Original Article

Outcome of Paediatric Kidney Transplant : An Experience From Lahore

Iftikhar Ijaz, Asif Manzoor Basra and Humayun Iqbal Khan

Objective: To analyze demography, clinical profile, complications & outcome of children after kidney transplant.
Methods: Eleven patients (6 boys & 5 girls) who underwent kidney transplant from September 2008 till September 2013 were included in the study. Retrospective analysis of their record was done.
Results: A significant improvement in growth parameters, hemoglobin level, cardiac function, blood pressure and bone diseases was noted after kidney transplant
Conclusions: Kidney transplant is treatment of choice for patients having irreversible kidney disease progressing toward end stage kidney disease. It is a superior modality offering not only excretory function but also metabolic, endocrine, erythropoitic and acid base and mineral homeostasis.
Keywords: Kidney transplant, Mineral homeostasis.

Introduction

In the setting of chronic kidney disease when GFR declines to < 15 ml/min/1.73m there emerges the definite need for renal replacement therapy, either in any form of dialysis or in the form of renal transplantation.[1] Various modifications of dialysis are in use since more than 3 decades ago but renal transplantation is the modality of choice in patients with End Stage Renal Disease (ESRD) as it offers better quality of life and lower risk of mortality; this risk being 4 times less than with dialysis. The dialysis provides only excretory function and some degree of fluid and electrolytes regulatory function, while the transplanted kidney provides additional physiological functions as well, these being metabolic, endocrine, immunoregulatory and cytokine homeostasis.[2,3]

Attempts at kidney transplant had been going on since beginning of the twentieth century. First remarkable success was kidney transplant between identical twins in 1954 in Boston. This ingenious approach bypassed the risk of immune incompatibility and reinforced the need to address this problem in the majority, that is, non-identical or non-related donors. There was a significant increase in graft survival with Azathioprine and prednisolone. Later improvements were cross match between donor lymphocytes and recipient serum and HLA matching. Finally, introduction of cyclosporine in the late 1970s led to dramatic improvements in graft survival. Though renal transplant is ultimate treatment in ESRD, yet it is far from reality for the majority of population in Pakistan, where 1/3rd population lives in poverty (<1 U$/day) with very low literacy rates along with other social and cultural problems. Health care budget is also negligible (only 0.7%)[4] Pakistan has population of 190 Millions and children comprise 38% of the total Population. Also limited availability of quality care and lack of expertise in Government centers is major barrier; very few patients who can afford high cost of kidney transplant avail this opportunity in private hospitals, while, majority remains deprived.

Reported worldwide CKD incidence has been as low as 4 per million children in Japan to as high as 14.8 per million population in United stated of America. Reported incidence of ESRD in children from western world is 1.53 children per million per year[5] CKD prevalence is probably quite high in Pakistan, owing to poor health facilities , undetected urinary tract infections and higher prevalence of inherited disorders due to frequent cousin marriages in Pakistan. Reported incidence of ESRD from Pakistan is 3.435 pmcp. Around 75%85% of children with ESRD do not go for RRT because of high cost and lack of access to available facility.[6]

Trained pediatric nephrologists in Pakistan are very few. Over the last one decade International Pediatric Nephrology Association (IPNA) has taken a unique initiative of training people from developing countries; so far three pediatric nephrologists from Pakistan have been trained by IPNA program. In Pakistan still there is no provision for Deceased kidney Transplant and only available source is living

Here we are describing results of our kidney transplant in Lahore, regarding demography, clinical profile and outcome in terms of patient and graft survival, complications including graft failure, infections, cardiovascular morbidity, bone mineral disease/growth and other parameters of Transplant recipient before and after Transplant.

Methods

We performed this retrospective review of medical records of eleven post transplant patients who underwent kidney transplant from September, 2008 till September, 2014 at Surgimed Hospital, Lahore and Lahore General Hospital. A written consent was taken from their parents and study was approved by local ethical committee. All patients were evaluated by same Pediatric Nephrologist before Transplant and also after transplant, for the total period of follow up. After review of medical record, information which was recorded on pre-designed proforma included growth parameters, duration of CKD, aetiological cause, BP, laboratory findings and duration of dialysis, transplant work up including tissue typing, cross match and panel reacting antibody testing was noted. Post transplant parameter were recorded which included growth parameters, Blood pressure, Hb, phosphate levels, iPTH, echocardiography findings. Donor was first degree relative in all patients.. Treatment protocols were same with small modifications for each patient. Both patients with posterior urethral valves had undergone surgical correction in infancy.

Pre-operative immunosuppression was started one day before transplant; Prednisolone 2mg/ kg as single morning dose was given, Mycophenolate mofetil was given in dose of 600mg/m^2 per dose twice a day and Tacrolimus 0.1 mg/Kg was given 6-12 hours before Transplant (max 10 mg).On day of operation Methylprednisolone 10mg/Kg (max 500mg) infused at time of induction. IV Cephazolin was also given before operation, 250 mg for body weight of <10 Kg, 500mg for 10- 30 Kg weight and 1 gm for >30 kg.

Post operatively IV methyl prednisolone was given in dose of 2mg /Kg on day 1, was shifted to oral prednisolone 2mg/Kg on day2, reduced to 1.5mg/Kg on D3- D4, then 1.2 mg /kg on D5 and D6 with further reduction to 1mg/Kg on day D7 . From 1st till 4th week , dose was reduced by 2.5 mg weekly to minimum of 0.3 mg/KG/day or minimum of 5 mg for weight <30 Kg and to dose of 2.5 5 mg weekly to a dose of 0.3mg/Kg /day for weight of >30 kg. from W5- w8 dose was reduced by 1 mg weekly, from w9- w12 by 1mg weekly till total dose of 0.2mg/kg/day or at least 5 mg daily for weight of >30Kg. From 6 months ->1 year for pre-pubertal , for those on Tac protocol and if no rejection after six months change to alternate day regimen at 0.2mg/Kg/EOD. For post pubertal PNL dose was kept at 5 mg OM (once in the morning) After 2 years in post pubertal dose was switched to 0.2mg/Kg/EOD or 10 mg EOD maximum if no rejection and stable renal function.[7]

Mycophenolate mofetil (MMF) was administerd to all patients with dose of 300mg/$m^{2/}$dose every 12 hrs (8 - 12 mgKg/dose) 12 hourly, max dose 500mg 12 hourly either one hour before or 2 hours after meals. This dose was reduced to 150 mg/$m^{2/}$ dose 12 hourly after 6 months. Dose adjustment is required for renal impairment, dose would be omitted if absolute neutrophil count <1.5× 10^{6}/L.

Tacrolimus was only started , 12 hours after surgery when creatinine would drop <150µmol/L, in dose of 0.15mg/Kg/ dose 12 H aiming at whole blood trough level of 10- 15ng/ml from 0- 1 month, and 8 10 ng/ml from 1 to 6 months post operatively and 5-8 ng/ml after 6 months. Ranitidine was given to all patients 3mg/Kg at bed time.

Oral Valganciclovir was given as prophylaxis for 3 months when donor was negative but recipient was positive or both were positive but 6 months when donor was positive and recipient was negative. Co-trimaxazole oral in dose of 3 mg/Kg /dose on alternate day was given for 3 months from day 4 on ward. IV cephazolin was started 1 day before Transplant and given till removal of Foley's catheter. Oral nystatin at dose of 250,000 units every 8 hourly for one month was given.

CMV immune-surveillance with PCR monitoring was done twice a month for one month, then monthly for 6 months and 3 monthly for one year. Data recorded and analyzed pre and post operatively and on each follow up visit included BP, body weight, height, number of symptomatic culture proven urinary tract infections, number and time point of rejection episodes if any , patient and graft survival, calcium, phosphorus and iPTH level, Hb level and left ventricular function and use of growth hormone. One patient received pre-emptive Transplant at GFR of 16 ml/min/1.73 $m^{2.}$ while all others received Hemodialysis for mean period of 6.5 months. Acute rejection was defined as decreased urine output, high B P, pyuria or worsening or new proteinuria and rise in serum creatinine and stoppage of urine flow within first 3 days after

Transplant. Chronic rejection will be diagnosed by gradual and asymptomatic slow rise in serum creatinine statistical analysis: Parameters before and after Transplant were compared by paired T test. A p value of less then 0.05 was considered significant.

Results

In our study there were 6 males and 5 females, mean age at time of transplantation was 112.36 month (SD ±16.65), range 84 132 month. Mean follow up period was 28.636 m (SD±19.663), range 5 months 70 months. All patients received Transplant from living- related donors. Nine patients were on HD (mean 6.5 months), two patients received pre-emptive transplant. Regarding diagnosis Primary diagnosis was obstructive uropathy due to posterior uretheral valves associated with vesicoureteral reflux in 2 boys, while 2 siblings having diagnosis of Familial hypercalciuric hypomagnesemic nephrocalcinosis, (FHHNC) , one each with Focal Segmental Glomerulosclerosis (FSGS), Systemic Lupus Erythematoses (SLE), recurrent UTI,s, renal hypoplasia/dysplasia and in three patients cause was not known. There was significant improvement in growth parameters after Transplant, Mean weight before Transplant was 25 ±5.752 (range 20-37), after Transplant mean weight was 41.0±8.19 (range 24- 29) with p value of 0.00001 95% CI (-22.0200 10.161), Mean height before Transplant 126 ± 6.55 (115-133) after transplant 144±7.0(134-156) with p value 0.000195%CI (-22.8±15.18). Echocardiography of all patients was performed by pediatric cardiologist, there was mild to moderate hypertrophy with left ventricular dysfunction in 8 patients and severe dysfunction in one. On serial echocardiography after transplant left ventricular function improved in all 8 but ejection fraction (EF) remained low in one with severe dysfunction, requiring anti cardiac failure treatment. Systolic BP before transplant 125±11.18 (110-150), while after transplant mean systolic BP remained 113±1.94 (110-115) p value of 0.004, mean diastolic BP before transplant was 86±8.60 (70-95). Mean diastolic BP after transplant was 72±9.1 (60-95) with p value of 0.003. Mean Hb before transplant was 8.30 g/dl±1.40(range 5.5-10), after transplant mean Hb was 11.2±1.4(range 9.5-14) with p value of 0.01, Intact parathormone (iPTH) before transplant was 475±175.7 (range200-900) mean iPTH after transplant was 55.27±49.75(15-200) with p value of 0.0002 . All patients had high phosphate levels before transplant with mean of 6.30±1.13 (range 4-7.5), this level dropped to 4.27±0.36 (range3.5-4.5) with p value of 0.0001 after transplant. Two patients received growth hormone therapy after transplant, in one patient attained peek height velocity > 12cm/year leading to height progress from 133 cm before GH to 148 cm 17 months later, and advancement of SMR by

Table-1: Demography of subjects.

Patient	Gender	Aetiology leading to ESRD	Age at the at the time of presentation	Follow up Period
1	M	Obstructive uropathy / VUR	120 months	46 months
2	M	Obstructive uropathy / VUR	125 m	42 m
3	M	FHHNC	132 m	70 m
4	M	FSGS	98 m	29 m
5	F	SLE	120 m	36 m
6	F	Idiopathic	96 m	31 m
7	F	FHHNC	132 m	26
8	F	Idiopathic	96 m	10 m
9	M	Idiopathic	84 m	8 m
10	108m	Renal hypoplasia/dysplasia	125 m	12 m
11	108m	Recurrent urinary tract infections	108 m	5 m
			Mean Age= 112.36m (SD + 16.65)	Mean Age= 112.36m (SD + 16.65)

** FHHNC = Familial Hypomagnesaemia with Hypercalciuria and Nephrocalcinosis*
** FSGS = Focal Segmental Glomerulosclerosis / * SLE = Systemic Lupus Erythematosus*

Table-2: Comparison before and after transplant.

	Before TX	Range	After Tx	Range	P-value
Weight (kg)	25±5.752	20-37	41.00±8.19	24-29	0.00001
Hight (cm)	126±6.55	115-133	144±7.00	134-156	0.0001
Systolic BP (mmHg)	125±11.18	110-150	113±1.94	110-115	0.004
Dystolic BP (mmHg)	86±8.60	70-95	72± 9.15	60-95	0.003
HB (g/dl)	8.30±1.40	5.5-10	11.2±1.400	9.5-14	0.001
IPTH (ng/l)	475±175.7	200-900	55.27± 49.75	15-200	0.002
Phosphate (mg/dl)	6.30± 1.13	4-7.5	55.27± 49.75	3.5-4.5	0.0001

Complications we experienced after transplant were graft loss in one due to renal artery thrombosis (RAT) on 6th post op day, which later underwent transplant nephrectomy. Second patient, case of posterior urethral valves with bilateral VUR had recurrent urinary tract infections that require ureteric re-implantation as well as oral tamsulosin.

Discussion

Pakistan is sixth most populous country; population has increased tremendousley over last 5 decades from 46,673,627 in 1961 to 179, 160,111 in 2012 with population density of 225, having male 51.36% and female 48.63%. Under 18 pediatric population makes considerable proportion.

Medical facilities never grew to match this population explosion, this situation is further compounded by the fact that country is still struggling with economic turmoil as well as infectious disease. So scarce facilities and development is seen in areas like Pediatric Nephrology and definitive therapy like kidney transplant is still a dream for majority.

Although Results of kidney transplant have improved over last few decades owing to better immunosuppressive protocols using CNIs (Cyclosporine and Tacrolimus) and antiproliferative medications like azathioprine or MMF.[8] Reported results by NAPRTCS 2010 as 96.5, 91.5 and 84.3% for living donor recipient and 95.1, 84.1 and 78% for deceased donor recipient.[9]

Factors other than effective immunosuppression also contribute to Outcome of kidney Transplant which includes age of donor and recipient, prolonged cold ischemia time, presence of preformed anti- HLA antibodies, episodes of acute rejection, ethnicity, infections, adherence to medications and bladder function are important determinants.

According to North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) report children who received Transplant kidney under the age of 12 years and with obstructive uropathy performed less well than those who got transplanted after 12 years of age.[10]

LVH is found in 47% of patients with CKD at start of diaysis and 75% of patients of on HD for 10 years [(11)]. Left ventricular hypertrophy and low ejection fraction are major determinant of cardiovascular morbidity and mortality in patients with ESRD.[12,13]

Regression of left ventricular hypertrophy and improvement in ejection fraction along with control of hypertention after kidney transplant has been documented in various studies.[14,15]

Anemia is an important and independent risk factor for LVH, HF and cardiovascular morbidity and mortality.[16]

Growth hormone has clearly shown benefit in post transplanted, growth retarded patients, provided the other amenable factors including anemia, nutrition, metabolic acidosis, fluid & electrolyte abnormalities and renal osteodystrophy has been addressed properly. Maximum benefit is obtained when started pre-pubertal [(17)]. Studies have also shown that risk of acute rejection or graft dysfunction does not increase with treatment of growth hormone.[18]

Conclusion

Kidney transplant is an ideal modality for children with ESRD, need to be offered to patients to with ESRD. Risk of complications is very small but benefit in terms of better quality of life, better growth and psychological well being is huge. After transplant children can attend school and live normal active life.

Department of Paediatric Medicine
Lahore General Hospital, Lahore

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Medical Guidelines