Protective Effect of Heparin and Aspirin Against Vascular Thrombosis in Pediatric Kidney Transplants

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Introduction. This study was conducted to evaluate preventive effect of a combination of heparin and aspirin on vascular thrombosis and kidney transplant outcomes of pediatric kidney transplant recipients.
Materials and Methods. Twenty-four pediatric kidney transplant recipients received heparin, 50 U/kg, every 8 hours for 7 postoperative days, and aspirin, 5 mg/kg, thrice a week from day 3 of transplantation for 3 months. These patients were compared with a matched group of pediatric kidney allograft recipients in terms of development of thrombosis and serum creatinine level at 1 year postoperation.
Results. The mean age of patients was 9.4 ± 3.2 years. No vascular thrombosis was developed among the 24 patients with anticoagulant therapy, while in the control group, 5 grafts (7.9%) developed thrombosis (P = .19). Serum creatinine levels at 1 year were lower in the children with anticoagulant therapy as compared with the controls (P = .02).
Conclusions. Our study revealed a reduction in kidney allograft thrombosis incidence in children who received heparin and aspirin after transplantation, which was clinically important although the difference was not statistically significant. Lower serum creatinine levels as compared with a historical cohort group were seen 1 year after transplant surgery. These findings are required to be confirmed by further studies.

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INTRODUCTION

Kidney transplantation is a treatment of choice for children affected with end-stage renal disease (ESRD). However, the risk of graft failure is still a great challenge in the management of these patients. According to the North American Pediatric Renal Transplant Cooperative Study, vascular thrombosis is the 3rd common cause of kidney allograft loss, causing 12.8% of total graft failures.[1,2] Graft loss risk factors deriving from thrombosis include younger recipient age (< 2 year), younger donor age (< 5 year), and long cold ischemic (> 24 hours) in cadaveric donors.[2] In addition, while antilymphocyte therapy reduces the risk of thrombosis,[3] continuous ambulatory peritoneal dialysis as pretransplant dialysis modality, occurrence of acute tubular necrosis, history of a previous transplantation (for recipients of living donor organs), hypotension or hypertension, pre-operative high urine production, previous nephrectomy, and early cyclosporine therapy are of other risk factors of thrombosis in pediatric transplantation.[4] Given the irreversibility nature of graft thrombosis, which results in nephroctomy,

prevention could be the most important measure to protect the graft.

To lessen the potential risk of thrombosis in pediatric transplantation, various studies have been conducted, recommending screening studies be performed for thrombotic risk factors and thrombophilia in all kidney transplantation patients,[5-7] such as protein C, protein S, and antithrombin III deficiency; factor V Leiden mutation (*FV506Q*), prothrombin mutation (*G20210A*), mutation in the *MTHFR* gene (*C677T*), and antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulants).[8-10] Administration of different medications in high-risk patients, especially with thrombophilia, are suggested including unfractional heparin and low-molecular weight heparin (LMWH),[11-13] followed by various combinations of warfarin or aspirin[14,15] on a prophylactic basis and even in case of finding no risk factors at all.

This study was conducted to evaluate 1-year effects of prevention of graft thrombosis after kidney transplantation using heparin and aspirin through measuring serum creatinine levels and graft survival rates.

MATERIALS AND METHODS

A noncontrolled trial study was conducted from 2007 to 2008 at Shahid Labbafinejad Medical center. Twenty-four pediatric kidney transplant recipients from living donors in 2007 received heparin and aspirin, according to the current protocol, aiming at preventing from graft thrombosis. All of the patients were well informed and provided consent. Heparin, 50 U/kg, was administered every 8 hours, for 7 postoperative days and aspirin, 5 mg/kg, thrice a week, from day 3 of transplantation for 3 months. Hemorrhagic and other side effects, including thrombocytopenia and hyperkalemia for heparin and gatrointestinal problems for aspirin were monitored.[16,17] For the first week, the prothrombin time was maintained to less than 1.5 times as high as the normal level.

An age- and sex-matched control group was selected from among recent pediatric kidney transplant recipients at the same center. Baseline data including age, gender, weight, mean donor age, causes of kidney failure, hematuria, proteinuria, pretransplant dialysis modality, and donor source were collected. Variables were compared between the two groups using the *t* test, chi-square test, and Mann-Whitney U test, where appropriate. The Kaplan-Meier method was used for the survival analyses, and the two groups were compared using the Breslow test. A *P* value less than .05 was considered significant.

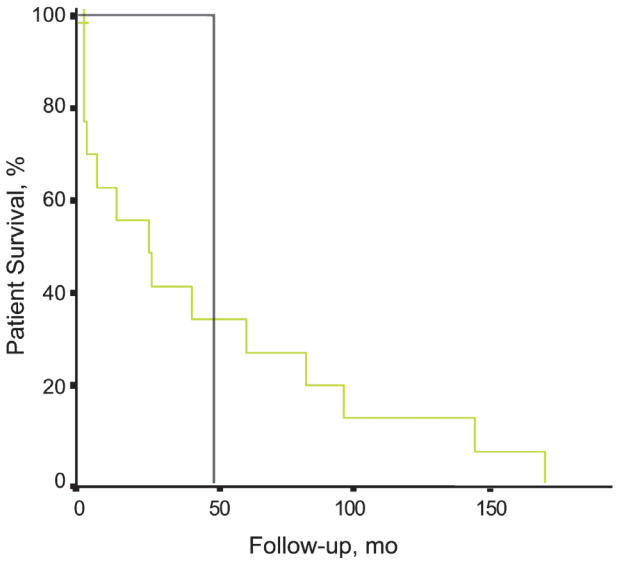
RESULTS

Twenty-four children who received a kidney transplant completed a 3-month prophylaxis therapy with heparin and aspirin after kidney transplantation. They were compared with 63 age- and sex-matched pediatric kidney transplant recipients who had not received postoperative heparin or aspirin therapy. The two groups were comparable for recipient's body weight, urine volume, serum creatinine level, cause of kidney failure, age and sex of donors, donor-recipient age and sex differences, diethylenetriaminepentaacetic acid renal scintigraphy results, and dialysis modality before transplantation (Table 1). All of the transplants were from living unrelated donors except for 3 in the control group whose donors were living related.

All of the participants in the study group were followed up for 24 months. The maximum follow-up period was 170 months for the controls. All the patients in the study group who were not lost to follow-up survived during the 48 months of follow-up period. However, the mean survival

Table1. Baseline Characteristics of Pediatric Kidney Transplant Recipients With and Without Anticoagulant Therapy

Parameter	Group		Mean Difference (95% CI)	*P*
	Study	Control		
Age, y	9.67	10.49	-0.82 (-2.38 to 0.73)	.29
Sex				
Female	11 (45.8)	24 (38.1)	…	
Male	13 (54.2)	39 (61.9)	…	.51
Weight, kg	24.83	25.78	-0.95 (-6.43 to 4.52)	.73
Donor-receiver age difference, y	18.25	16.02	2.23 (-0.33 to 4.80)	.09



Patient survival functions of pediatric kidney transplant recipients with and without anticoagulant therapy.

time in the control group was 46.35 ± 14.77 months. Comparison of the survival rates showed no significant differences between the two groups (P = .49). Survival rates at 1, 2, 5, and 10 years were 75%, 56%, 38%, and 19%, respectively in the control group (Figure).

Serum creatinine level at 1 year was significantly lower in the study group than that in the control group (P = .02). Kidney allograft failure developed in 1 patient (4.2%) in the study group and 15 (23.8%) in the control group (P = .03). Vascular thrombosis had been documented in 5 patients (7.9%) in the control group, while none of the children in the study group experienced thrombosis (P = .19; Table 2).

DISCUSSION

In order to decrease the risk of thrombosis, we used a low dose of unfractional heparin followed by aspirin. No case of thrombosis was developed in our 24 pediatric kidney transplant recipients, while 5 cases of thrombosis were reported among 63 patients of a historical control group. Moreover, the 1-year posttransplant serum creatinine level was found to be significantly lower than that in the control group.

Early graft loss driven by acute thrombosis is an important and fairly ever increasing complication in pediatric kidney transplant.[1,2] To lessen the potential risk, various studies have been conducted recommending screening studies be performed for thrombotic risk factors and thrombophilia in all kidney transplantation patients, such as protein C, protein S, and antithrombin III deficiency; factor V Leiden mutation (*FV506Q*), prothrombin mutation (*G20210A*), mutation in the *MTHFR* gene (*C677T*), and antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulants).[5-10] Prophylactic administration of anticoagulant agents in high-risk patients is also suggested.[11-16] However, the optional schedule for initiating early systemic postoperative anticoagulation in kidney allograft recipients remains to be determined.

In a study by Murphy and colleagues[16] on adult patients, 105 recipients of cadaveric kidney transplant received aspirin (150 mg/d) for 3 months and were compared with 121 patients as a control group. This study showed significantly lower rates of allograft thrombosis and chronic allograft nephropathy (biopsy proven) in the aspirin-receiving group. This is the only available study that not only examined the coagulants effects on thrombosis risk, but also studied their effects on longer-term complications of the kidney transplantation. Failure to perform needle core allograft biopsies on the patient caused that comparison of serum creatinine level was to be done 1 year after transplantation between the two groups. Concordant with Murphy and colleagues' study, we demonstrated that the suggested therapy

Table 2. Outcomes of Pediatric Kidney Transplant Recipients With and Without Anticoagulant Therapy

Parameter	Group		Mean Difference (95% CI)	*P*
	Study	Control		
Posttransplant creatinine change, mg/dL	-6.05	-6.42	0.37 (-1.14 to 1.87)	.62
Posttransplant urinary volume change, mL	1347.92	951.67	396.25 (-0.53 to 793.03)	.50
Serum creatinine at 1 year, mg/dL	1.6	2.55	-0.95 (-1.04 to -0.86)	.02
Graft failure	1 (4.2)	15 (23.8)	…	.03
Acute tubular necrosis	7 (29.2)	14 (22.2)	…	.28
Thrombosis	0	5 (7.9)	…	.19

not only decreased thrombosis rate, but also revealed an optimum effect on long-term outcome of the patients. In another study by Robertson and colleagues,[15] the aspirin prophylactic effect against renal vein thrombosis significantly decreased thrombosis incidence rate (6 cases of renal vein thrombosis out of 480 grafts compared with 27 cases out of 475 cases in the control group). The long-term complications of transplant were not studied in this study. Both studies were conducted on adults. Given the significant reduction of thrombosis rate in abovementioned studies, we selected aspirin as a prophylactic agent followed by administrating heparin during the first week for reduction of thrombosis rate, which is seen in higher rates among children. The unfractionated heparin was employed instead of LMWH, owing to the potential kidney dysfunction in the early days after transplant and hemorrhagic complications.

Nagra and colleagues[11] found no difference in early kidney allograft thrombosis with perioperative heparin (12 of 128 pediatric kidney transplant recipients receiving perioperative heparin versus 14 of 126 children undergoing transplant without heparin). After heparin withdrawal, they did not continue employing other agents (such as aspirin), which could possibly explain lack of a significant effect in their study, as compared to better results by using anticoagulant in our study (heparin and aspirin). Kranz and colleagues[19] examined patients with a hypercoagulable state (thrombophilia) and used heparin and aspirin for patients revealing no risk factor. However, for thrombophilia-inflicted group, heparin for 14 days, LMWH for 8 weeks, and finally aspirin were employed consecutively for a duration of 1 year finding no case of thrombosis in these two groups. No significant difference was found between these two groups in terms of creatinine serum level. In our study, the thombophilia state of the patients was not examined and a same treatment was employed for all, which showed acceptable results.

Dick and associates[20] used heparin or agratroban (for one patient who suffered from heparin-induced antibody) followed by switching to LMWH or cumarin for long-term therapy, resulting a zero prevalence of the thrombosis. Lack of thrombotic events history among our patients made us to believe using such a therapy could increase the potential of hemorrhagic complications. Long-term outcome of the patients is not discussed in this study. In contrast to Broyer and colleagues[14] and Shullo and coworkers[18] studies, hemorrhagic complications necessitating blood transfusion or re-exploration with heparin therapy at this dosage were not seen. No case of heparin-induced thrombocytopenia or lymphocele were found among the patients.

Our study was not a randomized controlled trial and it is unlikely that such a trial would be undertaken due to such a low number of patients. Only a large multicenter randomized trial can determine the safety, efficacy, and optimal duration of the therapy with heparin and aspirin for the prevention of kidney allograft thrombosis.

CONCLUSIONS

Our study revealed a reduction in kidney allograft thrombosis incidence in children who received heparin and aspirin after transplantation, which was clinically important although the difference was not statistically significant. Lower serum creatinine levels as compared with a historical cohort group were seen 1 year after transplant surgery. These findings are required to be confirmed by further studies.

CONFLICT OF INTEREST

None declared

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