Accepted: 18 May 2017

DOI: 10.1111/petr.13006

ORIGINAL ARTICLE

WILEY

Incidence and risk factors of early surgical complications in young renal transplant recipients: A persistent challenge

Nathan Rodricks[1] | Rahul Chanchlani[1,2,3,4] | Tonny Banh[1] | Karlota Borges[1] | Jovanka Vasilevska-Ristovska[1] | Diane Hebert[2] | Viral Patel[1] | Armando J. Lorenzo[5] | Rulan S. Parekh[1,2,4,6,7]

[1]Child Health Evaluative Sciences, Research Institute, Hospital for Sick Children, Toronto, ON, Canada

[2]Department of Pediatrics, Division of Nephrology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

[3]Department of Pediatrics, Division of Nephrology, McMaster Children Hospital, McMaster University, Hamilton, ON, Canada

[4]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

[5]Division of Urology, Hospital for Sick Children and Department of Surgery, University of Toronto, Toronto, ON, Canada

[6]University Health Network, Toronto, ON, Canada

[7]Dalla Lana School of Public Health, Toronto, ON, Canada

Correspondence
Rulan S. Parekh, Division of Nephrology, The Hospital for Sick Children, Toronto, ON, Canada.
Email: rulan.parekh@sickkids.ca

Abstract

There is a paucity of data on the rate of urological and vascular complications in very young children after kidney transplant. We conducted a study on the incidence and risk factors for early post-transplant surgical complications in young recipients (<5 years) over three decades. The primary outcome was any urological or vascular complication within 30 days of transplant, and the secondary outcome was incidence rate of graft failure reported as per 1000 person-years. Risk factors associated with surgical complications were analyzed by logistic regression. There were 22 (26.5%) complications in 21 children with vascular thrombosis being the most common complication. There was no significant difference in the number of complications in period 1 (1985-1994) and period 2 (1995-2014) (P=.1). The incidence rate of graft failure was higher in period 1 (IR 70.8, 95% CI 41.1, 121.9) compared to period 2 (IR 20.7, 95% CI 9.3, 46.0). Cumulative incidence of graft survival at 1, 3, and 5 years' post-transplant was 96.5%, 92.6%, and 90%, respectively, in those without compared to 71%, 65.1%, and 58.6%, respectively, in children with complications. In conclusion, early surgical, especially vascular, complications are quite common in young renal transplant recipients and lead to significantly reduced graft survival.

KEYWORDS

outcome, renal transplantation, surgical complications, time trends, young children

1 | INTRODUCTION

Kidney transplantation is the best therapy for management of children with ESRD.[1] For years, very young children were maintained on dialysis as they were not considered optimal transplant recipients because an adult-size allograft may not be positioned appropriately within a small cavity, and also the need for higher blood flow not achievable given a small child's hemodynamics and vessels diameter. Nevertheless, over the last two decades, the number of young children with ESRD receiving kidney transplantation has increased. The driving force has been the growing number of encouraging post-transplant outcomes primarily due to improvements in immunosuppressive medications, surgical technique, and peri-transplant management. Data from the North American Pediatric Renal Trials and Collaborative Studies' (NAPRTCS) 2014 annual report demonstrate that the 5-year graft survival of children <5 years of age is 85% and 70% for living and deceased donor transplantation, respectively.[2]

Despite these improvements in graft and patient survival, renal transplantation in young children remains quite challenging, incurring a higher risk of potential surgical and vascular complications and the requirement of prolonged intensive care monitoring post-transplantation. Surgical complications, especially those in the first month of transplantation, are important causes of morbidity, and

Abbreviations: BMI, body mass index; ESRD, end-stage renal disease.

Nathan Rodricks and Rahul Chanchlani contributed equally to the manuscript.

sometimes mortality.[3] Due to a relatively low number of young recipients in most studies, there are few published reports focusing on post-transplant urological and vascular complications.[4,5] Moreover, there is a noticeable heterogeneity in the reported incidence of surgical complications, likely due to paucity of standard definitions for complications, and variable post-transplant follow-up. Previous studies have also not addressed the association between prophylactic heparin use and screening for coagulation abnormalities and incidence of surgical complications.

To address these limitations in the published literature, we conducted a longitudinal study on the incidence and risk factors of early post-transplant surgical complications in young recipients in a large tertiary pediatric center over the last three decades.

2 | METHODS

2.1 | Study design and participants

We performed a retrospective cohort study on young renal transplant recipients <5 years who received their first transplant between January 1, 1985, and December 31, 2014, at the Hospital for Sick Children, Toronto. Children were followed until 18 years of age, last clinic visit, graft failure, or censored on June 30, 2015. We excluded children who had less than 30 days' post-transplant follow-up at our center. The study was approved by the SickKids Research Ethics Board.

Data were collected from the electronic medical records, which included clinical information on recipient and donor characteristics, medications, laboratory parameters during the post-transplant period.

2.2 | Outcomes assessment

The primary outcome of interest was surgical complication after transplantation. A surgical complication was defined as an adverse event directly associated with the transplant surgery and presented within 30 days after the transplant. Surgical complications were categorized into two groups, urological and vascular. Urinary leak and urinoma formation were considered the main urological complications, while lymphocele, renal vein or artery thrombosis, and vascular anastomotic leak were considered the main vascular complications. These complications were diagnosed by either Doppler ultrasound, nuclear scan, percutaneous aspiration, contrast studies, or voiding cystourethrogram. The secondary outcome was graft failure, which was defined as the return to chronic dialysis or need for a second transplant.

2.3 | Exposure assessment

The main exposure was the time period of the kidney transplant between 1985-1994 (period 1) and 1995-2014 (period 2).

2.4 | Transplant procedure

All recipients and donors underwent an extensive pretransplant evaluation by a multidisciplinary team. We accepted donors up to 45 and 50 years of age for deceased and living donation, respectively. No en bloc kidney transplantation was performed. A majority of transplants were conducted using an extraperitoneal approach; the grafts were placed on either the right or left iliac fossa through a Gibson-type incision. Following contemporary institutional protocols, children received triple-immunosuppressive regimen of prednisone, an antiproliferative agent (azathioprine or mycophenolate mofetil), and a calcineurin inhibitor (cyclosporine or tacrolimus). Children also received induction therapy with polyclonal or monoclonal antibodies depending on their immunological risk.

2.5 | Covariates

Pretransplant characteristics included primary disease leading to ESRD, dialysis modality (hemodialysis vs peritoneal) and duration, recipient's body mass index (BMI) z-score at the time of transplant, and donor status (living vs deceased). Additional data included detailed coagulation profile as part of the routine pretransplant evaluation from 2009 onwards, which consisted of factor V Leiden, prothrombin gene mutation, protein C and S, antithrombin III levels, lupus anticoagulant, and anticardiolipin antibodies. From 2009, all children under 20 kg or with abnormalities in the coagulation profile were considered as high-risk and routinely received prophylactic heparin (10 units/kg/h) for the first 7 days after transplantation, and if required, continued on low-molecular-weight heparin. Post-transplant characteristics included immunosuppressive medications received since the time of transplantation and trends in graft function over time.

2.6 | Statistical analyses

Continuous variables were reported as mean and standard deviation, and categorical variables were reported as numbers and percentages. Univariate analysis of categorical variables was carried out using the chi-square or Fisher's exact test, as appropriate, and continuous variables were analyzed using *t* tests.

A Kaplan-Meier analysis was conducted to determine the probability of graft survival stratified by the period of transplant and surgical complications. The incidence rate of graft survival (per 1000 person-years) was calculated by censoring the observation period on the date of graft failure, last follow-up or June 30, 2015. Stepwise backward multivariable logistic regression model was used to analyze risk factors (defined a priori such as age at transplant, BMI z-score, gender, receipt of pretransplant dialysis, period of transplant, living vs deceased donor) associated with surgical complications post-transplant. A subgroup analysis was also carried out to determine the risk factors associated with vascular complications. A two-sided *P*-value less than .05 was considered significant. Analyses were conducted by STATA 14 (College Station, TX, USA) software.

3 | RESULTS

3.1 | Patient characteristics

Table 1 shows the characteristics of the children less than 5 years of age who received a kidney transplant in periods 1 and 2. Of the 90

children, seven were excluded due to less than 30 days of follow-up. There were fewer (30.1%) transplants in period 1 (1985-1994) as compared to period 2 (1995-2014) (69.9%), yet the clinical and demographic characteristics did not differ by era. There was a significant increase in the number of living donor transplants in period 2 (55%) as compared to period 1 (16%, *P*=.001). Renal dysplasia was the most common cause of ESRD in both periods. Children stayed on dialysis for a considerably longer duration in period 1 as compared to period 2 (*P*=.07).

Overall, 28 children were screened for coagulation abnormalities since 2009, and of them, 10 (35.8%) had factor V Leiden mutations (n=2), protein S deficiency (n=1), protein C deficiency (n=4), and antithrombin III deficiency (n=3).

3.2 | Surgical complications

There were 22 (26.5%) complications in 21 children within 30 days post-transplant with vascular thrombosis being the most common complication in both periods. Table 2 shows the details of complications. There was no significant difference in the number of complications in both periods (*P*=.1). Of 10 patients with abnormal coagulation profile, two (20%) had a vascular complication. In period 2, 27 (46.5%) children received heparin prophylaxis post-transplant. Of them, three (11.1%) had a vascular complication as compared to 5 (16.1%) children who did not receive heparin prophylaxis (*P*=.7).

TABLE 2 Surgical complications in children less than the age of 5 who received a renal transplant from 1985 to 2014

Complications	Period 1 (n=25) (1985-1994)	Period 2 (n=58) (1995-2014)
Urinary leak	1 (11.1)	5 (38.5)
Thrombosis	3 (33.3)	6 (46.1)
Lymphocele	1 (11.1)	-
Anastomotic leak	1 (11.1)	2 (15.3)
Other[a]	3 (33.3)	-
Total (%)	9 (36)	13 (24.1)

[a]Other: bowel obstruction.

3.3 | Risk factors for post-transplant surgical complications

A stepwise backward multivariate logistic regression analysis was performed with a priori defined risk factors. Age at transplant (OR 0.94, 95% CI 0.51, 1.73), dialysis pretransplant (OR 0.31, 95% CI 0.07, 1.26) and BMI z-score (OR 1.41, 95% CI 0.87, 2.27) were included in the final model but were not found to be statistically significant risk factors for surgical complications (Table 3).

In a subgroup analysis of those with only vascular complications, abnormal coagulation profile had a 3 times higher odds of having vascular complications, but it was not statistically significant (OR

TABLE 1 Characteristics of children less than 5 y of age who received a renal transplant from 1985 to 2014 at a tertiary center

Characteristics	n	Period 1 (1985-1994) (n=25) Mean±SD/n (%)	Period 2 (1995-2014) (n=58)	*P* value
Males	83	19 (76)	35 (60)	.17
Mean age at transplant, years	83	3.6±1.2	3.3±0.9	.25
Mean weight at transplant, kg	73	14.0±2.3	14.4±2.3	.48
BMI (z-score)	71	1.26±1.73	1.26±1.06	.99
Living donor	83	4 (16)	32 (55)	.001
Pretransplant dialysis	83	19 (76)	49 (84.5)	
Hemodialysis		9 (47.4)	21 (42.8)	.99
Peritoneal dialysis		10 (52.6)	28 (57.1)	.49
Time on dialysis pretransplant (days)	76	800.6±503.4	551.4±404.1	.07
Primary diagnosis	83			
Congenital		20 (80)	39 (67)	
Acquired		5 (20)	19 (33)	
Immunosuppressants				
Prednisone	83	25 (100)	58 (100)	
Tacrolimus	83	1 (4)	47 (81)	
Cyclosporine	83	21 (84)	12 (20.7)	
Mycophenolate mofetil	83	0	46 (79.3)	
Azathioprine	83	19 (75)	4 (7)	

TABLE 3 Univariate logistic regression model for risk factors associated with surgical complications after transplant

	Univariate analysis		
Variable	**Odds ratio**	**95% CI**	***P* value**
Period 2 (1995-2014)	0.48	0.17, 1.35	.2
Age at transplant (years)	0.95	0.60, 1.51	.8
Dialysis pretransplant	0.47	0.14, 1.52	.2
Body mass index z-score	1.46	0.92, 2.32	.1
Females	0.81	0.28, 2.28	.7
Deceased donor	0.92	0.34, 2.45	.9

3.2, 95% CI 0.15, 67.7) after adjusting for age, gender, and BMI z-score.

3.4 | Graft survival

After 473.9 person-years of follow-up, 13 (IR 70.8 per 1000 person-years, 95% CI 41.1, 121.9) had a graft failure in period 1 compared to 6 (IR 20.7 per 1000 person-years, 95% CI 9.3, 46.0) in period 2. Overall graft survival of patients in period 2 was better as compared to those in period 1 (log rank *P*=.005; Figure 1).

Two patients with vascular thrombosis lost their grafts within 2 weeks of transplant. The incidence rate of graft failure was significantly higher in children with early post-transplant complications (IR 86.6 per 1000 person-years, 95% CI 45.0, 166.4) as compared to those without (IR 27.2 per 1000 person-years 95% CI 14.7, 50.7; Figure 2). The cumulative incidence of graft survival at 1, 3, and 5 years' post-transplant was 96.5%, 92.6%, and 90%, respectively, in those without complications compared to 71%, 65.1%, and 58.6%, respectively, in children with complications.

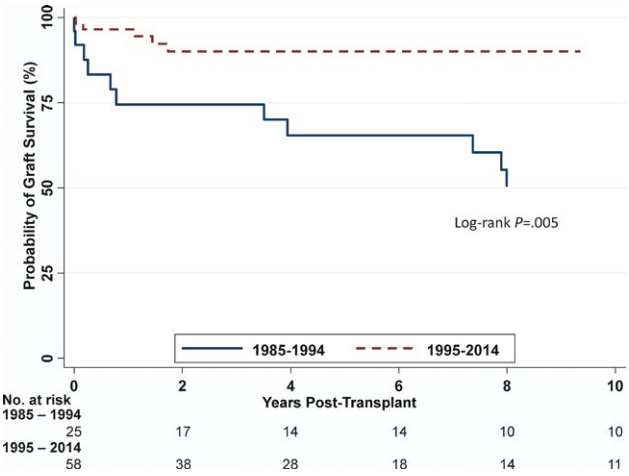

FIGURE 1 Kaplan-Meier curves for graft survival in pediatric kidney transplant recipients in period 1 (1985-1994) and period 2 (1995-2014)

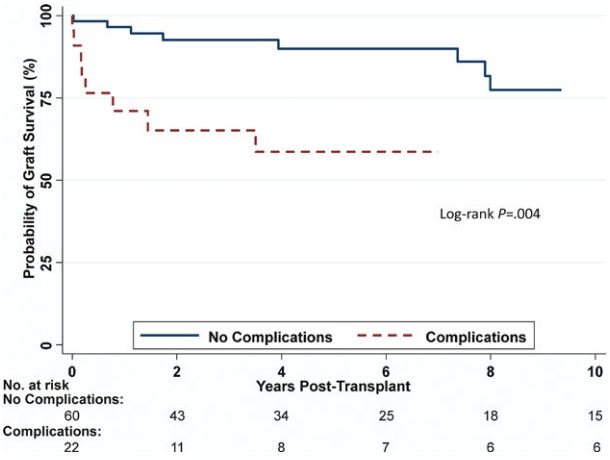

FIGURE 2 Kaplan-Meier curves for graft survival in pediatric kidney transplant recipients, stratified by post-transplant complications

4 | DISCUSSION

In this retrospective study in young kidney transplant recipients over the last three decades at a tertiary care center, we report an incidence of 26.5% for surgical complications within the first 30 days of transplant, with vascular complications being the most common. We also report a higher cumulative incidence and incidence rate of graft failure in children with early surgical complications. However, due to small sample size, we were not able to identify clinically significant risk factors that are associated with the surgical complications.

Renal transplantation in children less than 5 years of age is technically quite challenging and associated with increased mortality and graft loss.[6] There is a higher risk of post-transplant surgical complications in children, with an overall incidence between 1 and 33%.[7,8,9] Our study shows a risk of around 27%, which is consistent with the literature. The significantly reduced 1- and 5-year graft survival with early post-transplant complications in this study also highlights the importance of pretransplant screening for clinically significant risk factors in young children so that appropriate preventive steps can be taken well ahead in time.

Among all surgical complications, vascular complications are the most common and most severe in children, especially the younger age group with an estimated incidence of 4-18%.[10,11] Data from NAPRTCS reveal that graft thrombosis constitutes the main cause of graft failure in the first year.[12] The discrepancy in vessel size between donor and recipient and the presence of coagulation abnormalities are the main reasons for higher risk of graft thrombosis in young children receiving a kidney transplant. Hypovolemia, technical issues, and long cold ischemia time also contribute to graft thrombosis.[12]

In our study, vascular thrombosis was also the most common complication accounting for approximately 40% of these, with an overall incidence of around 11%. This highlights the main challenge in this

patient population, and the need to focus on preventive and early proactive interventions to address issues with allograft perfusion. We also analyzed various risk factors leading to early vascular complications in this cohort. Importantly, we studied the children with coagulation abnormalities.

Inherited and acquired prothrombotic factors have been identified to increase the risk for allograft vascular thrombosis and acute rejection episodes. Data on pediatric renal transplant recipients with abnormal coagulation profile are scarce.[13] In our cohort, 28 children were screened, and 10 (35.7%) were found to have either inherited or acquired coagulation abnormalities. Children with abnormal coagulation profile had 3 times higher odds of having a vascular complication but lacked power due to the small sample size. There are also no consensus recommendations on optimal anticoagulation prophylaxis in the peri-transplant period.

There are mixed reports[14,15] regarding the use of prophylactic heparin in pediatric kidney transplant recipients with or without thrombotic risk factors. Moreover, the duration of prophylactic therapy is also unclear.[16] A small study demonstrated no allograft thrombosis in 24 children who received prophylactic low-dose unfractionated heparin followed by aspirin compared to five cases of thrombosis among 63 historical controls (7.9%) who did not receive prophylaxis.[17] However, Kranz et al. also reported a cohort of 66 children who were screened for thrombophilia. Patients with thrombophilia received intensified anticoagulation through a combination of intravenous heparin, low-molecular-weight heparin, followed by aspirin for the first year. Patients without thrombophilia received only low-dose heparin and aspirin. There were no thromboembolic events in either group. The kidney function was comparable in both groups after 3 years of follow-up.[13] Unfortunately, our data suggest that despite more comprehensive evaluation and routine prophylaxis with systemic anticoagulation, thrombosis remains an important cause of graft loss.

There are important limitations to our study. The number of children in this age group is small, thus hampering the ability to detect important differences between groups. Data on important risk factors such as cold ischemia time, which could affect graft survival, are not available. However, compared to other pediatric renal transplant programs, we present a relatively large sample size of young renal transplant recipients spanning over a period of three decades. We also provide data on thrombophilia risk factors, which are known important predictors for graft thrombosis, yet lack power to show a significant benefit of prophylactic heparin on the vascular complications in children with abnormal coagulation profile.

5 | CONCLUSIONS

Early surgical complications after renal transplantation in young children are quite common and an important cause of graft failure and mortality. With improved surgical outcome and graft survival, kidney transplantation should be considered in young children. However, prevention of vascular complications requires further optimization. Prospective trials are required to determine the type, duration, and benefits of prophylactic anticoagulation therapy in young children.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

AUTHORS' CONTRIBUTIONS

Nathan Rodricks and Rahul Chanchlani: Data analysis, statistics, drafting the manuscript, and approval of article; Tonny Banh, Karlota Borges, Jovanka Vasilevska-Ristovska, Viral Patel, and Diane Hebert: Critical revision of article and approval of article; Armando J. Lorenzo and Rulan S. Parekh: Concept/design, critical revision of article, and approval of article.

ACKNOWLEDGMENTS

We gratefully acknowledge funding from the Transplant & Regenerative Medicine Centre (TRMC) Catalyst Grant at The Hospital for Sick Children, and Canadian Institutes of Health Research (CIHR). We would also like to thank Richard Child and Tony Pyle for their advice and insight into the electronic patient record at SickKids.

REFERENCES

1. Benfield MR, McDonald RA, Bartosh S, Ho PL, Harmon W. Changing trends in pediatric transplantation: 2001 Annual Report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant*. 2003;7:321-335.
2. North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS) 2014 annual transplant report. Available at: https://web.emmes.com/study/ped/annlrept/annualrept2014.pdf
3. Irtan S, Maisin A, Baudouin V, et al. Renal transplantation in children: critical analysis of age related surgical complications. *Pediatr Transplant*. 2010;14:512-519.
4. Shokeir AA, Osman Y, Ali-El-Dein B, El-Husseini A, El-Mekresh M, Shehab-El-Din AB. Surgical complications in live-donor pediatric and adolescent renal transplantation: study of risk factors. *Pediatr Transplant*. 2005;9:33-38.
5. Heap SL, Webb NJ, Kirkman MA, Roberts D, Riad H. Extraperitoneal renal transplantation in small children results in a transient improvement in early graft function. *Pediatr Transplant*. 2011;15:362-366.
6. Millan MT, Berquist WE, So SK, et al. One hundred percent patient and kidney allograft survival with simultaneous liver and kidney transplantation in infants with primary hyperoxaluria: a single-center experience. *Transplantation*. 2003;76:1458-1463.
7. Nuininga JE, Feitz WF, van Dael KC, de Gier RP, Cornelissen EA. Urological complications in pediatric renal transplantation. *Eur Urol*. 2001;39:598-602.
8. Almeida F, Branco F, Cavadas V, et al. Urological complications after 134 pediatric kidney transplants: a single-center study. *Transplant Proc*. 2013;45:1096-1098.
9. Rossi V, Torino G, Gerocarni Nappo S, et al. Urological complications following kidney transplantation in pediatric age: a single-center experience. *Pediatr Transplant*. 2016;20:485-491.
10. van Lieburg AF, de Jong MC, Hoitsma AJ, Buskens FG, Schroder CH, Monnens LA. Renal transplant thrombosis in children. *J Pediatr Surg*. 1995;30:615-619.

11. Vitola SP, Gnatta D, Garcia VD, et al. Kidney transplantation in children weighing less than 15 kg: extraperitoneal surgical access-experience with 62 cases. *Pediatr Transplant*. 2013;17:445-453.
12. Ponticelli C, Moia M, Montagnino G. Renal allograft thrombosis. *Nephrol Dial Transplant*. 2009;24:1388-1393.
13. Kranz B, Vester U, Nadalin S, Paul A, Broelsch CE, Hoyer PF. Outcome after kidney transplantation in children with thrombotic risk factors. *Pediatr Transplant*. 2006;10:788-793.
14. Broyer M, Gagnadoux MF, Sierro A, Fischer AM, Niaudet P. Preventive treatment of vascular thrombosis after kidney transplantation in children with low molecular weight heparin. *Transplant Proc*. 1991;23:1384-1385.
15. Nagra A, Trompeter RS, Fernando ON, et al. The effect of heparin on graft thrombosis in pediatric renal allografts. *Pediatr Nephrol*. 2004;19:531-535.
16. Parajuli S, Lockridge JB, Langewisch ED, Norman DJ, Kujovich JL. Hypercoagulability in kidney transplant recipients. *Transplantation*. 2016;100:719-726.
17. Esfandiar N, Otukesh H, Sharifian M, Hoseini R. Protective effect of heparin and aspirin against vascular thrombosis in pediatric kidney transplants. *Iran J Kidney Dis*. 2012;6:141-145.

How to cite this article: Rodricks N, Chanchlani R, Banh T, et al. Incidence and risk factors of early surgical complications in young renal transplant recipients: A persistent challenge. *Pediatr Transplant*. 2017;21:e13006. https://doi.org/10.1111/petr.13006