Outcome and complications of living donor pediatric renal transplantation: Experience from a tertiary care center

Priyank Bijalwan, Kalavampara V. Sanjeevan*, Anil Mathew[1], T. Balagopal Nair

Departments of Urology and [1]Nephrology, Amrita Institute of Medical Sciences, Kochi, Kerala, India
*E-mail: drsanjeevan@hotmail.com

ABSTRACT

Introduction: We retrospectively reviewed the patient characteristics, outcome, and complications of renal transplantation in pediatric age group performed at our center and compared the results with various centers in India and other developed countries.
Materials and Methods: Patients younger than eighteen years of age who underwent renal transplantation from 2003 to 2014 at our institute were reviewed. Demographic data of the transplant recipients and donors, etiology of ESRD, mode of dialysis, surgical details of renal transplantation, immunosuppression, medical and surgical complications, and post-transplant follow-up were assessed. Graft survival was determined at 1, 3 and 5 years post-transplant. All data collected were entered into Microsoft excel program and analyzed using SPSS 20. Kaplan–Meier method was applied to determine the graft survival at 1, 3, and 5 years. The log-rank test was applied to test the statistical significance of the difference in survival between groups.
Results: Thirty-two children underwent transplantation comprising of 18 females and 14 males. The mean age was 14.5 years (range 10–17 years). The primary cause of renal failure was glomerular diseases in 53% (17/32) of patients. Seventeen postsurgical complications were noted in our series. Two grafts were lost over a follow-up of 5 years. The 1, 3, and 5 year graft survival rates were 96.7%, 92.9%, and 85%, respectively. There was no mortality.
Conclusion: The etiology of ESRD in our region is different from that of developed countries. The mean age at which children undergo renal transplantation is higher. Graft survival at our center is comparable to that of developed nations. Renal transplantation can be safely performed in children with ESRD.

INTRODUCTION

Renal transplantation is the logical and physiological option that can be offered to children suffering from advanced chronic kidney disease (CKD) requiring renal replacement therapy (RRT). Beside providing superior quality of life, it is more economical in the long term compared with other forms of RRT such as continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis, and maintenance hemodialysis, which are especially difficult in children.[1] Successful kidney transplantations in children improve the quality of life evidenced by the disappearance of fatigue, anorexia, itching, and improvement in growth.[2,3] Pediatric renal transplantation is performed at many centers in India but there is a paucity of data on their outcome and complications.[4] We conducted a retrospective study to evaluate the outcome of pediatric renal transplantation at a tertiary center in South India and compared the results with other centers in India and other developed countries.

MATERIALS AND METHODS

Inpatient and outpatient case files of all consecutive patients younger than 18 years of age, who underwent live-related renal transplantation from 2003 to 2014 at our institute were reviewed. The variables analyzed were the etiology of CKD, relationship to donors, kidney retrieval approach, donor renal vessel anatomy, surgical complications, immunosuppression regimens, rejection episodes, and graft survival at 1, 3, and 5 years. Human leukocyte antigen (HLA) typing (for HLA-A, HLA-B, HLA-DR) and B-lymphocyte crossmatch were performed as part of the pretransplant assessment. Donor nephrectomies were performed laparoscopically on the left side and by open or retroperitoneoscopic method on the right. All recipient surgeries were performed in the pelvis on the right side, extraperitoneally through a modified Gibson's oblique lower quadrant abdominal incision. Venous anastomosis was always performed with the renal to external or common iliac vein in an end-to-side manner. Arterial anastomosis was by renal to internal iliac end-to-end or to common/external iliac end-to-side method or a combination of both depending on the anatomy of the recipient and donor vasculature. The modified Lich-Gregoir technique was used for ureteroneocystostomy over a double J ureteral stent in all cases. The ureteral stent was removed usually on the seventh postoperative day in the absence of any complication.

Definition of complications

Urinary leak was defined as persistent drain output after the seventh postoperative day with drain fluid creatinine higher than the serum levels. *Persistent lymphorrhea* was defined as drain output more than 100 mL/day after the seventh postoperative day with the drain fluid creatinine levels close to the serum levels. *Delayed graft function* was defined as the need for dialysis in the 1st week of transplantation.[5] *Chronic graft dysfuncton* was defined as persistently raised serum creatinine to 2 mg/dL or more for more than 3 months.[6] *Graft loss* was defined as the need for nephrectomy, persistent rise of serum creatinine to 5 mg/dL or more, or patient death with a functioning graft.[6] *Graft rejection* was diagnosed based on clinical suspicion aided with graft Doppler study and confirmed with graft biopsy. *Calcineurin inhibitor toxicity* was excluded in all patients suspected to have graft rejection by serum level estimation and biopsy.

Immunosuppression protocol

Cyclosporine A was started 2 days before transplantation at a dose of 6 mg/kg/day and withheld after the surgery until serum creatinine dropped to 1.5 mg/dL or less in the postoperative period. Mycophenolate mofetil (MMF) was started at 600 mg/m^2/day, 1 day before transplantation, changing over to azathioprine at a dose of 2 mg/kg/day after the initial 3 months in patients who could not afford MMF. Immunosuppression protocol comprised of induction therapy with Basiliximab/antithymoglobulin (ATG) in selected cases followed by triple maintenance therapy with prednisolone, MMF, and cyclosporine A. Parenteral methylprednisolone was given at a dose of 10 mg/kg/day during surgery, just before releasing the vascular clamps, followed by 0.5 mg/kg/day from the 1st day after transplantation. Cyclosporine A was substituted with tacrolimus in patients with uncontrolled pretransplant hypertension, female recipients, and in cases of acute rejection. All acute rejection cases received methylprednisolone 12 mg/kg for 3 days. Steroid-resistant acute cellular rejections were treated with ATG at a dose of 1.5 mg/kg. Antibody-mediated rejections (AMR) were treated with plasmapheresis followed by intravenous immunoglobulin to a total cumulative dose of 800 mg/kg given over 6 days. Rituximab was used for AMR patients not responding to conventional methods of treatment.

Follow-up protocol

Patients were followed up twice a week for the 1st month, once a week for the next 2 months, once a fortnight for the following 3 months, once in a month for the subsequent 6 months, and then once in 2 months thereafter.

Statistical analysis

All data collected were entered into Microsoft excel worksheet and analyzed using SPSS software version 20 (SPSS for Windows, version 20.0; IBM Corp., New York, USA). Kaplan–Meier method was applied to determine graft survival at 1, 3 and 5 years.

RESULTS

Thirty-two children underwent transplantation in the study period. The mean age of recipients was 14.5 years (range 10–17 years). The primary cause of renal failure was glomerular in 53% cases [Table 1]. All 32 transplants had ABO compatible recipients and donors. B-lymphocyte crossmatch was negative for all patients except one, who had marginally positive crossmatch. HLA typing was done for all patients. The mean weight for our patient population was 35 kg (range 17–63, median 34.5). Two patients weighed <20 kg, smallest recipient weighed 17 kg. 44% of patients were underweight (BMI <10th percentile for age).[7] Parents were the donors for 30 patients. Only three open donor nephrectomies were done, one for right kidney and two nephrectomies were converted to open due to intraoperative difficulties (early cases of laparoscopic donor nephrectomies) [Table 2]. Single donor artery was anastomosed to the internal iliac artery in 21 patients and to common or external iliac in others. In six patients with double renal arteries, anastomosis of the accessory artery was performed to external iliac artery; in the two patients with three arteries, two arteries were anastomosed to external iliac and one to the internal iliac artery. Venous anastomosis was performed to external iliac vein in

Table 1: Etiology of chronic kidney disease	
Cause of CKD	**Total**
Glomerular (*n*=17)	
Focal segmental glomerulosclerosis	8
Membranoproliferative glomerulonephritis	4
Systemic lupus erythematosus	2
IgA nephropathy	3
Tubulointerstitial (*n*=12)	
VUR	5
MCDK	1
Juvenile nephronophthisis	1
PUV	1
Chronic interstitial nephritis	4
Unknown (*n*=3)	3

VUR=Vesicoureteral reflux, MCDK=Multicystic dysplastic kidney, PUV=Posterior urethral valve, CKD=Chronic kidney disease

Table 2: Patient characteristics	
Patient characteristic	**% (*n*=32)**
Sex (%)	
Male	56.25
Female	43.75
HLA mismatch (%)	
3 out of 6	63
2 out of 6	31
1 out of 6	6
BMI distribution (%)	
<10th percentile (underweight)	44
10–85th percentile (normal)	44
>85th percentile	12
Donor relationship (%)	
Mother	81.25
Father	12.5
Grandmother	6.25
Donor nephrectomy (%)	
Laparoscopic	84
Open	16
Graft artery (%)	
Single	75
Double	18.75
Triple	6.25
Mode of dialysis (%)	
Hemodialysis	90.6
Peritoneal	6.25
Preemptive	3.12
Graft biopsy (10 in 8 patients)	
Antibody-mediated rejection	2 (at 3 months)
Acute cellular rejection	2 (at 3 and 16 months)
Acute tubular necrosis	2
Calcineurin toxicity	2

HLA=Human leukocyte antigen, BMI=Body mass index

30 patients and to common iliac vein in two patients. No difficulty in closure of the extraperitoneal incision was encountered in any patient.

Two patients underwent a pretransplant intervention. One patient underwent bilateral nephrectomies for uncontrolled hypertension. The other patient, who had posterior urethral valves fulgurated transurethrally at 5 months of life, underwent left-sided nephroureterectomy for Grade 5 vesicoureteral reflux (VUR) with recurrent urinary tract infections (UTI). Lower urinary tract evaluation for this patient was however normal.

Pretransplant nephrectomy was not done in any other patient of VUR ending in renal failure in the absence of UTI.

Surgical complications were encountered in 21.8% (7/32) of patients [Table 3]. Two patients (6%) developed perirenal hematoma in the immediate postoperative period, both of which were managed conservatively. One patient with lymphorrhea required a single instillation of sclerosant (povidone iodine 0.1%). None of the patients had urine leak or surgical site infection. UTI, including asymptomatic bacteriuria, occurred in five patients in the early postoperative period, which was treated with culture-specific antibiotics. A total of ten graft biopsies were performed in eight patients for graft dysfunction. Details of the graft biopsy results are shown in Table 2. One patient was diagnosed to have developed pelviureteral junction (PUJ) obstruction in the graft kidney one year after transplantation when the recipient presented with worsening of renal function. This was managed successfully by pyeloureterostomy of the graft renal pelvis to the native ureter.

Delayed complications included one ureterovesical junction obstruction eight years after transplantation. It was managed successfully by initial percutaneous nephrostomy of the graft kidney followed by balloon dilatation and antegrade ureteral stenting. All patients at one year and more than 90% of the patients at three years were compliant with immunosuppressive therapy. Immunosuppression-related complications were seen in 12 patients. Major complications included fungal endophthalmitis for which evisceration was done and osteopenia with compression fracture of vertebra in two patients. Steroid-induced hypertension was seen in two cases, which was managed with antihypertensive drugs.

Overall, there were two graft losses including one patient with AMR who failed to respond to treatment. He was dialysis dependent within three months after transplantation. This patient had marginally positive B-lymphocyte crossmatch (10%–15%) with the donor. There was no mortality in our study group. Details of all postoperative complications are shown in Table 3.

The 1, 3, and 5 year graft survival rates were 96.7%, 92.9%, and 85% respectively in our series [Figure 1]. The graft survival was comparable in laparoscopic versus open donor nephrectomy (*P* = 0.309) and single versus multiple renal arteries in the donor kidney (*P* = 0.450).

DISCUSSION

We analyzed the complications and long-term outcome of pediatric transplantation at our center and compared the patient characteristics and graft survival with developed countries. The mean age of our patient population was

Table 3: Postoperative complications

Complication	n
Surgical complications	
Perirenal hematoma/bleeding	2
Persistent lymphorrhea	3
Graft PUJ obstruction	1
Graft VUJ obstruction	1
Delayed graft function	3
Postoperative UTI (including asymptomatic bacteriuria)	5
Graft loss	
Antibody-mediated rejection	2
Chronic allograft nephropathy (at 5 years)	
Immunosuppression related	
Steroid-induced cataract	2
Osteopenia/fracture	2
Fungal endophthalmitis with meningitis	1
Adenoviral keratoconjunctivitis	1
Steroid-induced hypertension	2
Cytomegalovirus colitis	1
Lower respiratory tract infection	3

PUJ=Pelviureteral junction, UTI=Urinary tract infection, VUJ=Vesicoureteral junction
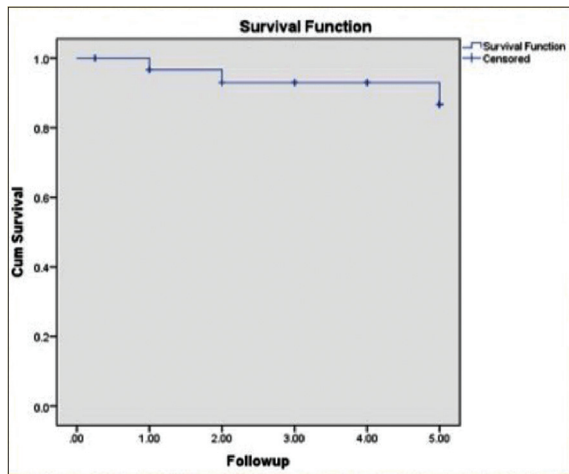

Figure 1: Kaplan–Meier graft survival curve

14.5 years (range 10–17) with 59% patients aged more than 15 years of age. Other centers from India have comparable mean recipient age in their studies.[4,8] Emiroglu *et al*. had similar age distribution of the recipient population (14.9 ± 2.2 years).[9] Data from North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2010 annual report show 52.8% of recipients at or below 12 years of age at the time of transplant.[10] It is thus clear that transplantation is performed in comparatively older children (range 10–17 years) in our region. Small-sized recipients, i.e., age <10 years and weight <20 kg are considered as high-risk category for renal transplantation considering the technical challenges experienced due to the small sizes of vascular structures.[8] We had only two recipients with weight <20 kg and no recipient <10 years of age.

About 56% of transplant recipient were female in our study that is in distinct contrast to the 18% female recipients seen by Srivastava *et al*.[4] NAPRTCS 2010 report shows 40.8% female transplant recipients in the pediatric age group.[10] This may reflect the social bias toward female sex prevalent in certain parts of our country. The annual report of the NAPRTCS in 2010 shows 25% of their recipients had renal aplasia or hypoplasia, 20% had obstructive uropathy, and 25% had glomerular diseases as cause for CKD. The major etiology for CKD in our group of patients was glomerular disease (53%), and no recipient had renal aplasia or hypoplasia.

The majority of our recipients were on hemodialysis at the time of transplantation. Peritoneal dialysis is underutilized at our center with only two patients on CAPD at the time of transplantation. Sathe *et al*. reported similar trend of RRT with only three out of 17 patients being on CAPD.[8] Preemptive transplantation was performed in one patient. Srivastava *et al*. reported 5% rate of preemptive transplantation in their series.[4] This is much less as compared to 24.4% preemptive transplantation in the NAPRTCS registry.[10] This can be attributed to lack of awareness or access and support for our patient population for CAPD and lesser availability of cadaver kidneys in our country. Mother was the donor in 81% of all cases. Data from other centers also show mother to be the donor in most cases.[8,10]

In our series, the arterial anastomosis was done with internal iliac artery that is in contrast to Srivastava *et al*. where the majority of arterial anastomoses were to the external iliac artery and Rabih *et al*. where arterial anastomosis was with common iliac artery.[4,11] The difference in surgical technique can be attributed to surgeon preference and recipient anatomy. Unlike many other centers following intraperitoneal approach in pediatric recipients, we uniformly performed extraperitoneal graft placement at our center which avoids the risk of gastrointestinal complications seen otherwise.[12] The higher mean age of the children made this approach feasible, which might not have been feasible in smaller children.

Seven surgical complications were noted in our series. There was no case of postoperative hematoma or bleeding requiring re-exploration as seen by Srivastava *et al*. and Emiroglu *et al*.[4,9] We had no case of renal arterial or venous thrombosis in our series. Sathe *et al*. had reported one case each of renal vein thrombosis and one renal artery thrombosis in their series of twenty patients; both grafts were salvaged on re-exploration. Srivastava *et al*. report no case of vascular thrombosis in their study.[4,8]

We had 16% rate of postoperative UTI which is much less compared to 40% reported by Sathe *et al*. in their patients.[8] Acute rejection was seen in four (12.5%) of our patients, one patient with AMR had graft loss. Srivastava *et al*. reported 20% (14/70) rate of early rejection, all of these

patients recovered well. Sathe *et al.* repored 15% rate of acute rejection.[4,8]

We had no case of symptomatic VUR in graft kidney. Engelesbe *et al.* in their series of 147 children reported the incidence of VUR requiring surgical correction in 4.8%.[13] Srivastava *et al.* found VUR in five patients during evaluation for recurrent UTI, and all were managed conservatively.[4] One patient presenting with worsening renal function was found to have developed PUJ obstruction in the graft kidney for which pyeloureterostomy to the native ureter was done. Review of donor DTPA scan and computed tomography urogram showed no such finding. No such observation was made in other studies.

There were two (6%) graft loss over a follow-up period of 5 years with no mortality. Srivastava *et al.* report four patient losses, primarily due to pulmonary complications. Compliance with immunosuppressive therapy was not a major issue in our study as seen by other groups in India and abroad.[4] This can be attributed to the socioeconomic status of patients visiting our center and the parental counseling offered to them.

The NAPRTCS registry data show 1- and 5-year graft survival rates of 95.5% and 85.7% (1995–2010) in living donor pediatric renal transplantations. Our 1-, 3-, and 5-year graft survival rate was 96%, 92.9%, and 85%, respectively. Srivastava *et al.* had 1-, 3-, and 5-year graft survival rate of 94.3%, 89.2%, and 66.8%, respectively. Rosati *et al.* have shown graft survivals of 88%, 84%, and 76% at 1-, 3-, and 5-year posttransplantation, respectively.[14] We found no difference in the graft survival between the donor kidneys with single or multiple arteries, which was similar to that reported in the literature.[15] The overall survival in our patient cohort was 100% at 5 years. Srivastava *et al.* had overall survival of 94% at the end of 5 years. Sathe *et al.* report 100% patient survival in their study.

CONCLUSION

The spectrum of etiology of CKD in developing nations differs from that of developed countries. The mean age at which children undergo renal transplantation is higher in this region. Renal transplantation can be safely performed in children with CKD, is relatively free of major complications and is associated with favorable outcome. Kidney retrieval method and as well as the presence of multiple vessels do not necessarily affect graft survival adversely.

REFERENCES

1. Furth SL, Gerson AC, Neu AM, Fivush BA. The impact of dialysis and transplantation on children. Adv Ren Replace Ther 2001;8:206-13.
2. McDonald RA, Watkins SL. Progress in renal transplantation for children. Adv Ren Replace Ther 1996;3:60-8.
3. Haberal M, Arda IS, Karakayali H, Emiroglu R, Bilgin N, Aslan G, *et al*. Renal transplantation in children. Transplant Proc 2000;32:520-1.
4. Srivastava A, Prabhakaran S, Sureka SK, Kapoor R, Kumar A, Sharma RK, *et al*. The challenges and outcomes of living donor kidney transplantation in pediatric and adolescent age group in a developing country: A critical analysis from a single center of North India. Indian J Urol 2015;31:33-7.
5. Rodrigo E, Ruiz JC, Piñera C, Fernández-Fresnedo G, Escallada R, Palomar R, *et al*. Creatinine reduction ratio on post-transplant day two as criterion in defining delayed graft function. Am J Transplant 2004;4:1163-9.
6. Gulati S, Kumar A, Sharma RK, Gupta A, Bhandari M, Kumar A, *et al*. Outcome of pediatric renal transplants in a developing country. Pediatr Nephrol 2004;19:96-100.
7. Khadilkar VV, Khadilkar AV. Revised Indian Academy of Pediatrics 2015 growth charts for height, weight and body mass index for 5-18-year-old Indian children. Indian J Endocr Metab 2015;19:470-6
8. Sathe KP, Joshi SS, Mehta KP. Pediatric renal transplantation: 5 years experience from Jaslok Hospital, Mumbai. Indian J Transplant 2014;8:3-7.
9. Emiroglu R, Moray G, Sevmis S, Sözen MH, Bilgin N, Haberal M. Long-term results of pediatric renal transplantation at one center in Turkey. Transplant Proc 2005;37:675-8.
10. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS): 2010 Annual Report. Available from: http://www.naprtcs.org. [Last accessed on 2015 Jan 15].
11. El Atat R, Derouiche A, Guellouz S, Gargah T, Lakhoua R, Chebil M. Surgical complications in pediatric and adolescent renal transplantation. Saudi J Kidney Dis Transpl 2010;21:251-7.
12. Tanabe K, Takahashi K, Kawaguchi H, Ito K, Yamazaki Y, Toma H. Surgical complications of pediatric kidney transplantation: A single center experience with the extraperitoneal technique. J Urol 1998;160(3 Pt 2):1212-5.
13. Englesbe MJ, Lynch RJ, Heidt DG, Thomas SE, Brooks M, Dubay DA, *et al*. Early urologic complications after pediatric renal transplant: A single-center experience. Transplantation 2008;86:1560-4.
14. Rosati P, Pinto V, Delucchi A, Salas P, Cano F, Zambrano P, *et al*. Paediatric Renal Transplantation: 13 Years of Experience-Report from the Chilean co-operative multicenter group. Transplan Proc 2005;37:1569-73.
15. Hsu TH, Su Li, Ratner LE, Trock BJ, Kavoussi LR. Impact of renal artery multiplicity on outcomes of renal donors and recipients in laparoscopic donor nephrectomy. Urology 2003;61:323-7.