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Rabbit antithymocyte globulin related decrease in platelet count reduced risk of pediatric renal transplant graft thrombosis

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Abstract: Graft thrombosis is a serious complication in pediatric renal transplantation. We assess a potential protective effect for the decrease in platelet count associated with RATG therapy against pediatric renal transplant graft vascular thrombosis. Between January 1986 and December 1998, 120 kidney transplants were performed in 95 pediatric recipients. Patients were divided into two groups. Group 1 (n = 61), non-RATG group received cyclosporine, azathioprine and steroids, while group 2 (n = 59), RATG group, received in addition, RATG at day 1 and continued for 4–10 days postoperatively. Platelet count prior to transplant, median change in absolute platelet count at 1 and 3 days post-transplant was recorded. Graft thrombosis incidence was examined. Six grafts (5%) developed thrombosis. All were in group 1 ($p = 0.028$). Median pretransplant platelet count ($\times 10^9$/L) in group 1 was 283 vs. 280 in group 2 ($p = 0.921$). Median decrease in absolute platelet count ($\times 10^9$/L) from pretransplant levels at one and three days post-transplant for group 1 and 2 was 18 vs. 83 ($p \leq 0.001$) and 39 vs. 105 ($p \leq 0.001$), respectively. Graft thrombosis risk factors were similar in both groups. RATG use was statistically significant ($p = 0.044$) for reduced risk of graft thrombosis in multivariate analysis. Patients receiving RATG showed significant decrease in both platelet count and graft thrombosis incidence. A role for RATG related effect on platelet count is assumed.

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The incidence of pediatric kidney graft thrombosis has been reported to be around 4.2% and varies from center to center (1). A higher incidence of graft thrombosis, up to 12% in pediatric *en bloc* deceased donor kidney transplants was reported (2). With the declining risk of acute cellular rejection as a cause of early graft loss, graft thrombosis is currently the most common cause of early graft loss in the pediatric population as stated in a recent report by the NAPRTCS (3).

RATG is a polyclonal antibody preparation widely used in transplantation as induction immunotherapy and for reversal of steroid resistant rejection. RATG has a pronounced effect on platelets causing marked decrease in platelet count (4). Platelets are a basic factor for the development of vascular thrombosis (5).

The aim of this study was to evaluate a potential role, for the drop in platelet count, commonly associated with RATG therapy, in

Abbreviations: ALG, anti lymphocyte globulin; APTT, activated partial thromboplastin time; ATG, antithymocyte globulin; CAPD, continuous ambulatory peritoneal dialysis; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; EBV, Epstein–Barr virus; ESRD, end stage renal disease; NAPRTCS, North American Pediatric Renal Transplant Cooperative Study; OKT3, orthoclone T3; PCP, *Pneumocystis carinii* pneumonia; PT, prothrombin time; PTLD, post-transplant lymphoproliferative disorder; PTT, partial thromboplastin time; RATG, rabbit antithymocyte globulin; RVT, renal vein thrombosis.

reducing the incidence of pediatric renal graft thrombosis performed at our center.

Materials and methods

Between January 1, 1986 and December 31, 1998, 120 deceased donor kidney transplants were performed in 95 pediatric recipients. These patients consisted of 53 males and 42 females and the mean age at transplantation was 12.4 yr (range from 2 to 17 yr). We divided patients into two groups. Group 1, non-RATG group (n = 61, transplant years 1986–1990), received cyclosporine, azathioprine and steroids. Group 2, RATG group (n = 59, transplant years 1991–1998), received in addition RATG at day 1 and continued for 4–10 days postoperatively. Mean age in group 1 was 11.8 yr (range 2–18) compared with 11.7 yr (range 2–17) in group 2 (p = 0.569). Table 1 illustrates cause of ESRD in the two groups.

Maintenance immunosuppression for the two groups consisted of cyclosporine, azathioprine and prednisolone. Cyclosporine dose was 500 mg/m^2 for children < 6 yr of age administered in three divided doses, and 15 mg/kg for older children administered in two divided doses. The dose of cyclosporine was adjusted to maintain a trough level of 250–300 ng/mL during the first post-transplant month and a trough level of 150–200 ng/mL thereafter. We aimed at the same cyclosporine trough levels during the whole study period. Cyclosporine assay used was the enzyme-multiplied immunoassay technique (Emit® 2000 Cyclosporine Specific Assay, Dade Behring limited, Milton Keynes, UK). Cyclosporine was started prior to implant in the two groups and continued postoperatively together with RATG in group 2. Azathioprine was given as a maintenance drug in a dose of 2 mg/kg/day with dose adjustment based on white cell counts. Prednisolone was tapered over a three months period following the transplant till the children were maintained on 5 mg alternate day dosing.

Table 1. Cause of ESRD

Cause of ESRD	Group 1	Group 2	Total
Glomerulonephritis (n = 32)			
FSGS	6	7	13
IGA nephropathy	1	1	2
MPGN	5	1	6
Rapidly progressing GN	3	3	6
Unspecified	5	–	5
Reflux nephropathy (n = 26)	17	9	26
Neurogenic bladder (n = 14)	6	8	14
Congenital nephrotic syndrome (n = 4)	0	4	4
Congenital and hereditary (n = 32)			
Medullary cystic disease	0	2	2
Cystnosis	2	0	2
Renal dysplasia	6	11	17
Multicystic kidneys	1	0	1
Bardet Biedl syndrome	2	0	2
Potters syndrome	0	1	1
Familial nephropathy (Finnish type)	2	1	3
Polycystic kidney disease	1	3	4
Miscellaneous (n = 12)			
Wilms tumor	0	2	2
Renovascular disease	0	1	1
HUS	2	1	3
SLE	1	0	1
Unknown	4	1	5
Total	61	59	120

FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; GN, glomerulonephritis; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus.

ATG; Fresenius® (Fresenius, HemoCare Immune Therapy GmBH, Gräfelfing, Germany) was given as 5 mg/kg IV over 4 h every 24 h for two doses followed by a dose of 2.5 mg/kg IV every 24 h for two to eight doses with the dose of RATG subsequently adjusted to maintain an absolute lymphocyte count of 0.1×10^9/L. Adjustment of the dose of RATG in the range of 20% was done if the desired absolute lymphocytic count was not achieved. In all our patients, RATG was administered via a central line. In none of RATG receiving patients, heparin was added to the infusion bag.

Patients on ATG with CMV, antibody-positive, donor-recipient combinations (i.e. D+/R−, D−/R+, D+/R+) received CMV prophylaxis of ganciclovir 2.5 mg/kg IV q 12 h. Patients after that continued on oral CMV prophylaxis, acyclovir 400 mg PO QDS for three months. Antifungal medication, fluconazole 3 mg/kg, was given as a prophylaxis and continued for the duration of therapy. We used smaller doses of cyclosporine if the cyclosporine trough level increased secondary to inhibition of the hepatic enzyme P450 by fluconazole. Reduction in cyclosporine dose was in the range of 30%. Bacterial and PCP prophylaxis was achieved with trimethoprim-sulphamethaxazole, pediatric suspension 240 mg/5 mL in young children or tablets in older ones, for six months. Patients in group 1 did not receive antiviral or antifungal prophylaxis. None of the patients in the two groups received post-transplant aspirin as a prophylaxis against graft vascular thrombosis. Routine preoperative transplant evaluation for children with renal failure awaiting renal transplantation included coagulation profile and assessment for bleeding and thrombophilia disorders (Protein C and S deficiencies).

Surgical technique

Kidney transplantation was performed in the standard way with midline transperitoneal approach in children ≤ 20 kg. In the setting of multiple renal veins, smaller ones were usually tied leaving one main renal vein draining the kidney. All recovered kidneys from different hospitals in our country are procured by one single team of expert surgeons. It is the same team that performed the transplant operation for these children at our national kidney transplantation center.

Statistical methods

Demographic and clinical characteristics were compared for the two groups using nonparametric Wilcoxon rank-sum and Fisher exact tests. Kaplan–Meier methods were used to construct survivor functions and group comparisons for survival outcomes were analyzed using the Wilcoxon (Breslow) test. A multi-factorial analysis of variance (ANOVA) model was used to determine if RATG use reduced risk of graft thrombosis in the study population. A p-value ≤ 0.05 was deemed to be significant. All of the analysis was conducted using Stata® (Version 8, College station, TX, USA).

Results

Median follow up time was eight yr (range 1 month to 15 yr). Median Hospital stay for

group 1 was 13 days (range 3–31) and for group 2 was 15 days (range 7–32, p = 0.490).

Overall actuarial 1, 3, 5 and 10 yr patient survival was 96%, 95%, 95% and 90%, respectively. Actuarial 1, 3, 5 and 10 yr patient survival for group 1 was 92%, 90%, 90% and 87% compared with 100%, 100%, 100% and 92% in group 2, respectively (p = 0.103).

Overall actuarial 1, 3, 5 and 10 yr graft survival was 76%, 69%, 64% and 49%, respectively. Actuarial 1, 3, 5 and 10 yr graft survival for group 1 was 62%, 57%, 51% and 36% compared with 90%, 82%, 79% and 69% in group 2, respectively (p = 0.014). Actuarial 1, 3, 5 and 10 yr graft survival for group 1 after exclusion of graft thromboses events was 72%, 67%, 60% and 42%, respectively (p = 0.070). Causes of failure in each group are summarized in Table 2.

Following reviewing pretransplant evaluation records, we did not notice any tendency for either group to have increased incidence of bleeding or thrombophilia disorders. Pretransplant, the median value of PT in group 1 was 13.7 s (range 11–16.9) compared with 13.5 s (range 11.9–16) in group 2 (p = 0.262). Pretransplant, the median value of partial thromboplastin time (PTT) in group 1 was 31.5 s (range 22.4–60.1) compared with 32.3 s (range 11.3–41.4) in group 2 (p = 0.901).

Details of thrombosed grafts

Six grafts (5%) developed thrombosis. All were in group 1 (p = 0.028). Five grafts developed RVT, three in the first postoperative day and the others at 5 and 6 postoperative day. One graft developed renal arterial thrombosis on day 1 post-transplant. All thrombosed grafts removed with no obvious technical problem in these kidneys. Also, there was no evidence of acute vascular rejection in these kidneys as confirmed by histological examination following allograft nephrectomy and pretransplant panel reactive antibodies did not rise in these patients. Patients developing graft thromboses were also examined for common types of thrombophilia and none of them was found to be affected by these disorders.

Table 2. Cause of graft failure

	Group 1	Group 2
Rejection		
Acute	12	2
Chronic	12	8
Total	24	10
Graft thrombosis	6	–
Recurrence of the primary disease	2	1
Primary non-function kidney	3	–
HUS	–	1
Unknown	2	–
Death with a functioning graft	2	1
Total	39	13

HUS, hemolytic uremic syndrome.

Table 3. Distribution of common graft thrombosis risk factors between the two groups

Variable	Group 1	Group 2	p-value
Recipient age			
≤ 5 yr	7	7	0.585
>5 yr	54	52	
Donor age			
≤ 6 yr	4	0	0.070
>6 yr	57	59	
Renal replacement therapy			
HD	16	16	0.501
CAPD	31	25	
Pre-emptive	14	19	
Primary/retransplant	11/50	17/42	0.198
Mean HLA mismatch ± s.d.	2.54 ± 1.26	2.78 ± 1.04	0.393
Mean CIT ± s.d.	21.46 ± 5.69	21.537 ± 0.07	0.505
Mean PRA (%) ± s.d.	10.32 ± 19.9	15.94 ± 26	0.600
DGF	3	3	1.000
Nephrotic syndrome	0	4	0.070
Renal dysplasia	6	11	0.543

HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis; HLA, human leukocytic antigen, CIT, cold ischemia time; s.d., standard deviation; PRA, panel reactive antibodies; DGF, delayed graft function.

Table 4. Risk factors for graft thrombosis in group 1 patients

Patients	1	2	3	4	5	*6
Risk factor						
Transplant number	1st	1st	1st	1st	1st	1st
Donor age (yr)	13	1	27	59	40	40
Recipient age (yr)	2	4	9	15	18	8
CIT (h)	N/A	N/A	17	20	26	26
Mode of dialysis	CAPD	CAPD	CAPD	Pre-emptive	CAPD	CAPD
DGF	No	No	Yes	No	No	No
Intra-operative complication	No	No	No	No	No	No

*Arterial thrombosis.
CIT, cold ischemia time; CAPD, continuous ambulatory peritoneal dialysis; N/A not available; DGF, delayed graft function.

Distribution of the common risk factors for graft thrombosis in the two groups was similar (Table 3). Details of six patients with graft thrombosis in group 1 in relation to common risk factors for pediatric kidney transplant vascular thrombosis are illustrated in Table 4. Results of a multi-factorial ANOVA model are illustrated in Table 5.

Platelet count

There was no difference in median platelet counts ($\times 10^9$/L) between the two groups prior to transplant, 283 (range 79–529) in group 1 compared

Table 5. ANOVA model for variables influenced incidence of graft thrombosis in study population

Variable	p-value
Recipient age (≤ 5 yr)	0.441
Donor age (≤ 6 yr)	0.541
Retransplants	0.470
High PRA (≥30%)	0.803
CIT (≥24 h)	0.356
Acute rejection	0.627
CAPD	0.842
RATG	0.044

CIT, cold ischemia time; CAPD, continuous ambulatory peritoneal dialysis; PRA, panel reactive antibodies; RATG, rabbit antithymocyte globulin.

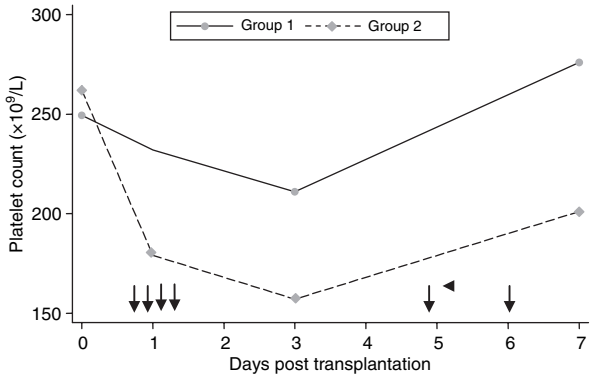

Fig. 1. Median change in platelet count post-transplant. ↓: graft thrombosis events in group 1.

with 280 (range 141–614) in group 2 ($p = 0.921$) The median drop in absolute platelet count ($\times 10^9$/L) at day 1 post-transplant in group 1 was 18 vs. 83 in group 2 ($p \leq 0.001$). The median drop in absolute platelet count at day 3 post-transplant in group 1 was 39 vs. 105 in group 2 ($p \leq 0.001$). The drop in platelet count associated with RATG use was not accompanied by an increased rate of platelet transfusion in group 2. Median drop in platelet count as well as times of graft thrombosis are illustrated in Fig. 1.

Complications

Eight infectious complications occurred in group 1 (bacterial in six and viral in two). Twelve infectious complications occurred in group 2 (bacterial in six and viral in six). There was no difference between the two groups in terms of increased risk of infection ($p = 0.334$). At a median follow-up time of eight yr there was no case of PTLD in either group.

Discussion

Graft thrombosis remains an important cause of graft failure in pediatric kidney transplantation (3). Many risk factors had been implicated as a cause of pediatric renal transplant vascular thrombosis, including; young recipients, use of pediatric donor kidneys, delayed graft function, prior transplant, lack of prophylactic use of T cell antibody (1), use of CAPD (3), technical cause as placing the venous anastmosis too low such that the vein and graft will be compressed or torsion of the transplanted kidney (6), early use of cyclosporine (7), immune mechanisms and unstable volemia (8), nephrotic syndrome (9) have all been implicated as a cause of graft thrombosis. The peak incidence of graft thrombosis is between three and nine days post-transplant. Although specific cases of graft salvage have been reported, graft thrombosis eventually result in graft loss (10).

ATG is a polyclonal anti T cell antibody used in induction immunotherapy and as a treatment of steroid refractory rejection. ATG has a well documented effect on platelet causing thrombocytopenia, possibly because of common antigens on thymocytes and platelets (11). Historical reports have pointed to a possible role of ATG in inducing vascular thrombosis (12). However recent basic science research provides new facts. Inbal et al. (13) studied the coagulation profile in patients receiving ATG based conditioning treatment for allogeneic stem cell transplantation. The authors did not find any difference in several thrombophillia markers, total and endothelial microparticles as well as other inflammatory mediators between patients who received ATG compared with those who did not. Also, ATG did not seem to affect pro coagulant levels with no prolongation in PTT, APTT with a significant decrease in platelet count in ATG treated patients that was not associated with any DIC. Pilhusch et al. (14) reported similar results.

Historically increased risk of thrombosis in patients receiving high dose of OKT3 induction immunotherapy was reported (15). More recently, Thibaudin et al. (16) confirmed the relative safety of the conventional doses of ATG used as induction immunotherapy in kidney transplantation. Also, the concept of adding antiplatelet medication in the early post-transplant period to reduce the risk of vascular thrombosis is well documented (17). In addition, Singh et al. (1) in a NAPRTCS report concluded that ALG was protective against graft vascular thrombosis in both living and deceased donor pediatric kidney transplant recipients. A possible explanation to this observation was not given.

We have mentioned the role of platelets in graft thrombosis together with the effect of RATG on platelets and the NAPRTCS report

pointing to the reduced risk of pediatric renal transplant graft thrombosis with ATG. The absence of graft thrombosis in group 2 patients can be attributed to the significant drop in platelet count in group 2. In our report, the drop in platelet count was most marked during the most critical time for pediatric renal graft thrombosis with all of the graft thrombosis events in group 1 occurring during this early post-transplant period. We believe the decrease in platelet count helped to reduce risk of graft thrombosis in the setting of other risk factors for thrombosis. As post-transplant, trimethoprim-sulphamethaxazole preparation was given routinely in both groups, the marked drop in platelet count in group 2 was mainly secondary to the use of RATG. We do not add heparin to the RATG infusion bag and we do not prescribe routine postoperative asprin prophylaxis to our pediatric renal transplant recipients. Added to this, all our deceased donor kidneys are locally procured with one transplant team. Following transplant nephrectomy for thrombosed grafts, acute vascular rejection was not confirmed in any of the six thrombosed kidneys and there was no obvious technical problem. Also, the overall graft survival in the non-RATG recipient group improved after exclusion of the thromboses events.

In this report, the distribution of vascular thrombosis risk factors was similar in the two groups with the use of RATG reducing risk of graft thrombosis in multifactorial analysis. There was absence of young donors (≤ 6 yr) in group 2 compared with group 1 (four donors), with one of the thrombosed grafts in group 1 from donor <6 yr. However, the incidence of nephrotic syndrome and re transplant, both risk factors for pediatric renal transplant graft thrombosis were higher in group 2 than group 1.

In our experience, judicious use of low dose RATG with the emphasis on intradermal testing for allergy prior to RATG administration together with the close daily monitoring of platelet, total leukocytic and lymphocytic counts resulted in a safe and excellent outcome to RATG with none of the patients in group 2 developed RATG related allergy. RATG had been reported the least of the polyclonal antibody preparations to cause cytokine release reaction (18).

In group 2 patients, we attempted to manage marked reduction in platelet count by either reducing or holding RATG for one or two doses. As shown in Fig. 1, the drop in platelet count in group 2 was in a relatively safe range. We did not encounter a case of serious postoperative bleeding and the use of RATG did not significantly increase the rate of platelet transfusion.

One criticism of the use of ATG was the marked increase in post-transplant infections. This had been reported by Dharnidharka et al. (19). Another criticism is the potential of increased risk of PTLD with induction immunotherapy (20). However there are reports of the efficacy of ganciclovir as a prophylaxis for EBV infection and PTLD (21). In a recent report, RATG was not associated with an increased risk of PTLD in pediatric renal transplantation (22).

Two possible criticisms to our study are the retrospective nature and the fact that these were consecutive rather than contemporaneous cases. We also acknowledge that the newer, better tolerated monoclonal IL-2 receptor antagonists are increasingly preferred over RATG in pediatric renal transplantation. Although the former have not yet proven to be more effective or to have less remote toxic side-effects than RATG (18). Our report, we hope, draws the attention for the need for further prospective trials attempting to explain the reported reduced risk of graft thrombosis with the use of T cell antibody preparation in pediatric renal transplantation (1).

We also address that improvements in surgical technique and postoperative patient care may account for some reduction in graft thrombosis risk encountered in group 2. However, part of the overall improvement in patient care, actually was the introduction of RATG to our immunosuppressive protocol.

Conclusions

This study was conducted on our pediatric kidney transplant recipients, a population in which induction immunotherapy is of immense importance for graft survival. The highest risk for both acute rejection and graft thrombosis is in the early post-transplant period. RATG helped our patients through reducing risk of acute rejection and may have reduced the risk of graft thrombosis by reducing platelet count early following the transplant.

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