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ORIGINAL ARTICLE

Interventions for impaired bladders in paediatric renal transplant recipients with lower urinary tract dysfunction

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Summary

Dysfunctional bladders in paediatric patients were thought to be a contraindication for renal transplantation, but advances in surgical techniques have meant that surgical correction can allow safe transplantation. This study compares the outcomes of renal transplantation for different interventions, and the timing of such interventions, in relation to transplantation. We identified all paediatric renal transplant recipients with LUTD that received intervention for their impaired bladders at two hospitals between 2002 and 2010. Outcome measures included patient and graft survival, perioperative complications, UTI incidence, acute rejection episodes and serum creatinine levels. A total of 288 allografts were transplanted, 77 were in 75 children with LUTD, of which 46 received intervention. Patient survival was 100% in the intervention group and 97% in the nonintervention group ($P = 0.815$). Death-censored graft survival was 96% and 100% respectively ($P = 0.688$). In the groups receiving intervention pretransplant or post-transplant, graft survival rates were 95% and 100% respectively ($P = 0.476$). The follow-up serum creatinine levels were higher in the pretransplant intervention group ($P < 0.001$). Interventions for dysfunctional bladders can be performed safely in paediatric renal transplant recipients. The mode of intervention and timing of intervention, in relation to transplant, do not influence outcomes if guided by careful assessment and investigation.

Introduction

Approximately 20% of end stage renal disease (ESRD) in paediatric patients is caused by lower urinary tract dysfunction (LUTD) [1]. The bladder is by nature, a low-pressure, highly compliant reservoir, for the storage of urine. In LUTD, the bladder may be poorly compliant and/or have a raised pressure, which can lead to impaired kidney function, and subsequent failure. Children that are more at risk of developing such bladders mainly include those with posterior urethral valves (PUV), prune belly syndrome and neuropathic bladders. Historically, it was believed that renal transplantation in these children should not be offered.

In recent decades, advancements in surgical techniques have meant that reconstruction of the lower urinary tract can correct or improve these dysfunctional bladders, making them suitable for transplantation [2–4]. Such interventions work to reduce the pressure within the bladder, or render it more compliant. There is, however, debate over which method of intervention is more effective and at which point it should be performed, in relation to the transplant [5].

In this study, we consider outcomes after different interventions and relate these to the timing of the intervention with respect to the transplant; in short, which intervention is best and when should it be done?

Materials and methods

We reviewed children that had received a renal transplant at Great Ormond Street Hospital for Children and Evelina Children's Hospital from January 2002–December 2010. Those with a diagnosis of LUTD were identified. Initially, this was carried out by searching our database for the relevant diagnosis, and then by examination of the case notes. The diagnoses of interest were PUV, prune belly syndrome, neuropathic bladders, dysplastic kidneys, idiopathic and VACTERL association.

A total of 288 renal transplants were carried out at the above institutions within the time period stated. Children with suspected impaired bladder function underwent renal and bladder ultrasound and were referred to the paediatric urology service. Urodynamic or other investigations, (such as videocystography), were carried out as necessary, with attention being paid to filling pressures, compliance, leakage and flow rates. Formal thresholds for urodynamic results were not set, as these will vary according to the size of the child. However, incomplete bladder emptying was deemed an indication for urinary diversion/Mitrofanoff formation and a small, noncompliant bladder resulted in bladder augmentation. Recipients were reviewed on a case-by-case basis by a multidisciplinary team, including transplant surgeons, nephrologists and paediatric urologists to determine which type of intervention would be most effective in creating a 'safe' bladder for transplantation, and the timing of such intervention.

Outcome measures included patient and graft survival, perioperative (within 30 days) complications, number of urinary tract infections (UTI) within 6 months of transplant, number of acute rejection episodes and latest follow-up serum creatinine. The perioperative complications were categorized into major and minor based on a modification in the Clavien classification system, which reports negative outcomes in surgery [6]. Major complications refer to those that can lead to death if no intervention is provided, or those that can cause allograft dysfunction. Minor complications include any events that can lead to prolonged patient recovery. The type of intervention and timing relative to transplant were recorded and outcomes assessed accordingly.

Types of intervention data were compared using one-way analysis of variance (ANOVA) for follow-up periods, UTIs within 6-months post-transplant and latest follow-up serum creatinine levels. Complication rates and acute rejection episodes were assessed using chi-square tests. Timing of intervention and nonintervention data were compared using *t*-tests for follow-up periods, UTIs within 6-months post-transplant and latest follow-up serum creatinine levels. Complication rates, acute rejection episodes and patient and graft survival rates were assessed using chi-square tests. For all analysis, a $P < 0.05$ was considered significant.

Results

Two hundred and eighty-eight renal transplants were performed of which 77 (26.7%) were in 75 children with LUTD. The proportions of underlying aetiologies associated with these dysfunctional bladders are shown in Table 1. Sixty-five(86.7%) of the 75 children were male patients, with a mean age of 9.2 ± 0.6 years at transplantation. The 62.7% received a live related transplant and 36% received a deceased donor transplant (one child's transplant type remains unknown). The mean follow-up was 3.6 ± 0.29 years after transplantation. 46 (61.3%) of those children received intervention for their bladders before or after transplantation and 29 underwent no intervention (three of whom had a vesicostomy or ureterostomy which was closed several years prior to transplant).

Preintervention urodynamics reports were available for 14 children. The type of intervention and the timing of intervention were guided by the results of these urodynamics assessments. Small noncompliant bladder, instability, leakage and detrusor overactivity were common findings in this group of children.

Type of intervention

The 15.2% of children received a Mitrofanoff only (Group 1), 37% received both bladder augmentation and a Mitrofanoff (Group 2), 8.7% received both urinary diversion (vesicostomy/ureterostomy) and a Mitrofanoff (Group 3), 30.4% received all three interventions (Group 4) and 8.7% received a urinary diversion only (Group 5) (Table 2). There were no significant differences in the relative follow-up periods for each of the groups ($F_{4,43} = 0.51$, $P = 0.732$). Patient survival rate at latest follow-up was 100% in all groups. Graft survival rate at latest follow-up was 100% in all groups except those in Group 1, for which it was 71.4%, with two grafts lost to acute rejection. There was no signifi-

Table 1. Underlying aetiologies in children with ESRD due to dysfunctional bladders.

Underlying Aetiology	Number of Children	Percentage (%)
Posterior urethral valves (PUV)	40	53.3
Dysplastic kidneys	15	20
Prune belly syndrome	6	8
Neuropathic bladder	4	5.3
Idiopathic	2	2.7
Other	8	10.7

VACTERL association, horseshoe kidney, duplex system, vesicoureteral reflux (VUR) and cloacal anomaly.

Table 2. Outcome data comparing the method of intervention groups.

	Mitrofanoff (Group 1)	Bladder Augmentation Mitrofanoff (Group 2)	Urinary Diversion Mitrofanoff (Group 3)	Mitrofanoff Bladder Augmentation Urinary Diversion (Group 4)	Urinary Diversion (Group 5)
Number	7 (15.2%)	17 (37%)	4 (8.7%)	14 (30.4%)	4 (8.7%)
Follow-up period	2.77 ± 0.98	4.09 ± 0.62	4.46 ± 1.14	3.52 ± 0.62	3.21 ± 1.44
Total complication rate	2 (28.6%)	8 (47.1%)	1 (25%)	7 (50%)	1 (25%)
Major complications	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	0 (0%)
Minor complications	2 (28.6%)	8 (47.1%)	1 (25%)	7 (50%)	1 (25%)
Mean number of UTIs within 6-months post-transplant	2.57 ± 0.69	3.24 ± 0.40	3 ± 0.58	3.15 ± 0.44	2.75 ± 0.63
Acute rejection episodes	2 (28.6%)	5 (29.4%)	1 (25%)	2 (14.3%)	1 (25%)
Mean latest follow-up serum creatinine (umol/l)	185 ± 51.8	98.9 ± 13.3	120 ± 27.1	154.4 ± 35.9	102.5 ± 22.7

$P > 0.05$ for all outcome measures.
UTI, urinary tract infection.

cant difference in the complication rates in these groups ($P > 0.05$ for all). The mean number of UTIs within 6-months post-transplant was similar between the groups ($F_{4,42} = 0.26$, $P = 0.899$). There was no significant difference in the number of children with acute rejection episodes, recorded at latest follow-up, between the different groups. Compared to the other groups, the latest follow-up serum creatinine level in Group 1 was higher. This difference, however, was not statistically significant ($F_{4,43} = 1.29$, $P = 0.289$).

Timing of intervention

The 80.4% of children received their intervention pretransplant and 19.6% received it post-transplant (Table 3). The relative follow-up periods for the two groups did not differ significantly ($P = 0.182$). There were no mortalities in either group at latest follow-up and graft survival rates were 94.6% in the pretransplant intervention group, with two grafts lost to acute rejection and 100% in the post-transplant intervention group ($P = 0.476$). The 37.8% of children in the pretransplant intervention group and 55.6% of children in the post-transplant intervention group suffered from complications ($P = 0.555$). The mean number of UTIs 6-months post-transplant was higher in the pretransplant intervention group compared with the post-transplant intervention group; however, this was not statistically significant ($P = 0.125$). There was no significant difference in the number of children with acute rejection episodes ($P = 0.895$). The latest follow-up serum creatinine levels were significantly higher in the pretransplant intervention group compared to the post-transplant intervention group ($P < 0.001$).

Table 3. Outcome data comparing the timing of intervention groups.

	Pre-Transplant Intervention	Post-Transplant Intervention
Number	37 (80.4%)	9 (19.6%)
Follow-up period	3.36 ± 0.35	5.11 ± 1.15
Total complication rate	14 (37.8%)	5 (55.6%)
Major complications	0 (0%)	1 (11.1%)
Minor complications	14 (37.8%)	5 (55.6%)
Mean number of UTIs within 6-months post-transplant	3.22 ± 0.25	2.25 ± 0.53
Acute rejection episodes	9 (24.3%)	2 (22.2%)
Mean latest follow-up serum creatinine (umol/l)	142.8 ± 17.1*	73.9 ± 7.52

*$P < 0.05$.
UTI, urinary tract infection.

Nonintervention

Of the 75 children with LUTD, 38.7% did not undergo intervention (Table 4). The relative follow-up period for these children was not significantly different to those that received intervention ($P = 0.754$). There was one patient death in the nonintervention group, documented as lymphoproliferative disease, yielding a patient survival rate of 96.6%, with no mortalities in the intervention group ($P = 0.815$). The death-censored graft survival rate was 100% in the nonintervention group and 95.7% in the intervention group ($P = 0.688$). The 31% of children in the nonintervention group had complications compared to 41.3% in the intervention group ($P = 0.516$). The mean number of UTIs 6-months post-transplant was 2.65 ± 0.30 in the nonintervention group and 3.05 ± 0.23 in the

Table 4. Outcome data comparing the nonintervention group to the intervention group.

	Nonintervention	Intervention
Number	29 (38.7%)	46 (61.3%)
Follow-up period	3.48 ± 0.51	3.67 ± 0.36
Total complication rate	9 (31.0%)	19 (41.3%)
Major complications	2 (6.9%)	1 (2.2%)
Minor complications	7 (24.1%)	19 (41.3%)
Mean number of UTIs within 6-months post-transplant	2.65 ± 0.30	3.05 ± 0.23
Acute rejection episodes	6 (20.7%)	11 (23.9%)
Mean latest follow-up serum creatinine (umol/l)	119.1 ± 18.8	130.5 ± 14.7

$P > 0.05$ for all outcome measures.
UTI, urinary tract infection.

intervention group ($P = 0.297$). There was no significant difference in the number of children with acute rejection episodes ($P = 0.967$), or the latest follow-up serum creatinine levels ($P = 0.634$). A Sidak-adjusted correlation analysis of all 75 children revealed no association between the number of UTIs 6-months post-transplant and the latest follow-up serum creatinine levels (correlation coefficient = 0.110, $P = 0.351$).

The specific minor and major complications are shown in Table 5. UTIs were more prevalent in Group 2 and Group 4 suggesting an association between UTIs and bladder augmentation, but with no statistical significance ($P > 0.05$ for all). There was a single case of urinary leak, in Group 2; this was successfully repaired within a few weeks of the transplant, with no complications. There was one case of reduced perfusion to the renal allograft, in the nonintervention group. There were two cases of haemorrhage, which required a return to theatre, and exploration of the transplanted allograft with an evacuation of a haematoma; one was from Group 2 and the other in the nonintervention group.

Discussion

This study, which includes the largest single report of paediatric patients with LUTD undergoing transplantation, has confirmed that interventions for dysfunctional bladders can be performed with a respectable outcome. In particular, perioperative complications and long-term graft survival are acceptable. This is in agreement with a recently published article examining outcomes following bladder augmentation or urinary diversion in a smaller cohort of children with ESRD as a result of LUTD [7]. Although the majority of children in our study had their intervention pretransplant, both the method of intervention and the timing of intervention, in relation to the transplant, did not

Table 5. Incidence of minor and major complications in the method of intervention groups, the timing of intervention groups, and the nonintervention/intervention groups.

	Mitrofanoff (Group 1)	Bladder Augmentation Mitrofanoff (Group 2)	Urinary Diversion Mitrofanoff (Group 3)	Mitrofanoff Bladder Augmentation Urinary Diversion (Group 4)	Urinary Diversion (Group 5)	PreTransplant Intervention	PostTransplant Intervention	Nonintervention	Intervention
Minor Complications:									
Hydronephrosis	1						1	1	1
Hydrocoele				1		1		1	1
Urinary tract infection		5		5	1	8	3	2	11
Wound dehiscence		1		1		1	1		2
Viral infection		1	1			1	1	1	2
Urosepsis	1					1		1	1
Urinary leak		1				1			1
Major Complications:									
Reduced perfusion								1	
Haemorrhage		1					1	1	1

seem to influence patient and graft survival, perioperative complications or acute rejection episodes. However, children that received their intervention pretransplant had higher follow-up serum creatinine levels than those who received their intervention post-transplant ($P < 0.001$). The cause of this remains unclear, but could reflect an increased risk of reflux into the allograft, resulting in subclinical infection and graft dysfunction. There was also a trend (but with no statistical evidence) towards a higher incidence of UTIs in the children that received a bladder augmentation compared to those that did not ($P > 0.05$ for all). There is a possibility that bacterial flora from the augment colonized the urinary tract in this group of children. However, in contrast, a recent study has discovered that the incidence of UTIs in children that received a bladder augmentation compared to those that did not, is similar [8]. Preference as to which type of intervention should be performed, and at what time in relation to the transplant, should be given on a case-by-case basis; taking into account patient priority and risks at that time.

Prior to the development of these interventions, it was widely believed that children with dysfunctional bladders should not be considered for renal transplantation. If the impaired bladder were the direct cause of ESRD then transplantation into that bladder would harm the new renal allograft [9–11]. Some small studies have reported no difference in graft and patient survival rates, and post-operative complications between children undergoing transplantation with a dysfunctional bladder and a normal bladder [12–19]. On the other hand, some studies have reported that children with dysfunctional bladders have lower graft and patient survival rates and are more likely to develop post-transplant complications [11,20–24]. The discrepancy can be attributed to the small number of children being studied, the wide spectrum of underlying aetiologies of dysfunctional bladders [5] and the individual child.

Recent surgical advancements have now meant that children with impaired bladders can undergo reconstructive intervention to create safer bladders for transplantation. There are no previous studies comparing the three intervention types and any studies relating to interventions have mainly focused on bladder augmentation. The first report of successful adult renal transplantation into an augmented bladder was by Marshall *et al.* in 1982 [25]. It was not until 1984 that Stephenson *et al.* reported the first successful paediatric renal transplantation into an augmented bladder [26]. Since then, several studies have shown that transplantation into augmented bladders produces similar rates of graft and patient survival as well as an insignificant difference in post-transplant complications, to those with normal bladders [9,27,28].

There remains great controversy as to the optimal timing of intervention, in relation to transplant. Four children received only urinary diversion in this study, all of which were given pretransplant, and resulted in good outcomes. In contrast, a study consisting of four patients who received post-transplant urinary diversion, in the form of an ileal orthotopic bladder substitution, also concluded that functional results of the renal transplant were good and within normal ranges [29]. Basiri *et al.* conducted a study in which they compared outcomes of renal transplantation in two groups of individuals; those that underwent a bladder augmentation pretransplant and those post-transplant [30]. They concluded that graft survival rates and number of rejection episodes in the two groups showed no significant difference. This present study confirms these results, although the latest follow-up serum creatinine levels were significantly higher in the pretransplant intervention group. Some authors believe that by providing intervention pretransplant we are avoiding the effect of post-transplant immunosuppressive regimes that could adversely affect the quality of the intervention due to wound healing effects [31]. On the other hand, it may not always be necessary to intervene if one were to assess function after restoration of urinary flow – a small, noncompliant bladder may improve after transplantation in some cases.

Although this is the largest report of transplantation in children with LUTD, it is not without limitations. The number of children receiving urinary diversion and a Mitrofanoff and urinary diversion only were low. These are a rare group of children and hence numbers available for review are reduced. In addition, the retrospective nature of this study makes it difficult to obtain complete data and therefore adequately assess decision-making prior to transplantation in children with LUTD. Finally, we are only able to compare serum creatinine rather than eGFR, as the latter was unavailable for all children; clearly, creatinine may not be a reliable marker in children.

We have confirmed that a dysfunctional bladder is not a contraindication for a renal transplant. Surgically reconstructed impaired bladders in paediatric transplant recipients produce results that are comparable to those of normal bladders. The type of intervention and timing, in relation to transplant, does not appear to significantly influence outcomes. It is therefore crucial to study both the bladder and the patient when making a decision regarding the mode of intervention and timing, such that patient priority and risks are taken into account. We also recommend that in children with LUTD, there should be a low threshold for urodynamics studies, which will assist in deciding management.

Authorship

NA-K: Participated in the design, data collection, data analysis and writing of the manuscript. PR, DYD, CR, SDM:

Participated in data collection. NM: Participated in the design, data analysis and editing and revision of the manuscript.

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