Original Article

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

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ABSTRACT

Introduction: Renal transplantation is the treatment of choice for children with end-stage renal disease (ESRD). We evaluated the outcome of renal transplantation in the pediatric and adolescent age groups in the perspective of a developing country as compared with developed nations while highlighting the challenges we have faced in a pediatric transplant programme.

Materials and Methods: Seventy live related pediatric and adolescent renal transplantations were reviewed retrospectively. Variables analyzed were etiology of ESRD, pre-transplant renal replacement modality, donor relationship, surgical complications, rejection episodes, immuno-suppression regimens, compliance to immunosuppression, graft survival and overall survival.

Results: The cohort consisted of 13 (18%) female and 57 male (82%) recipients. The mean age was 14 ± 1.4 years. The etiology of ESRD was chronic glomerulonephritis (n = 43), chronic interstitial nephritis (n = 26) and Alport's syndrome (n = 1). Fifty-six (80%) children were on hemo-dialysis and 10 (14%) on peritoneal dialysis prior to transplantation. 80.5% and 61% patients were strictly compliant to immunosuppresant medications at 1 and 5 years. The 1, 3 and 5 year graft survival rates were 94.3%, 89.2% and 66.8%, respectively. The overall survival rates were 95.7%, 96.4% and 94.1% for 1, 3 and 5 years, respectively.

Conclusions: The spectrum of etiology of ESRD differs in our patients from the west, with chronic glomerulonephritis being the most common etiology. Early graft survival is comparable, but the 5-year graft survival is clearly inferior as compared with developed countries.

Key words: Challenges, kidney transplantation, pediatric

INTRODUCTION

Renal transplantation (Tx) is considered the treatment of choice for children with end-stage renal disease (ESRD). Well-being often improves dramatically after a successful transplantation in a child who suffers from ESRD. The disappearance of fatigue, poor appetite, itching and improvement in growth after successful kidney transplantation also has a great impact on the standard of living.[1,2] The time saved from dialysis after kidney transplantation is several thousands of hours per year.[3]

Although pediatric renal transplantations are being performed at quite a few centers in developing countries, there is a paucity of data on their long-term outcome. We believe that the pediatric transplant programme in our country is associated with many limitations and challenges

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Access this article online

Quick Response Code:

Website: www.indianjurol.com

DOI: 10.4103/0970-1591.145290

affecting the long-term outcome. This retrospective study is an attempt to evaluate the outcome of pediatric renal transplantation at a tertiary center from a developing country and to highlight the differences in comparison with developed nations.

MATERIALS AND METHODS

After obtaining institutional review board approval, a retrospective analysis was performed on 70 pediatric patients (up to 18 years of age) who underwent live related renal transplant from 1995 to 2011. The variables analyzed were etiology of ESRD in these patients, relationship to donors, kidney retrieval procedure, donor renal vascular anomalies, surgical complications, rejection episodes, immunosuppression regimens, compliance to immunosuppression, graft survival and overall survival (at 1, 3 and 5 years). Prospective donors with diabetes mellitus and global GFR <60 mL were excluded from donation. Both laparoscopic as well as open donor nephrectomies were performed. We used a standard open surgical technique with right para-rectal incision with an extraperitoneal approach for renal transplant. Arterial anastomosis was either with the common iliac or the external iliac artery in an end-to-side manner or to the internal iliac in an end-to-end manner depending on the recipient and donor vascular anatomy. Venous anastomosis was always performed with the external iliac vein in an end-to-side manner. The modified Lich Gregoir technique was used for ureterovesical anastomosis (UVA) in all cases. All UVA were stented. The double J (DJ) stent was removed usually on the 12-14th post-operative day.

Persistent urinary leak was defined as more than 100 mL drain output after the seventh post-operative day with drain fluid creatinine of more than 10-times of the serum value. Persistent lymphorrhea was defined as drain output more than 100 mL/day after the seventh post-operative day and drain fluid was not consistent with urine. Delayed graft function was defined as the need for dialysis in the first week of transplant.[4] Chronic graft dysfunction was defined as a persistently raised serum creatinine of 2 mg/dL or more for more than 3 months.[5] Graft loss was considered as the need for nephrectomy, a persistent rise of serum creatinine to 5 mg/dL or more or patient death with a functioning graft.[5]

The immunosuppressant regimen changed between the periods spanning 1995-2004 and 2005-2011. Cyclosporine was primarily prescribed till 2004. There was a gradual shift from the use of cyclosporine to tacrolimus (TAC) by 2004. In 39 patients, cyclosporin A (CsA) 8 mg/kg and azathioprine (AZT) 2.5 mg/kg/day were started 2 days prior to transplant. The remainder of the 31 patients received tacrolimus and mycophenolate mofetil (MMF) instead of CsA and AZT. All patients received 50 mg dexamethasone on the day of the transplant. CsA was used in doses of 8-10 mg/kg to maintain trough levels of 150-250 ng/mL in the first 3 months post-transplant. AZT was reduced to 1.5 mg/kg/day from the day of transplant. Prednisolone was started from the first post-transplant day at a dose of 1 mg/kg/day and gradually tapered to 0.5 mg/kg/day by the end of 3 months. The CsA was slowly tapered by 3 months, until target CsA levels of 75-100 ng/mL were maintained, and thereafter continued at the same dose. TAC and MMF were started at a dose of 0.2 mg/kg/day and 600 mg/m^2/dose, respectively. TAC was tapered slowly to reach a target trough level of 10-12 ng/mL by 3 months.

Rejection episodes were diagnosed based on clinical suspicion, elevation of serum creatinine above 30% of the nadir value, graft Doppler study and biopsy. CsA and TAC levels were estimated to exclude CNI toxicity as a cause of graft dysfunction. Acute cellular rejections were treated with methylprednisolone 600 mg/m^2 daily for 3 days. Steroid-resistant rejections were treated with Rabbit anti-thymocyte globulin (Genzyme) at a dose of 1.5 mg/kg for 7-10 days depending on the response. Acute humoral rejections were treated with plasmapheresis and post-plasmapheresis intravenous immunoglobulin 400 mg/kg daily for 5-7 days depending on the response.

Patients were followed-up bi-weekly for the first 6 months, bimonthly for the next 2 years and three monthly thereafter. All follow-up visits as well as readmissions were noted.

Statistical analysis

Descriptive statistics were used to analyze the demographic data and surgical variables. The Kaplan–Meir curve was used to analyze graft survival and patient survival time. The log rank test was used to compare survival curves between groups. All statistical analyses were performed using SPSS 16.

RESULTS

There were 57 (82%) male and 13 (18%) female patients. The mean age of the cohort was 14 ± 1.4 years. The underlying causes of ESRD were chronic glomerulonephritis (CGN) (n = 43), tubulointerstitial nephritis (TIN) (n = 26) and Alport's syndrome (n = 1) [Table 1]. Fifty-six (80%) children were on hemodialysis and 10 (14%) on peritoneal dialysis prior to transplantation. Pre-emptive transplant was performed in four patients. The mean follow-up period was 66 ± 4.2 months.

All patients received grafts from their first-degree relatives. Parents comprised 95% of the donors, with mothers being the donor in 80% of the cases and fathers being the donor in 15%. The remainder of the donors were siblings, with brother and sister constituting 2.5% each. The gender ratio of the donors was 2.5:1 (F: M). The median age of the donor

was 40 years (range 18-52 years). Laparoscopic kidney retrieval was performed in 38 (54.3%) donors.

Sixty-one (87%) patients had single, eight had double and one donor kidney had three renal arteries. In recipients with single donor artery, arterial anastomosis was fashioned to the internal iliac arteries in 11, external iliac arteries in 28 and common iliac arteries in 22. In eight patients with double renal arteries, anastomosis was performed by the pantaloon method with common iliac or separately with iliac arteries or iliac and inferior epigastric artery. All patients in this cohort had a single renal vein and venous anastomosis was performed with the external iliac vein in an E–S manner.

Difficulty in closure of the extraperitoneal incision was encountered in three patients. All these patients were below 13 years of age and had stunted growth for their age due to their primary disease. Closure was performed by giving release incision over the external oblique aponeurosis and leaving the incised internal oblique muscle un-approximated. None had incisional hernia on follow-up.

Post-surgical complications (immediate and delayed) are enumerated in Table 2. Three patients had peri-renal hematoma/bleeding in the immediate post-operative period that required immediate re-exploration. There was bleeding from a tear on the inferior epigastric vessels in two patients and bleeding from arterial anastomosis in one patient. They were managed accordingly with ligation of the vessel or additional suturing at the bleeding site of the arterial anastomosis. Persistent lymphorrhea was noted in one patient and managed by a single dose of sclerosant instillation (povidone iodine 0.1%). Persistent urinary leak was noted in one patient, which subsided on conservative management within 2 weeks with DJ stent and per-urethral catheter drainage. Uretero-vesical junction (UVJ) obstruction was found in three patients, and all of them were managed initially by percutaneous nephrostomy of the transplanted kidney followed by balloon dilatation and antegrade DJ stenting. The stent was kept for 3 months in these patients. Two patients were successfully managed with the above approach. One patient who failed required ureteroneocystostomy. On follow-up, he had chronic allograft nephropathy and became dialysis dependent by 36 months post-transplant. Peri-graft collections were managed by percutaneous drainage. Patients with delayed graft function were managed successfully with maintenance hemodialysis as indicated until the graft function improved. Five patients were evaluated for recurrent urinary tract infection (UTI) and all of them had VUR in the graft kidney (grade 2 reflux in three patients and grade 3 reflux in two patients). They were managed successfully with antibiotic prophylaxis. Renal artery stenosis was detected in one patient, managed by balloon angioplasty with successful outcome. One patient developed single 8 mm stone in the inferior calyx of the transplanted kidney. Retrograde intra-renal surgery was performed with complete clearance of the stone.

Table 1: Cause-wise distribution of ESRD

Glomerular diseases	(*n*=43)
FSGS	14
MPGN	5
Undetermined	24
Tubulointerstitial diseases	(*n*=26)
Posterior urethral valve	6
Vesico-ureteric reflux	6
Neurogenic bladder	6
Undetermined	8
Alports syndrome	(*n*=1)

ESRD = End-stage renal disease, FSGS = Focal segmental glomerulosclerosis, MPGN = Membranoproliferative glomerulonephritis

Table 2: Post-operative complications: Immediate and delayed

Perirenal hematoma/bleeding	3
Persistent lymphorrhea	1
Persistent urinary leak	1
Delayed graft function	1
Uretero-vesical junction obstruction	2
Vesico-ureteric reflux	5
Transplant renal artery anastamosis	1
Transplant kidney urolithiasis	1

A total of 30 biopsies were performed for suspected rejection in 26 patients till end of follow-up. A total of 14 acute rejection episodes were observed in the first 6 months of the transplant. The late acute rejections between 6 months and 1 year of transplantation were observed in six patients. All 14 acute rejections that occurred in the first 6 months recovered completely after treatment. Of the six late acute rejections, four reversed completely and two had partial recovery. The remaining 10 biopsies, which was performed after 1 year of transplantation, showed evidences of chronic allograft nephropathy (n = 6, 8.5%) and CNI toxicity (n = 4, 5.7%).

Four patients expired in our series. Three patients died in the perioperative period due to respiratory complications. The fourth patient died of pneumocystis carini pneumonia 6 years following the transplantation. There were four graft losses in the first month of transplant. Of these, three were due to perioperative deaths and one patient underwent graft nephrectomy due to acute vascular rejection with cortical necrosis.

Compliance to immunosuppressant at 1- and 5-year post-transplantation was assessed with respect to compliant and poorly compliant or non-compliant (who missed more than one dose in a week) to immunosuppressive therapy.

We found that 80.5% of the patients were strictly compliant whereas 19.5% patients were poorly compliant at 1 year post-transplant. At 5 years post-transplantation, only 61% of the patients were found to be strictly compliant to immunosuppressant. Financial constraint was found to be the most important reason for poor compliance.

The 1, 3 and 5 year graft survival rates were 94.3%, 89.2% and 66.8%, respectively [Figure 1]. The graft survival was comparable in laparoscopic versus open donor nephrectomy (P = 0.62) and single versus multiple renal arteries in the donor kidney (P = 0.67). The overall patient survival was 95.7%, 96.4% and 94.1% for 1, 3 and 5 years, respectively.

DISCUSSION

Kidney transplantation, although the treatment of choice for children with ESRD, is still infrequently performed in developing countries. This study analyzes the long-term outcome of pediatric transplantation at a tertiary care center in a developing country considering the limitations and challenges we have faced.

According to the North American Paediatric Renal Transplant Co-operative Study (NAPRTCS) 2010 annual report, 52.8% of recipients were at or below 12 years of age.[6] The mean age of our cohort was 14 ± 1.4 years. Another report from a developing country by Emiroglu *et al*. had a similar mean age of the recipient population (14.9 ± 2.2 years).[7] It is thus clear that transplantation is performed in comparatively older children (range 8-12 years) in our set up. This difference may be attributed predominantly to the lack of a cadaveric donor programme and to the limited neonatal and pediatric care in a developing country.

The annual report of the NAPRTCS in 2010 also states that 40.8% of pediatric transplant recipients were female.[6] In our series, female recipients constituted only 18%. This may reflect the social bias and attitude toward female children prevalent in our country, especially in northern India. Five percent of the transplants were pre-emptive in our series as compared with 24.4% in the NAPRTCS registry.[6] This is probably due to inadequate medical facilities, financial constraints and lack of awareness among our population. It is also worth mentioning here that all patients in this series received living donor renal transplantation compared with the NAPRTCS registry data, which showed 49.2% cadaveric renal transplantations.[6]

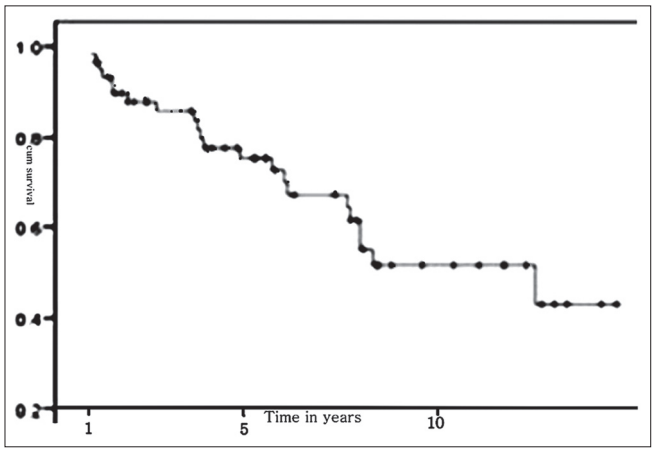

Figure 1: Graft survival curve

All transplant recipients received grafts from first-degree relatives, and the gender ratio of donors was 2.5:1 female to male. Parents were donors in 95%, with the mother being a donor in 80% of cases. This finding was in concordance with the NAPRTCS registry data, which showed parents as donors in 79.2% cases, with mothers comprising majority of the parent donors.[6] The mean age of the donors in our study was 40 ± 3.5 years, comparable to 37.6 ± 7.5 years as mentioned by Mehrabi *et al*.[8]

In a series by Rabih *et al*., the authors used the common iliac artery for anastamosis in 50 cases and the internal iliac artery in two cases.[9] In our series, majority of arterial anastamoses were to the external iliac arteries (n = 3128 in case of single vessel and three cases of multiple vessels). The common iliac artery was used in 25 recipients (22 single vessel and three multiple vessel donors), whereas internal Iliac arterial anastomosis was used in 16 cases (11 single vessel and five multiple vessel donors). These variations are likely to be attributed to the age differences in patient's cohort as well as institutional experience and surgeon preferences.

In our cohort, 15 post-surgical complications (immediate and delayed) were noted in 13 patients [Table 2]. Emiroglu *et al*. in their series of 73 patients had reported the incidence of perirenal hematoma that required early post-operative re-exploration in two patients (2.7%).[7] Both patients were explored surgically and bleeding at the venous anastomosis site was detected. We had a similar immediate exploration in three patients. The other early surgical complications in the aforementioned series[7] were lymphocele (four cases, 5.5%) and urinary leakage (one case, 1.4%), which resolved spontaneously in all five cases. We had an incidence of persistent lymphorrhea and urine leak in one patient each that was managed conservatively. In our cohort, delayed graft function was seen only in one patient who had three arteries in the donor kidney.

Engelesbe *et al*. in their series of 147 children reported the incidence of VUR requiring surgical correction to be 4.8%.[10] We have found VUR in five patients during evaluation for recurrent UTI, and all were managed conservatively. The incidence of transplant renal artery stenosis in our study was 1.4% (n = 1) as compared with 0.6-3.7% in different series on pediatric renal transplantations.[9,11,12]

The NAPRTCS registry data shows 1- and 5-year graft survival rates of 95.5% and 85.7% (1995-2010) in living donor renal transplantations.[6] The 1- and 5-year graft survival rates noted in our cohort were 94.3% and 66.8%, respectively. Even though the 1-year graft survival was comparable, the long-term (5 years) graft survival is clearly inferior. It is possible that this difference is due to non-compliance with immunosuppressants necessitated by financial constraints in our study population. A study by Rosati *et al*. from Thailand, with a similar economic profile as our patients, has also shown graft survivals at 1, 3 and 5 years post-transplantation of 88%, 84% and 76%, respectively, for living donor renal transplantation.[12] They have also cited non-compliance to immunosuppressants as the primary reason for allograft failure.

Greco *et al*. have reviewed various methods of live donor nephrectomies by systematically analyzing 57 comparative studies available in the literature. There was no difference in functional graft outcome between open and laparoscopic donor nephrectomies.[13] Likewise, we also found no functional difference in outcome between the two groups.

In our series, there was no difference in graft survival between donor kidneys with single or multiple arteries, which was similar as reported in the literature.[14,15]

The overall patient survival in our cohort at 1 and 5 years was 95.7% and 94.1%, which is comparable to the NAPRTCS data.[6]

Finally, we would like to emphasize that we may have to face many hurdles in executing this transplant program successfully in pediatric populations. We need to determine the appropriate solution to face these challenges and limitations. These may include creation of successful models of kidney transplant for the pediatric population, ensuring the availability of less-expensive immunosuppressive agents, establishing adequate transplant centers dedicated to the pediatric age group and a successful cadaveric programme to provide kidneys to these patients at the appropriate time. Apart from an active initiative from the medical fraternity, participation of government and other agencies with optimal funding support is highly desirable as an initial step to achieve our goal.

CONCLUSION

In the developing countries, the spectrum of etiology of chronic kidney disease differs from that of developed countries. Renal transplant recipients are predominantly male with a much older age. The surgical outcome is comparable to the advanced countries. The kidney retrieval method and as well as the presence of multiple vessels do not adversely affect graft survival. The 1-year graft survival was satisfactory but the 5-year graft survival was clearly inferior as compared with the developed countries, which reflect the limitations and challenges we faced in the perspective of a developing nation. Poor compliance to immunosuppressant secondary to financial constraints was likely to be one of the major contributors for unsatisfactory long-term outcome.

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How to cite this article: 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.

Source of Support: Nil, **Conflict of Interest:** None declared.