Research Article

J Ped. Nephrology 2017;5(1)
http://journals.sbmu.ac.ir/jpn

Profile of Pediatric Kidney Transplantation at a Tertiary Care Centre in Southern India

How to Cite This Article: Ganesh K, Sreedharan S, Paul Z, Mathew A, Kurian G, Nair R. Profile of Pediatric Kidney Transplantation at a Tertiary Care Centre in Southern India. J Ped. Nephrology 2017;5(1)

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Introduction: Renal transplantation offers the best chance of survival to children with End Stage Renal Disease (ESRD). Patient survival and growth are superior in children with a renal allograft compared to dialysis. The aim of the study was to evaluate the outcomes of pediatric transplants done at a tertiary care hospital in Kochi, India over the study period.

Materials and Methods: In this retrospective study, the data of children who underwent renal transplantation at Amrita Institute of Medical Sciences from 2002 to 2016 Kochi were analyzed.

Results: Thirty-four children underwent renal transplantation over a 14-year period. Thirty-three underwent live related transplant whereas one underwent deceased donor transplantation. The mean age and weight of the recipients at transplantation was 14.3 years and 35.7 kg, respectively. Fourteen children were boys and twenty were girls. Thirty-one patients underwent hemodialysis prior to transplant, 2 were taken up preemptively, and 1 patient was on continuous ambulatory peritoneal dialysis. There were 5 documented urinary tract infections. No surgical complications were noted in the immediate post-transplant period. There were 5 episodes of acute rejection (14.7%). Two cases experienced Delayed Graft Function and the patient survival rate was 100%.

Conclusions: Renal transplantation is a viable option to manage children with ESRD with satisfactory long term results and can be done in a developing nation's set-up.

Keywords: Kidney transplantation; India; Child.
Running Title: Pediatric kidney transplantation in Southern India

Received: Dec-2016
Revised: Dec-2016
Accepted: Dec-2016

Introduction

The incidence of end-stage renal disease in children varies worldwide. Some studies have indicated a rise in pediatric renal diseases [1]. There are reports showing the prevalence varying from 14.8 cases per million children in the United States to 4 cases per million children in Japan [2]. The prevalence of end stage renal disease (ESRD) in the pediatric population is 55 per million children [3]. In the absence of a national registry, the exact incidence and burden of chronic kidney disease in India is unknown. However, a single center from India has reported an incidence of 8-10% for chronic kidney disease in the outpatient department [4].

As in adults, renal transplantation offers the best chance of survival to children with ESRD compared to other forms of renal replacement therapy. The pediatric transplant program significantly lags behind the adult program worldwide, but is now being increasingly adopted by various centers as a viable option. Patient

survival and growth are superior in children with a renal allograft as opposed to those who remain on dialysis [5]. The quality of life is much better after renal transplantation. Therefore, renal transplantation is the preferred renal replacement therapy for children with end-stage renal disease (ESRD). Few Indian centers have undertaken pediatric renal transplantation [6-8].

The aim of the study was to evaluate the profile of the outcomes of pediatric transplants done at Amrita Institute of Medical Sciences, Kochi, Kerala, South India.

Materials and Methods

We retrospectively analyzed the data obtained from our transplant database for kidney transplant recipients who were below 18 years at the time of transplantation from 2002 to 2015 at Amrita Institute of Medical Sciences, Kochi. The data of donor characteristics, recipient's age, weight at transplantation, primary renal disease, mode and duration of prior dialysis therapy, surgical technique of transplantation, immunosuppression protocol, pre-operative, intra-operative, and post-operative medical and surgical complications, and the eventual outcome(s) were assessed.

Results

Thirty-four pediatric patients underwent renal transplantation over a 14-year period. Thirty-three underwent live related transplant whereas one underwent deceased donor transplantation. All had negative cross matches. Nineteen patients had an HLA match of 3/6, and 15 had an HLA match of more than 3/6 with three of them having a 6/6 HLA match. There were 5 cases of HLA-DR match, two of whom had documented rejections. The mean age and weight of the recipients at transplantation was 14.3 years and 35.7 kg, respectively. Demographic characteristics are shown in Table 1.

Thirty-one patients underwent hemodialysis prior to transplant, 2 were taken up prior to initiation of dialysis, and 1 patient was on continuous ambulatory peritoneal dialysis. Vascular access included venous catheters (69%) and AV fistulas (31%). The native kidney disease profile in our recipients was heterogeneous, including chronic glomerulonephritis (CGN), reflux nephropathy (RN), congenital anomalies of the kidney and urinary tract (CAKUT), IgA nephropathy, focal segmental glomerulosclerosis (FSGS), and pauci-immune glomerulonephritis (Table 2).

Table1. Demographic characteristics of the study group

Recipients	
Males: Females	11:19
Mean age	14.3 years
Blood group distribution	A+: 14, A-:1, O+:13, B+:5, AB+:1
Age distribution	<12yrs: 5, 12-15 yrs: 18, >15yrs: 11
Donors	
Males: Females	7:27
Mean Age	31.8 years
Donor to recipient relation	
Mother	25 (73.5%)
Father	6 (17.5%)
Grandmother	2 (6%)
Deceased donor	1 (3%)

Table 2. Spectrum of native kidney disease

Native kidney Disease	Numbers
Chronic Glomerulonephritis	10 (29.5%)
Unknown	9 (26.5%)
Reflux Nephropathy	5 (15%)
CAKUT	3 (9%)
Henoch Schonlein Purpura Nephritis	2(5.5%)
Focal Segmental Glomerulosclerosis	2(5.5%)
Pauci-immune glomerulonephritis	1(3%)
Chronic Interstitial Nephritis	1(3%)
Mesangioproliferative Glomerulonephritis	1(3%)

Pre-operative urological intervention was done in three patients who all underwent bilateral nephrectomy, with the indication of uncontrolled hypertension in two and persisting urinary sepsis in one patient. None of our patients required bladder augmentation prior to surgery. There was no difficulty in bed preparation during the surgery in any of our patients and an extra peritoneal surgical approach was practiced in all cases. All grafts were placed in the right iliac fossa. Ureteral anastomosis was performed using the modified Lich Gregor technique. All patients had a ureteric stent in situ. Arterial anastomosis was done using the internal iliac artery in 18 patients, external iliac artery in 12 patients, both arteries in 3, and

the common iliac in 1 patient. In seven cases, arterial anastomosis was done in an end-to-side fashion. There were four cases with 2 renal arteries, in whom the upper pole arteries were anastomosed end-to-end and the lower pole was anastomosed end-to-side. The remaining 23 cases had a single renal artery and were anastomosed in an end-to-end fashion. Venous anastomosis was done end-to-side with the external iliac vein in 80.6% of the cases and end-to-side with the common iliac vein in the rest. Post-operative Doppler indices were normal in 32 cases. In the remaining 2 patients, a hematoma was detected, one needed surgical evacuation on the 15th post - operative day due to graft compression. The other hematoma resolved spontaneously. Both patients had a good graft function 1 year after the transplant.

The mean BMI was 17.3 kg/m^2. Before transplant, eighteen patients (60%) had stunted growth and 10 patients (33%) had height between the 5th and 20th percentile. Weight was checked at 1 year and 5 years post-transplant to assess weight gain. The results showed that 55% of the children had weight for age below the 5th percentile prior to transplant. At the end of 1 year, only 22% had stunted growth, and the rest showed catch-up growth.

There were five documented urinary tract infections: 1 occurred in the first 2 weeks' post-transplant, one in the first 4 months, and three UTIs were seen more than 1 year after the transplant. The time profile of infections in the study group is given in Table 3.

Table3. Time profile of post- transplant infections in the study group

Duration post-transplant	Infection
< 2 weeks	UTI: Ecoli
2 weeks to 4 months	CMV disease UTI-Pseudomonas
4 months to 1 year	Pneumonia Acute gastroenteritis
More than 1 year	Pneumonia Acute gastroenteritis UTI (3): Ecoli

Fourteen patients underwent protocol biopsy immediately after anastomosis, of whom 9 showed acute tubular injury and the remaining 5 were normal. There were 5 episodes of acute rejection (14.7%), of whom 3 were live related recipients and two were deceased donor recipients. The rejection profile is presented in Table 4. There were 2 cases of Delayed Graft Function. One-year patient and graft survival was 100% and 96% respectively and 3-year patient and graft survival was also 100% and 96%, respectively.

Table 4. Time profile of rejection and treatment response

Type	Donor	Cross Match	Induction	Maintenance Immunosuppression	Duration post transplant
ACR	Live related	Negative	No	CsA/ MMF/ Pred	40 days
ACR	Live Related	Negative	No	CsA/ Aza/ Pred	13 days
ACR	Deceased	10-12%	Yes	Tac/ MMF/ Pred	45 days
ACR + AMR	Deceased	10-12%	Yes	Tac/ MMF/ Pred	36 days
ACR	Live Related	Negative	Yes	CsA/ Aza/ Pred	20 days

CsA: Cyclosporin A; MMF: Mycophenolate Mofetil; Pred: Prednisolone; Aza: Azathioprine; Tac: Tacrolimus

According to institutional protocols at the time, 11 patients (32.3%) underwent induction therapy with IL-2 blockers and 23 (67.7%) patients were transplanted without induction. In the induction group, 3 patients (27%) had rejection, 3 had infection (27%), and none had graft loss. In the non-induction group, 2 patients had rejection (8.6%), 5 had infection (21.7%), and one had graft loss (4.3%). These differences were not clinically significant (p=0.3).

Eleven patients (32.3%) had a Tacrolimus based immunosuppression regimen and 23 (67.7%) patients were transplanted with a Cyclosporin A based regimen. The incidence of acute rejection, infection, and graft loss was similar (p= 0.5).

Eleven patients (32.3%) had an Azathioprine based immunosuppression regimen and 23 (67.7%) patients were transplanted with a Mycophenolate Mofetil based regimen. The incidence of acute rejection, infection, and graft loss was similar in both groups (p= 0.5).

Regarding the comparison of the rejection rate, infection episodes, and graft loss between Groups I, II and II described above, Group I (CsA/MMF/Pred) had an incidence of 9%, 18%, and 0%, Group II (CsA/Aza/Pred) had an incidence of 18%, 27%, and 9%, and Group III (Tac/MMF/Pred) had an incidence of 8.3%, 16%, and 0%, respectively. There were no clinically significant differences (p= 0.7, 0.8, and 0.3, respectively).

Discussion

Renal transplantation is a viable treatment option in children with end stage renal disease. In the United States, approximately 800 renal transplants are performed in children below 18 years of age every year [9,10]. Indian pediatric patients are increasingly being taken up for renal transplantation at various centers [7,8,11]. Results have been encouraging with good 1- and 5-year graft survival.

Girls comprised the majority (64%) of our transplant recipients. In the North American Pediatric Renal Trials and Collaborate Studies (NAPRTCS) registry, more male children (approximately 60%) received kidney transplants, due to the higher number of males with congenital anomalies of the kidney and urinary tract (CAKUT) [9]. Other Indian studies have showed a male preponderance with 17.5% [7] and 36.1% [8] of the sample populations being girls.

There was a higher ratio of chronic glomerulonephritis, biopsy proven or presumed (33%), in our study. Only 10% of the patients had CAKUT. Other Indian studies have also shown the predominance of renal parenchymal disease over congenital anomalies: [7,8]. This is in contrast to the NAPRTCS data, where CAKUT formed the majority of causes of ESRD [9]. A final conclusion as to Asian etiology of pediatric ESRD is perhaps premature at this point, limited by a low sample size, lack of a national registry, and a higher mean age of the study sample, but is worth bearing in mind. Only two out of 34 (5.8%) patients underwent preemptive transplantation. Other Indian studies have reported preemptive rates of 14% [7] and 5% [8]. In the NAPRTCS registry [9], the rate of preemptive transplant in children is 24%. It is unclear whether preemptive transplantation is associated with better long-term outcomes as compared with transplantation while undergoing dialysis. In a study conducted in the United States Renal Data System (USRDS), preemptive transplantation was associated with a reduced risk of graft failure and death [12]. In both our patients who underwent pre-emptive transplantation (ages 14 and 15 years), 1-year graft function was serum creatinine 1.3mg/dl and 1.4mg/dl, respectively. One of the children's 5-year graft survival was serum creatinine 1.3mg/dl and neither had rejection.

Rejections were observed in the first three months following transplant. Four of these children were successfully treated and their renal function normalized after treatment. Three out of the five had normal renal functions five years after transplant. One patient had severe rejection and developed graft failure despite intensive treatment. He was a deceased donor recipient while the others were live related recipients. In children, the rate of acute rejection has decreased over the past 30 years [10]. Previous studies, notably the one conducted in CMC Vellore [11], have showed a higher rate of rejection than our population (46.7%). A similar scenario was seen in another study [13], in which incidence of acute rejection was 37% in their study population aged below 12 years. Both these studies used triple immunosuppression with Cyclosporin A, Azathioprine, and steroids. Our immunosuppression protocol was also the use of three immunosuppressants with nearly equal number of patients in three groups:

Group 1 (n=11): Cyclosporin A (6mg/kg/day), Mycophenolate Mofetil (600mg/m^2/dose), Prednisolone (0.5mg/kg)

Group 2 (n=11): Cyclosporin A, Azathioprine (2mg/kg/day), Prednisolone; and

Group 3 (n=12): Tacrolimus (0.1mg/kg/day), Mycophenolate Mofetil and Prednisolone.

Out of 5 rejection episodes, one was in Group 1, two were in Group 2, and two in Group 3. Overall graft function follow up post-transplant was equal in all three groups. The NAPRTS data on rejections [14] analyzed a larger sample size (3004) to find a total of 3453 rejection episodes. Examined by age, (0-1 vs. 2-5 vs. 6-12 vs. >=13), annual rejection frequency, time to first rejection, and mean number of rejections were not elevated in the younger patients. However, for the initial rejection episode, recipients below six years of age had a poorer outcome from the rejection episode with increased risk of graft failure. The effect of age on the rejection outcome was only seen in the first rejection episode and was not observed in the subsequent rejection episodes [14].

Post-transplant infections now exceed acute rejection as a reason for hospitalization [15]. Based on the NAPRTCS data, hospitalization

within the first 24 months following transplantation is more frequently caused by post-transplant infections as compared to acute rejection [15]. Previous studies have shown that although urinary tract infections are common after transplant, especially in patients with a urologic etiology of ESRD, they do not appear to affect graft function [16,17]. UTI has been seen in up to 32% of patients after transplantation in these studies [17]. In one study, the median time after transplantation for post-transplant UTI was 18 months [17]. The most common organisms were Klebsiella pneumonia (30%) and Escherichia coli (25%). Graft function did not correlate with a history of pre- or post-transplant UTI [17]. The distribution of UTI in our study varied and is shown in Table 3.

Conclusions

Pediatric renal transplantation is a viable option in children with ESRD. Better overall results were seen in live related donor recipients. Chronic glomerulonephritis was the most common cause of ESRD and most of them were girls. Preemptive transplantation was done in 2 patients, and 90% received hemodialysis. Rejection was observed in the first 3 months after transplantation. UTIs were the most common infection in the post-transplant period. Renal transplantation is the most optimal way to manage children with ESRD with satisfactory long-term results and can be done in a developing nation set-up.

Acknowledgement

We were supported by Departments of Urology, Anesthesia, and Pathology in Amrita Institute of Medical Sciences, Kochi, Kerala.

Conflict of Interest

None declared

Financial Support

None declared

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