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Post-Transplant Blood Transfusions and Pediatric Renal Allograft Outcomes

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Abstract

The association of blood transfusions with graft survival after pediatric kidney transplant (KTx) is unclear. We retrospectively analyzed blood transfusions post-KTx and subsequent outcomes. Between 1984 and 2013, 482 children (<18 years of age) underwent KTx at our center. Recipient demographics, outcomes and transfusion data were collected. Cox regression with post-KTx blood transfusion as a time-dependent covariate was performed to model the impact of blood transfusion on outcomes. Of the 208 (44%) that were transfused, 39% had transfusion <1 month post-KTx; 48% > 12 months. Transfused and non-transfused recipients were not significantly different. In univariate and multivariate analyses, there was no difference between transfused and non-transfused recipient patient survival; antibody-mediated and acute cellular rejection, and donor-specific antibody (DSA) free survival. Transfusions <1 month post-KTx did not impact death-censored graft survival (DCGS) ($p=NS$). Patients transfused >12 months post-KTx had significantly lower 12 month estimated glomerular filtration rate (eGFR) (compared to non-transfused) and worse subsequent DCGS. Post-KTx blood transfusions have increased in pediatric KTx over time but have no negative association with rejection or DSA production. DCGS is unaffected by transfusion within first month. Transfusions after the first year occur in patients with more advanced chronic kidney disease and are associated with significantly worse DCGS.

Keywords

Transfusions; Donor-Specific antibodies; Sensitization; Graft-survival; Blood transfusions; Anemia

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Author Contributions

Priya Verghese: Participated in concept and research design, writing of the paper, performance of the research and data analysis

Kristen Gillingham: Performance of the research and data analysis

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Introduction

Early in the history of kidney transplantation, pre-transplant transfusions were reported to be associated with increased long-term graft survival (1, 2). but this was quickly proved to erroneous and in fact pre-transplant transfusions are now considered immunogenic and are avoided (3). Although there is an extensive body of literature on the impact of *pre-transplant* blood transfusions (1, 3–6) there is little information on the impact of post-kidney transplant (KTx) transfusions. Although recipients are on immunosuppression post-KTx, there is still the possibility of sensitization and development of donor specific antibodies (DSA), rejection, and decreased graft survival. An older study on the impact on post-KTx transfusions in 746 adults of which solid phase HLA antibody testing was available in 199 reported that 80% of the transfusions took place in the first month post-KTx; and the transfusions had no statistically significant impact on antibody formation, rejection or graft outcomes (7). Conversely, a very recent publication reported that early posttransplant blood transfusion was associated with increased DSA without increased rejection. Neither study included any children (8). Herein we report outcomes after post-KTx transfusions in children.

Materials & Methods

All clinical kidney transplant information is maintained on an University of Minnesota Institutional Review Board-approved database. Information entered into the database includes donor and recipient demographics, pre- and post-KTx co-morbidities, post-KTx rejections, infections, and graft outcomes. In addition, we have documented all blood transfusions given in the immediate post-operative period as well as those given months or years later (at our center or elsewhere). All pediatric KTx recipients were given leucocyte-depleted blood. Leucocyte depletion, washing and filtering occurred at the source, the American Red Cross.

Between 1984 and 2014, 482 consecutive children (<18 years of age) underwent KTx at our center. Immunosuppression protocols used at our center have been previously published (9–11). Protocols differed by era: Era 1 from 1984 to 1996 included Minnesota anti-lymphocyte globulin induction and maintenance immunosuppression with steroids, cyclosporine and azathioprine. In 1996, Era 2 included an immunosuppression protocol change to Thymoglobulin induction with steroids, mycophenolate mofetil and calcineurin inhibitor maintenance. In 2002, Era 3 was the initiation of a steroid avoidance protocol with Thymoglobulin induction and calcineurin inhibitor and mycophenolate mofetil maintenance in patients over 5 years of age with first or second transplants who were not on steroids at the time of KTx. Calcineurin inhibitor 12 hour trough targets were uniformly applied to all patients (tacrolimus 10–12, 8–10, 6–8, 4–6 mcg/L or cyclosporine 175–200, 150–175, 125–150 or 100–125 mcg/L for month 1–3, 4–6, 7–9 and >9 post-KTx as measured by high performance liquid chromatography).

We studied the impact of post-KTx blood transfusions on graft, DSA and rejection free survival and patient survival. Graft loss was defined as return to dialysis, pre-emptive second renal transplant or surgical removal of renal allograft and time to graft loss was calculated

for each patient. Our transplant database also tracks graft loss by linking to the UNOS database so even patients not followed in our center did have reliable data on graft loss. The date of last follow up was documented based on last available date of serum creatinine in the hospital database. Acute rejection was a categorical yes/no variable defined as yes if the patient was treated for rejection and no if not. In >90% of cases this diagnosis was based on allograft renal biopsy. Allograft biopsies were triggered by graft dysfunction, defined as serum creatinine >25% of baseline. All acute cellular rejection (ACR) episodes were biopsy proven and described as per Banff criteria [7, 8]. ACR was treated with steroid pulse and taper, or with lymphocyte depleting antibody if steroid resistant (Thymoglobulin®). Banff guidelines were updated for antibody-mediated rejection (AMR) in the late 1990s and were implemented and added to our center database in 2002. AMR was diagnosed when 2 of 3 findings (light microscopic changes of AMR, diffuse (>50%) C4d staining, or circulating DSA) were present; or when staining was diffusely C4d positive with otherwise unexplained graft dysfunction [9]. AMR was treated with 5 or more treatments of plasma exchange/ intravenous immunoglobulin, as needed. HLA antibody profiling of KTx recipients using solid phase, single antigen bead technology for Panel Reactive Antibody (PRA) and DSA (sequential testing with LABScreen® Mixed Antigen, PRA and Single Antigen assays (One Lambda, Inc.)) began in March 2006 at our center. Therefore only patients transplanted after 2006 (n=134) were included for the **Kaplan–Meier** probability estimate of AMR free and DSA free survival analysis and a sub-analysis **Kaplan–Meier** probability estimate of graft and patient outcomes was done on these kidney recipients. Estimated glomerular filtration rate (eGFR) was calculated at 6 and 12 months for all patients using the modified Schwartz formula (12).

Patients were classified as DSA positive if antibody was detected to any Class I or II Human Leucocyte Antigen at a mean fluorescence intensity >500.

This study was approved by The U of MN Institutional Review Board (Study Number: 1411E55944).

Statistical Analysis

Chi-square test was used for nominal variables. Actuarial graft survival, acute rejection free survival, DSA free and patient survival rates were computed by cox regression with post-KTx blood transfusion as a time-dependent covariate and hazard ratios calculated to model the effects of blood transfusion on KTx outcomes in univariate and multivariate analyses. The analyses were repeated by era – 1984–1995; 1996–2005 and 2006–present to account for changes in immunosuppression and definitions of AMR. Variables included in the multivariate model were age, sex, primary renal disease, donor type, duration of dialysis, KTx era and degree of HLA match. P values <0.05 were considered statistically significant. All statistical analyses were performed using SAS™ Software Version 9.2, Cary, NC, USA.

Results

Of the 482 pediatric KTx recipients, 223 (46%) had received blood transfusions post-KTx and 259 (54%) did not although the proportion of children transfused after KTx has significantly fluctuated through the years with a trend for increasing transfusions with time

[Figure 1]. Between 1984–95, 1995–2002 and 2002–14, 64 (31%), 57 (53%) and 102 (60%) recipients were transfused respectively. Of the 223 receiving transfusions, 39% were transfused within 1 month post-KTx; 13% between 1 and 12 months; and 48% >12 months [Figure 2]. Of the transfused patients; 74% were >10 years of age at KTx and 49% were female. The proportion of living and deceased donors transfused was not significantly different [Figure 2] but since we have performed more living donor kidney transplants, they were over-represented in all groups. Mean time to transfusion for deceased and living donor kidney recipients was 103 and 104 days respectively (p 0.9). There were no significant differences between recipients transfused and not in recipient age, race, cause of ESRD, number of previous transplants, delayed graft function, peak PRA, PRA at KTx, degree of HLA mismatch and donor type and demographics. There were a greater proportion of females and older donors in the transfused recipients than non-transfused [Table 1]. Compared to those not transfused, recipients transfused >12 months post-KTx had a significantly lower eGFR at 12 months post-KTx (mean eGFR 55.1+/- 25.6 for transfused; 87.5+/- 27.3 cc/min/1.73m², not transfused; p =0.002).

The effect of blood transfusions post-KTx on KTx outcomes is summarized in [Table 2]. For KTx recipients transfused at any time, in a univariate analysis where blood transfusions is a time dependent covariate, there was no difference between transfused recipients in patient survival and rejection-free graft survival; however, transfused patients had significantly worse graft survival (GS) and death-censored GS (DCGS) [Table 2]. Univariate analysis by era was not different. A multivariate analysis with included variables of age, sex, primary renal disease, donor type, duration of dialysis, KTx era, HLA match, had similar results.

In a sub-analysis of the 82 patients transfused within the first month, there was no significant difference between transfused and non-transfused patients in DCGS and GS [Figure 3]. In contrast, sub-analysis of the 100 recipients transfused after the first year post-KTx, continued to show significantly worse GS and DCGS for the transfused group [Figure 3]. Importantly, these patients had significantly worse eGFR at 12 months post-KTx (p 0.002) (prior to transfusion). We attempted to do a multi-variate analysis including eGFR but since this analysis had to be restricted to recipients with >=1 year graft survival without prior transfusions, the numbers were too small. There were too few patients transfused 1–12 months post-KTx to do a meaningful sub-analysis in this cohort.

The etiology of graft loss in transfused pediatric KTx recipients was more often chronic rejection [Table 3].

Role of Post-Transplant Blood Transfusions on Donor Specific Antibody Production and Antibody-Mediated Rejection

Since DSA testing was only initiated at our center in 2006, we restricted the analysis of AMR free survival and DSA free survival to the 134 transplants (82 transfused) done after 2006. The hazard ratios for the development of Class I or II DSA following a blood transfusion post-KTx was not significant (HR 0.9; 95% CI 0.6–1.4; p=0.65) regardless of whether the donor was living (HR 0.8; 95% CI 0.43–1.44; p=0.43) or deceased (HR 1.05; 95% CI 0.5–2.3; p=0.65) [Figure 4]. Similarly the hazard ratios for the development of

AMR following a blood transfusion post-KTx was not significant (1.6; 95% CI 0.65–4; $p=0.3$).

In this era, in a univariate analysis where blood transfusions is a time dependent co-variate, there was also no difference between transfused recipients in patient survival and (ACR)-free graft survival; however, as in previous eras and total analysis, transfused patients had significantly worse GS (HR 6.5; 95% CI 1.8–23.4; $p<0.0001$) and DCGS (HR 6.2; 95% CI 1.6–23.9; $p=0.008$). A multivariate analysis with included variables of age, sex, primary renal disease, donor type, duration of dialysis and HLA match, had similar results.

Discussion

Little is published on the effect of post-KTx blood transfusions and their effect on graft outcomes in children with functioning kidneys. Both leukocytes and red cells carry a significant HLA antigen load, and it is plausible that residual leukocytes and/or red cell HLA in the standard leukocyte-reduced blood units could pose as substrate for the formation of DSA to the kidney and thereby become an immunologic threat (13–15). However, all post-KTx patients are on chronic maintenance immunosuppression which could allay the increased theoretical rejection risk of blood transfusions or even be protective of the graft by immune down-regulatory effects.

To our knowledge, the only reports of the impact of post-KTx transfusions are of adult kidney recipients only (7, 8). Our findings are similar to theirs in some areas, different in others. In the older paper of 746 recipients transplanted between 2000–2005, there were more transfusions in DD KTx which we did not observe. They found that 80% of transfusions occurred in the first month and the recent publication in 423 adult recipients transplanted between 2008–2012 also had a median time to transfusion of 3 days. In our series it was 38% but we had a much longer follow up and so direct comparison is impossible. While it is possible that the pre-transplant hemoglobin in children is higher than adults given the smaller size of pediatric dialysis centers with a much lower physician to patient ratio, we do not have this data.

Scornik et al found no difference in GS whereas we report a decrease in GS and DCGS survival in transfused patients but once again our follow up was very long and most importantly all of our patients received thymoglobulin. When we restricted to recipients transfused in the first month we, like Scornik et al, found no difference in outcomes and perhaps our long-term outcomes may have been different in patients receiving lighter protocols for example with Basiliximab or no induction. Our decreased graft survival was associated with late transfusions (7) and it is unclear from our data whether the poor graft survival related to transfusions >1 year post-KTx was due to an impact of the transfusions or related to the fact that those getting transfusions already had significantly reduced eGFR. The requirement for late blood transfusions may be simply a function of the patient's approaching end stage renal failure with transfusions being a surrogate marker for end-stage renal disease requiring dialysis or erythropoietin therapy. It is therefore clear that post-KTx recipients require more vigilance for anemia with more aggressive pre-emptive therapies

such as surveillance and iron therapy to avoid and reduce the need for blood transfusions after KTx.

Finally; both previous publications found increased donor specific antibody in transfused recipients; we did not. But of critical importance is the marked difference in immunosuppression. In the Scornik study, specifics of immunosuppression were not given but induction varied between IL-2 blockers and Thymoglobulin. In the Ferrandiz study, only 12% of patients received Thymoglobulin contrary to our 100% and interestingly DSA production was noted to be significantly lower ($p\ 0.0007$) in patients treated with Thymoglobulin. Therefore we suggest that the lack of difference in DSA production in patients transfused and not in our center was quite likely due to our universal induction with Thymoglobulin.

We found a trend over time toward increasing transfusions particularly in the first month post-KTx over time which is supported by the Scornik paper (7) which showed transfusion rate of 51% in DD KTx, 30% in LD KTx in recipients transplanted between 2000–2005; compared to the more recent Ferrandiz study (8) in which 64% of recipients transplanted between 2008–2012 were transfused which is consistent with our most recent era data (2002–2014) of 60% transfusion rates. This is interesting since ever since the approval of recombinant human erythropoietin by the US Food and Drug Administration, erythropoiesis-stimulating agents have become the standard of care for the treatment of the anemia associated with advanced chronic kidney disease and end-stage renal disease. As a result, mean Hgb and hematocrit levels in patients with CKD, particularly those on dialysis, rose steadily and by 2006, 90 percent of patients maintained on chronic dialysis in the United States received ESAs, with a mean Hgb level among dialysis patients of 12.0 g/dL; two-thirds of all patients had Hgb levels between 11 and 13 g/dL (16). Thus patients presumably are coming to transplant with a higher Hgb. The increase in the proportion of patients transfused more recently might be explained by: 1. Our more potent immunosuppression and anti-viral prophylaxis with marrow suppressive side effects; 2. Our conservative avoidance of pre-KTx transfusions to avoid sensitization; 3. An increase in the degree of high-risk pediatric KTx performed (example KTx after BMT or malignancy) as we have become more adept in the field and outcomes have improved; 4. The recent increased erythropoietin use described above, especially in the children with advanced chronic kidney disease with / without dialysis, may be lowering iron levels/load at the time of transplant contributing to post-transplant anemia. Unfortunately, the exact indication for the blood transfusion in our series was not documented.

This study has obvious limitations of being retrospective and single-center as does both previous adult studies. Since it was a data-base review the exact indication for transfusions was not available. In addition since the study spans several years, there have been variations in our immunosuppressive management, anti-viral prophylaxis, and the introduction of Banff criteria modifying our interpretation of renal transplant pathology. There was increased graft loss due to chronic rejection in all eras but with changing Banff definitions, we are unable to confirm that this was a significant finding related to transfusions. In addition, although we did not demonstrate increased AMR or DSA following transfusions, we do not present data on subsequent transplants where there could be issues related to this

sensitization. Nevertheless this study provides very important prevalence data across time and is suggestive that we must as a pediatric nephrology community, must be more aggressive in our post-KTx anemia management in patients with advanced chronic kidney disease. It also provides suggestive evidence that the potency of immunosuppression in our pediatric KTx recipients is likely mitigating the immunogenic effects of transfusions after KTx and therefore there is not any observed decrease in DSA, AMR or ACR free survival.

In summary, blood transfusions after KTx in children are common, mostly in the first month and after the first year of transplant. Patients transfused after the first year post-KTx had significantly more advanced chronic kidney disease and therefore this likely contributed to the observed lower GS and DCGS in these patients. Therefore more vigilant anemia management in pediatric transplant recipients with advanced CKD and graft impairment is advisable. Transfusions are not associated with increased DSA, ACR or AMR while on standard immunosuppression protocols with or without steroids / calcineurin inhibitors.

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Abbreviations

KTx	Kidney transplant
AMR	Antibody-mediated rejection
ACR	Acute cellular rejection
DSA	Donor-specific antibody
DCGS	Death-censored graft survival
eGFR	Estimated glomerular filtration rate
PRA	Panel Reactive Antibody
HLA	Human Leucocyte Antigen
Hgb	Hemoglobin
GS	Graft survival
HR	Hazard ratio
aHUS	Atypical Hemolytic Uremic Syndrome

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Figure 1.
Transfusions over time

Figure 2.
Timing of blood transfusions in pediatric deceased and living donor KT_x.

Figure 3. Kaplan-Meier Death-Censored Graft Survival Curves for pediatric kidney transplant recipients in patients transfused in 1st month (Left panel) and after first year (Right panel)

Figure 4. Time to DSA in Pediatric Kidney Recipients after first blood transfusion (left panel) and 19 Kaplan-Meier DSA-Free Survival Curves in first year after transfusion (right panel)

TABLE 1

Demographics in patients transfused and not transfused after pediatric kidney transplant

	Post-Tx Blood Transfusion + (n=223)	NO Post-Tx Blood Transfusion (n=259)	P value
Age at Tx:			0.9
5–9 years	58 (26%)	72 (28%)	
10–14 years	82 (37%)	91 (35%)	
15–18 years	83 (37%)	96 (37%)	
Female	109 (49%)	98 (38%)	0.02
Caucasian recipient	192 (86%)	223 (86%)	0.3
Etiology of ESRD			0.4
Urologic / Anatomic	105 (47%)	103 (40%)	
Glomerular	59 (26%)	70 (27%)	
aHUS	7 (3%)	14 (5%)	
Pre-emptive dialysis	133 (60%)	162 (63%)	0.5
Donor Type:			0.08
DD	72 (32%)	97 (37%)	
LRD	124 (56%)	145 (56%)	
LURD	27 (12%)	17 (7%)	
Donor:			
Age (mean±SD) in yr	35.6±12.1	32.5±13	0.02
Caucasian Race	207 (94%)	239 (93%)	0.8
Female	107 (48%)	131 (51%)	0.5
Primary transplant	166 (74%)	187 (72%)	0.6
>3 previous transplants	0	5 (2%)	
Delayed Graft Function*	26 (12%)	33 (13%)	0.7
Peak PRA			0.18
0%	120 (54%)	129 (50%)	
51–100%	28 (13%)	47 (18%)	
PRA at Transplant			0.5
0%	128 (57%)	165 (64%)	
51–100%	19 (9%)	28 (11%)	
Degree of HLA mismatch			0.5
0	7 (3%)	22 (8%)	
1–3	131 (59%)	163 (63%)	
4–5	67 (30%)	56 (22%)	
6	18 (8%)	18 (7%)	

TABLE 2

Effect of Post-KTx Blood Transfusions on Pediatric Graft Outcomes

Effect of ANY Post-KTx Blood Transfusions on Pediatric Graft Outcomes						
	ALL (n=482)		Deceased Donor Recipients (n=169)		Living Donor Recipients (n=313)	
	Hazard Ratio (95% CI) ^d	P value	Hazard Ratio (95% CI) ^d	P value	Hazard Ratio (95% CI) ^d	P value
Graft Failure ^d	3.3 (2.5–4.3)	<0.0001	2.9 (2–4.4)	<0.0001	3.7 (2.6–5.2)	<0.0001
Death-Censored Graft Failure	3.5 (2.6–4.6)	<0.0001	3 (2–4.6)	<0.0001	3.5 (2.5–5)	<0.0001
Patient Death	1.4 (0.9–2.2)	0.1	1.2 (0.6–2.3)	0.5	1.6 (0.9–3)	0.08
Acute Cellular Rejection	0.9 (0.7–1.2)	0.5	1.2 (0.8–1.9)	0.4	0.8 (0.5–1.1)	0.2
MULTIVARIATE ANALYSIS ^b						
Graft Failure ^d	5.2 (3.9–6.8)	<0.0001	3.5 (2.2–5.5)	<0.0001	7.5(5.1–10.9)	<0.0001
Death-Censored Graft Failure	5.1 (3.7–6.8)	<0.0001	3.5 (2.1–5.7)	<0.0001	7.2 (4.9–10.8)	<0.0001
Patient Death	1.5 (0.9–2.4)	0.07	0.9 (0.4–1.8)	0.8	2.1 (1.1–3.8)	0.02
Acute Cellular Rejection	1.2 (0.8–1.7)	0.3	1.6 (0.96–2.8)	0.07	1 (0.7–1.6)	0.8
Antibody-Mediated Rejection ^c	1.6 (0.7–4)	0.3	0.8(0.4–1.4)	0.43	1.1(0.5–2.3)	0.65

^a CI = Confidence Interval^b Variables included in the multivariate model were age, sex, primary renal disease, donor type, duration of dialysis, eGFR, year of transplant, HLA match^c Analysis is restricted to 2006-present when DSA testing and latest Banff definitions were implemented at our center^d GS and DCGS were NOT significantly different in patients transfused <1 year post-KTx. Patients transfused >1 year post-KTx had significantly lower baseline eGFR prior to the transfusion

Table 3

Etiology of graft loss by era

	1984–1995 transfusion			1996–2002 transfusion			2002–present transfusion		
Cause of graft loss	+ n=64	– n=142	P 0.02	+ n=57	– n=50	P 0.003	+ n=102	– n=67	P 0.09
Acute rejection	0	11 (8%)		3 (6%)	2 (4%)		4 (4%)	1 (1.5%)	
Chronic rejection	30 (47%)	54 (38%)		15 (26%)	2 (4%)		8 (8%)	1 (1.5%)	
Disease recurrence	2 (3%)	8 (6%)		5 (9%)	2 (4%)		2 (2%)	2 (3%)	