.

27. Feltran LS, Nogueira PC, Silva FA, Ajzen SA, Pacheco-Silva A. A one year prospective comparison of kidney growth and function in children recipients of grafts from children and adults. Transplantation. 2010;90:777–781.

28. Sureshkumar KK, Patel AA, Arora S, Marcus RJ. When is it reasonable to split pediatric en bloc kidneys for transplantation into two adults? Transplant Proc. 2010;42:3521–3523.

29. Borboroglu PG, Foster CR, Philosophe B, et al. Solitary renal allografts from pediatric cadaver donors less than 2 years of age transplanted into adult recipients. Transplantation. 2004;77:698–702.

How to cite this article: Wang H-y, Li J, Liu L-s, et al. En bloc kidney transplantation from infant donors younger than 10 months into pediatric recipients. Pediatr Transplant. 2017;21:e12845. https://doi.org/10.1111/petr.12845