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Renal Transplantation in Patients with Lower Urinary Tract Dysfunction: A Single Center Experience from a Developing Country

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Abstract

Objectives: Historically, patients with lower urinary tract dysfunction (LUTD) were considered poor candidates for renal transplantation (RT). We aimed to review our experience with this procedure for its safety and efficacy.

Methods: We reviewed the case records of patients with LUTD who underwent RT at our center. Graft and patient survival were analyzed.

Results: Out of 2053 RTs, 26 (1.2%) patients had LUTD as the primary cause of end-stage renal disease (ESRD). All patients underwent cystourethroscopy prior to transplantation, had abnormal bladders and all underwent bladder augmentation. Only 16 (61.5%) patients had urodynamic (UDN) evaluation prior to transplantation. Pretransplantation augmentation cystoplasty (AC) was performed in 24 (92.3%) patients, and post-RT in two (7.7%). Mitrofanoff channel was made in 25 (96.1%) patients using appendix in 14 (56%) patients and native ureter in 11 (44%). Double-J (DJ) stents were placed in all patients peroperatively. All patients developed 156 episodes of urinary tract infections (UTIs), with an average of 6 UTIs/ patient. All patients except three are maintaining their graft function within acceptable limits. We observed 100% patient and graft survival rates in this series.

Conclusions: In conclusion, RT combined with AC is a feasible option for patients with LUTD with good results in the medium term and should be explored in selected patients.

Keywords: Augmentation cystoplasty; Graft outcome; Lower urinary tract dysfunction; Renal transplantation; Urodynamics

Abbreviations: BOO: Bladder Outflow Obstruction; CISC: Clean Intermittent Self Catheterization; DJ: Double J; ESRD: End Stage Renal Disease; LUT: Lower Urinary Tract; LUTD: Lower Urinary Tract Dysfunction; PUV: Posterior Urethral Valves; RT: Renal Transplantation; UTI: Urinary Tract Infection; VUR: Vesicoureteral Reflux

Introduction

Renal transplantation (RT) is considered the treatment of choice for patients with end-stage renal disease (ESRD). There are many causes of ESRD, out of which lower urinary tract dysfunction (LUTD) contributes to approximately 7-20% of cases in children and adults [1,2]. Traditionally, patients with LUTD have been considered poor candidates for RT [3-5]. However, innovative techniques of diagnosis and reconstructive surgery, together with better understanding of the physiological aspects of RTs, excellence in surgical skills, diagnostic tools and the introduction of novel immunosuppressive regimens and antibiotics have led to a better outcome of RTs in LUTD [6-8]. Excellent patient and graft survival rates have been reported in these patient cohorts in different studies. Most of these studies have been reported from centers in the developed world with very few reports from developing countries [5-8]. However, to the best of our knowledge, no such experience with a fair number of patients is available in the literature from Pakistan.

In this study, we analyzed the safety and outcome of RTs in patients with LUTD who underwent bladder augmentation surgery prior to or after RT.

Materials and Methods

From 1985 to 2011, a total of 3448 RTs were performed at our center. Case records of these patients were analyzed retrospectively for identifying RTs in LUTD with bladder augmentation procedures. A total of 26 such cases were identified who were transplanted for LUTD. First transplant for this indication was performed in 2005. Their case files were scrutinized in detail. The specific causes of renal failure for the patients who had LUTD were noted. Pretransplant urodynamic (UDN) findings and any surgical procedures done were recorded. Peroperative and post-transplant complications were also recorded. Written informed consent was obtained from patients or parents prior to performance of surgical procedures. Standard techniques were used for the RT and the augmentation cystoplasty (AC) in all patients. They all were transplanted kidneys from living-related donors. Standard triple immunosuppressive therapy was used in standard dosages, as described in our previous study [9]. Briefly, the immunosuppressive regimen used at our center comprised of a combination of calcineurin inhibitors (CNIs), anti-proliferative agents and steroids. CNIs included cyclosporine in a dose of 6 mg/kg/day tapered to 3 mg/kg/day by the end of 6 months. Tacrolimus was used in high immunological risk groups. Anti-proliferative agents used included azathioprine in a dose of 1.5-2 mg/kg/day for standard risk patients and mycophenolate mofetil (MMF) in high risk patients. Steroids were used in a dose of 0.5 mg/kg/day tapered to 7.5-10 mg/day by the end of three months. Prior to 1991, azathioprine was used in combination with steroids. One patient with 0 haplotype 1 antigen match was induced with

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antithymocyte globulin (ATG) and six children less than 12 years were induced with interleukin-2 receptor blocker, basiliximab. Renal graft biopsies were performed and interpreted according to Banff 97 classification as described earlier [9]. The patterns of serum creatinine at defined time intervals were analyzed. Episodes of urinary tract infection (UTI) with causative organisms were analyzed. UTI was defined as midstream urine with $\geq 10^5$ organisms/ml of a single organism irrespective of symptoms [10,11]. Any rejection episodes and the treatment with antithymocyte globulin (ATG) were also recorded. Peroperative placement of double-J (DJ) stent and clean intermittent self-catheterization (CISC) were also recorded. Graft and patient survival were analyzed at last follow-up. A matched control population of 28 non-LUTD renal transplant recipients were analyzed was graft survival. Graft failure was defined as return to dialysis.

Statistical Methods

Statistical analysis was performed by SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). Data were presented as median ± interquartile range (IQR) for continuous variables and numbers (percentages) for categorical variables.

Results

Out of 3448 RTs, 2053 were performed during the last seven years of study (2005-2011). Among the later, 26 (1.2%) patients underwent RT with LUTD. All of them had undergone bladder augmentation procedures. The demographic characteristics of these patients and specific causes of renal failure (Table 1). The median age of recipients was 21 (IQR: 15-27) years and of donors, 35 (IQR: 25-48) years. All patients were transplanted kidneys from live related donors. All the patients included in this study underwent cystourethroscopy prior to transplantation, and all showed abnormal bladders (thick walled, trabeculations, small capacity, bladder outflow obstruction (BOO)). Only 16 (61.5%) patients had UDN studies prior to RTs, the findings of which are shown in Table 1. AC with ileal patch was carried out before RTs in 24 (92.3%) patients. In two (7.7%) patients, the procedure was performed after transplantation. Mitrofanoff channel was made in 25 (96.1%) patients using appendix in 14 (56%) patients while native ureter was used in 11 (44%) patients. The duration between RTs and cystoplasty is shown in Table 1. DJ stents were placed in 22 patient's preoperatively. Postoperative complications of urinary fistula, ureteric obstruction, anastomotic leakage and lymphocoele, one each, were observed in 4 (15.3%) patients.

The pattern of serum creatinine over time for two years and at the last follow-up and the best serum creatinine values are shown in table 2. The median lowest serum creatinine was 0.9 (0.8 - 0.99) mg/dl and was achieved over a median of 6 (5-8) days. The median serum creatinine at last follow-up was 1.48 (1.21-1.92) mg/dl. Regarding infectious complications, all patients developed UTIs with a total number of episodes of 156, and an average of 6 UTIs/patient. Asymptomatic UTIs were seen in 13 (50%) patients with total episodes of 28 UTIs, while symptomatic UTIs were seen in 23 (88.46%) patients with total episodes of 128 UTIs (Table 3). The specific microorganisms causing UTIs are shown in Table 3. Renal allograft biopsies were performed in seven patients for unexplained rise in serum creatinine. Two patients showed acute vascular rejection of IIA and IIB types according to Banff classification, two showed acute cellular rejection (type IA), while three patients showed borderline rejection. Only 1 (3.8%) patient had received ATG for the treatment of II B type of rejection and had UTI. Post-transplant bladder emptying with CISC was performed by 13 patients (50%). All these patients also developed both symptomatic and asymptomatic UTIs during CISC. The median follow-up period was 3.09 (IQR: 2.04-3.50 years; range: 0.42-10.23 years) years. Three patients had serum creatinine of 6.31, 6.51 and 6.39 mg/dl at last follow-up but they are still dialysis free. We thus observed 100% patient and graft survival in this series till last follow-up. A well matched control population of 28 non-LUTD renal transplant recipients was also analyzed for graft survival during the above study period, which showed 96% and 72% graft survival at one and five years respectively.

Discussion

Patients with congenital or acquired lower urinary tract (LUT)

Demographics of patients	**n**	**%**
Male	24	92.3
Female	2	7.7
M:F ratio	1:12	
Median age (interquartile range) in years	21 (15-27	
≤ 18 years	11	42.3
> 18 years	15	57.6
Causes of renal failure		
Neurogenic bladder	11	42.6
Posterior uretheral valves	3	11.5
Vesico-ureteric reflux	6	3
Bladder outflow obstruction	4	15.3
Genito-urinary tuberculosis	2	7.6
Pretransplantation urodynamic findings (n=16)		
Low capacity low pressure	5	31.2
Low capacity high pressure	9	56.2
Small capacity normal pressure	2	12.4
Posttransplantation urodynamic findings (n=20)		
Normal capacity low pressure	4	16.6
Normal capacity normal pressure	14	70
Normal capacity high pressure	2	10
Duration between cystoplasty and transplantation in pretransplant cystoplasty (n= 24) in months		
1-3	4	16.6
4-6	5	20.8
7-12	10	41.6
13-18	3	12.3
19-24	2	8.3
Bowel segment used (n=26)		
Ileum	26	100
Mitrofanoff channel (n=25)		
Appendix	14	56
Ureter	11	44

Table 1: Demographic and clinicopathological findings in 26 patients with abnormal lower urinary tracts who were transplanted kidneys at our centre.

Serum creatinine values in mg/dl	**Median (IQR)**	**Range**
Best serum creatinine	0.9 (0.8-0.99)	0.28 - 2.44
Normalization of serum creatinine in days	6 (5-8)	4 - 23
Serum creatinine at 4 weeks	1.0 (0.89-1.28)	0.35- 3.86
at 3 months	1.19 (0.91-1.49)	0.39 - 4.36
at 6 months	1.1 (0.94-1.56)	0.45 - 6.57
at 12 months	1.2 (1.11-1.53)	0.50 – 3.10
at 24 months	1.6 (1.07-1.9)	0.56 - 2.5
at last follow-up	1.48 (1.21-1.92)	0.70-6.51
Duration of follow-up in years	3.09 (2.04-3.5)	0.42-10.23

Table 2: Pattern of serum creatinine over time in 26 patients with LUTD who underwent renal transplantation.

Total episodes of UTIs	156	
Mean UTIs/patient	6	
Median (interquartile range)	5(3-8)	
Range of UTIs/patient	1-19	
Micro-organisms causing UTI	N	%
E.Coli	74	47.3
Klebsiella	35	22.4
Pseudomonas	17	10.89
Morgnella	10	6.4
Acinetobacter	8	5.1
Enterococcus	8	5.1
Others	7	4.4

Table 3: Urinary tract infection (UTI) episodes in all 26 patients and the causative organisms.

disease frequently develop ESRD requiring renal replacement therapy. Abnormal LUTs of these patients should be managed surgically or sometimes conservatively to preserve normal renal functions. However, patients developing ESRD are scheduled for RTs and augmented procedures to make the reservoir more optimal to sustain the precious renal graft function [3,4].

We herein report our experience with 26 patients who underwent RT for ESRD secondary to LUTD, out of which 24 (92.3%) patients had AC before RTs. The advantages of pretransplantation AC include avoidance of the interaction of the augmentation surgery with immunosuppressive drugs and the facilitation of antireflux mechanisms [5]. Contrary to this, Mc Inerny et al. advocate the policy to perform cystoplasty after RT to avoid dry reservoir, interference with its vascular pedicle at the time of ureteric implantation and to allow renal functions to stabilize [6].

The timing of cystoplasty before RT varies in the literature from 10-12 weeks to 5 years [5,7]. We strongly advocate pretransplantation AC at our center. In this series, we performed 24 AC before RT and the time period between AC and RT was >6 months in the majority of cases (62.5%) (Table 1). The main reason for this somewhat extended time interval was lack of interest for organ donation on the part of the family. In this part of the world there is no deceased donor programme and there are multiple social issues which hinder kidney donation among families.

To achieve the most optimal results in RT especially in LUTD patients, pretransplant LUT UDN studies should be performed with cystoscopy so that any correctable or palliative surgical procedure could be offered to these patients. We performed UDN in 16 patients before RT. The majority of these patients (56.2%) had low capacity and high pressure urinary bladders and 4 patients had low capacity and low pressure bladders (Table 1). All these patients were managed with pre-RT AC. Later, the majority of these patients had LUT UDN in post-RT phase, which showed an adequate volume and pressure in the LUT, which was in concordance with an earlier study [8]. This low pressure and adequate volume of LUT provides an environment for the allograft to function in an optimal manner.

UTI in RT patients is a major concern for the graft well being and can increase the morbidity. The overall incidence of UTI in RT patients varies from 30% to 65% [10-14]. Multiple factors affect UTI in RT: among these, DJ stent placement is a major factor and provides an excellent nidus for the colonization of the foreign body in the immunosuppressed patients. The incidence of UTIs with DJ stenting is markedly high and varies between 14 to 71% [11,15,16]. Augmented bladders also provide a favorable atmosphere for the occurrence of UTIs. The incidence of UTIs in RTs with augmented bladders has been reported to be up to 100% [17]. We also observed an incidence of UTIs of 100% with augmented bladders and DJ stenting, which is comparable to that observed in the above mentioned studies.

In this cohort, 50% of the patients required CISC and managed it successfully. All of these patients had at least one episode of UTI with significant episodes of symptomatic UTIs. UTI in CISC is not an infrequent finding owing to the bladder enlargement and repeated introduction of catheters in Mitrofanoff channel. Personal hygiene and social factors also play a part in the occurrence of UTIs in CISC. The combination of CISC, augmented bladders and DJ stenting are the strong risk factors for UTIs but the important point to be emphasized here is to construct a technically correct antireflux ureteric reimplant to prevent graft pyelonephritis [8] and to maintain graft function in normal and acceptable range.

Gill et al. reported UTIs with CISC in RT of 33% [18], which is somewhat low as compared to other studies, which showed higher incidence [19]. We report 100% incidence of UTIs, but we think that the objective of CISC in Mitrofanoff channel should be the complete and frequent emptying of the bladder under sterilized measures. This coupled with a good antireflux ureteric reimplant technique may minimize the chances of UTIs and graft pyelonephritis which is a requirement for the better graft survival. We therefore advocate CISC in selected cases despite high incidence of UTI as frequent CISC is a requirement to keep a high LUT pressure under control to minimize the chances of graft hydronephrosis and maintain an optimal graft function.

A total of 156 episodes of UTI were documented among these patients in this study. The maximum numbers of UTIs in a single patient was 19. *E. coli* was the most common organism isolated in this study followed by Klebsiella, Pseudomonas and Morganella. Multiple studies have shown high incidence of UTI with *E. coli* and *Klebsiella* [11,20-22]. This high incidence of UTIs led the transplant physicians to stringent follow-up of these patients and diagnostic protocols in which urine analysis and serum creatinine monitoring are mandatory.

The median best serum creatinine in this series was less than 1.0 mg/dl with an excellent graft and patient survival as compared with a small control population of 28 patients well matched for all other parameters except LUTD. This excellent graft survival has also been substantiated by other authors and may be due to more rigorous follow-up and prompt treatment [8, 22-26]. However, this study has some limitations as graft function depends on multiple factors and these factors should be assessed carefully. The follow-up period is also not very long. The study originates from a single center. Despite these limitations, we believe that our results are promising and support the safety and efficacy of RT in this group of patients.

Conclusions

In conclusion, our results show that AC is a safe and feasible procedure in patients with LUTD and RTs can be done in these patients under a multidisciplinary care with excellent patient and graft survival in the medium term.

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