Mean Platelet Volume as a Potential Predictor of Renovascular Thrombosis After Renal Transplant

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Abstract

Objectives: **We sought to evaluate the importance of mean platelet volume as a marker to follow-up, the tendency for hemorrhagic diatheses, and/or thrombotic complications in patients before and after renal transplant.**

Materials and Methods: **Thirty-four patients (aged, 5 to 18 y) were included. Demographics of the patients, cause of chronic renal failure, dialysis modality, duration of dialysis, arterio-venous fistula thrombosis, and posttransplant immunosuppressive regimens were recorded and laboratory variables were evaluated.**

Results: **At the end of the first posttransplant month, mean platelet volume level was decreased significantly when compared with pretransplant levels (8.3 ± 1.5 vs 7.7 ± 0.9; *P* = .04). A significant increase was observed in platelet levels during posttransplant measures (273.750 ± 97.700 vs 318.740 ± 84.586; *P* = .02). Prothrombin time and partial thromboplastin time levels did not differ before and after transplant. None of the patients had any thrombotic events and/or renal allograft loss. A negative correlation was observed between mean platelet volume and C-reactive protein (r=-0.53). Mean platelet volume level was not found to be related to the cause of renal failure, pretransplant dialysis modality, or posttransplant immunosuppressive regimens.**

Conclusions: **Platelet numbers increased and mean platelet volume decreased after pediatric renal transplant, but the potential for increased thrombosis was not observed.**

Key words: *Mean platelet volume, Renovascular thrombosis, Renal transplant, Allograft loss, Childhood*

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Introduction

Renal diseases are associated with a host of hematologic abnormalities affecting erythropoiesis, thrombopoiesis, platelet function, coagulation, fibrinolysis, and immune function.[1] Platelet dysfunction is the main factor responsible for hemorrhagic tendencies in advanced kidney disease and occurs both as a result of intrinsic platelet abnormalities and impaired platelet-vessel wall interaction. Uremic toxins, anemia, dialysis, the accumulation of medications owing to poor clearance, and anticoagulation used during dialysis have some role in causing impaired hemostasis in end-stage renal disease patients. Dialysis may partially correct these defects, but it cannot totally eliminate the risk of hemorrhage. On the other hand, the hemodialysis process itself can contribute to bleeding and/or thrombosis through the continual platelet activation induced by the interaction between blood and artificial surfaces. However, despite decreased platelet function, these patients have a high prevalence of cardiovascular and thrombotic complications.[1-6]

Today, kidney transplant is the preferred modality for treating patients with end-stage renal disease. Kidney transplant may reverse those hemorrhagic diatheses and/or thrombotic complications. Despite cause, renal transplant

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patients are at increased risk of developing thromboembolic events, such as deep vein thrombosis and renovascular thrombosis after an allograft. These events can be caused by a prothrombotic state generated by the use of immunosuppressive agents, although other risk factors such as acquired or inherited disorders of the clotting system may increase the risk of thrombosis.[7] Recent studies have reported that not only the number of platelets but also mean platelet volume (MPV) may play a decisive role in various diseases, and measuring MPV has predictive values for risk of bleeding tendency and thrombosis.[8,9]

To the best of our knowledge, no study has investigated platelet function, measured as MPV, as a risk factor for renovascular thrombosis after kidney transplant. To address this question, we sought to evaluate the importance of MPV as a marker to follow the tendency toward hemorrhagic diatheses and/or thrombotic complications in patients before and after renal transplant.

Materials and Methods

This was a prospective study of 34 pediatric patients with a diagnosis of chronic renal failure who had undergone a kidney transplant under the care of pediatric nephrology unit at Baskent University Faculty of Medicine over a 2-year period.

The demographic characteristics of the patients (age, sex, weight), cause of chronic renal failure, dialysis modality, duration of dialysis, arterio-venous fistula thrombosis, posttransplant immunosuppressive regimens were recorded, and laboratory parameters including hemoglobin, hematocrit, mean corpuscular volume, red cell distribution width, white blood cell, platelet counts, MPV, prothrombin time, partial thromboplastin time, C-reactive protein, blood urea nitrogen, creatinine, electrolytes, albumin, alanine aminotransferase, and aspartate aminotransferase were evaluated. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. Written, informed consent was obtained from all patients.

Biochemical and hematologic parameters and platelet markers were evaluated immediately before transplant in blood samples taken from morning hours in peritoneal dialysis patients and before dialysis sessions in hemodialysis patients, and at the first posttransplant month. Full blood counts (in K_3 EDTA) of all patients were measured on a Coulter Abbott Cell-Dyn 3700 system (Abbott Diagnostics, Santa Clara, CA, USA). Ranges of 7 to 12 fL were considered to be normal for MPV values.

Statistical analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 11.0, IBM Corporation, Armonk, New York, USA). Chi-square and pared *t* tests were used and possible correlations between variables were tested by Pearson product moment correlation analysis. Data are given as means ± SD or median (minimum-maximum) for descriptive statistical measures and a value for $P < .05$ was considered statistically significant.

Results

Thirty-four patients (16 female, 18 male; age range, 5 to 18 y; median age, 15 y) with chronic renal failure who were underwent kidney transplant were included in this study. Before transplant, 18 of 34 patients (52.9%) were on hemodialysis, 13 (38.2%) were on continuous ambulatory peritoneal dialysis, and 3 (8.8%) were free of any dialysis modality. The demographic characteristics of the patients (age, sex, weight), the cause of chronic renal failure, dialysis modality, duration of dialysis, arterio-venous fistula thrombosis, posttransplant immunosuppressive regimens, and laboratory parameters were evaluated (Table 1).

Table 1. Demographic Findings of Patients

N=34	n (%)
Age	14.2 ± 3.3
Sex (F/M)	16/18
Weight (kg)	14.2 ± 3.3
Cause of chronic renal failure	
Urologic problems	17 (50)
Glomerulonephritis	11 (32.4)
Cystic diseases of the kidney	4 (11.8)
Unknown	2 (5.9)
Dialysis modality	
Hemodialysis	18 (52.9)
Continuous ambulatory peritoneal dialysis	13 (38.2)
No dialysis	3 (8.8)
Duration of dialysis (y)	
Hemodialysis	3.5 ± 2.5
Continuous ambulatory peritoneal dialysis	3.4 ± 2.5
Arterio-venous fistula thrombosis	5 (14.7)
Immunosuppressive regimen	
Cyclosporine	18 (52.9)
Tacrolimus	16 (47.1)

Before transplant, although the MPV of patients in the hemodialysis group (8.05 ± 1.31) was higher than it was in the peritoneal dialysis group (7.79 ± 1.0) and the nondialysis group (7.45 ± 1.00), there was no significant difference between the groups ($P > .05$).

None of the patients in our study group had any thrombotic event and/or renal allograft loss at the posttransplant period. Five of them (14.7%) had arterio-venous fistula thromboses before transplant, and 1 (2.9%) had his second renal transplant because of focal segmental glomerulosclerosis. In the whole study group, at the end of the first posttransplant month MPV level was decreased significantly when compared with pretransplant levels (8.3 ± 1.5 vs 7.7 ± 0.9; $P = .04$). A significant increase was observed in platelet levels during posttransplant measures (274 ± 98 vs 319 ± 84; $P = .02$). Hemoglobin and hematocrit levels were found to be increased during the posttransplant measures as expected (Table 2). Prothrombin time and partial thromboplastin time levels did not differ before and after transplant. A positive correlation was found between MPV and serum albumin and aspartate aminotransferase levels (r=0.48 and r=0.61). However, a negative correlation was observed between MPV and C-reactive protein (r=-0.53). Mean platelet volume level was not found to be related with cause of renal failure, pretransplant dialysis modality, or posttransplant immunosuppressive regimens.

Table 2. Laboratory Evaluations of the Patients Before and After Transplant

N=34	Pretransplant	Posttransplant	*P* Value
Hemoglobin (g/dL)	9.9 ± 2.2	12 ± 1.8	< .05
Hematocrit (%)	29.4 ± 7.0	36.2 ± 5.5	< .05
Mean corpuscular volume (fL)	87.1 ± 4.4	84.1 ± 5.8	> .05
Red cell distribution width (%)	15.1 ± 1.4	15.9 ± 1.9	> .05
White blood cell count (/µl)	7232 ± 2754	8087 ± 2923	> .05
Platelet count ($\times 10^3$/µL)	274 ± 98	319 ± 84	< .05
Mean platelet volume (fL)	8.3 ± 1.5	7.7 ± 0.9	< .05
C-reactive protein (mg/L)	10.2 ± 24.8	12.4 ± 28	> .05
Albumin (g/L)	4 ± 0.6	4.6 ± 0.5	> .05
Aspartate aminotransferase (U/L)	23.9 ± 26	23 ± 7.1	> .05
Alanine aminotransferase (U/L)	14.3 ± 12.3	18 ± 10	> .05
Prothrombin time (s)	12.7 ± 2.5	11.2 ± 3.1	> .05
Partial thromboplastin time (s)	35.8 ± 7.3	34.7 ± 6.8	> .05

Discussion

Kidney transplant is the treatment of choice for end-stage renal disease. It offers a survival advantage over dialysis treatment in essentially all patient subgroups; however, the survival of kidney transplant recipients is inferior to that of the general population.[10,11] Vascular complications in kidney transplant are not uncommon and often may lead to allograft loss. The most common vascular complications are transplant renal artery stenosis, transplant renal artery/vein thrombosis, biopsy-induced vascular injuries, pseudoaneurysm formation, and hematomas.[12] Transplant renal artery/vein thrombosis generally occurs during the first 2 postoperative weeks and is reported in up to 6% of kidney transplants.[13,14]

In pediatric kidney transplant, graft loss due to thrombosis is a major problem.[15] According to the data from the North American Pediatric Renal Transplant Cooperative Study, vascular thrombosis accounts for 11.6% of graft losses in pediatric renal transplant.[15] The risk factors identified for graft thrombosis are surgical technique, perfusion, and reperfusion damage, young donor age (< 2 y) as well as young recipient age (< 5 y), long cold ischemia time (> 24 h), arterial hypotension or hypoperfusion; in particular, in small children receiving an adult kidney transplant (large for size), history of prior renal transplant, pretransplant thrombocytosis, high hematocrit and use of erythropoietin, perioperative hemodynamics, and prior peritoneal dialysis.[15-21]

In adults, inherited and acquired thrombophilic risk factors, for example, factor V Leiden, prothrombin, and MTHFR gene mutations have been associated with early graft loss and increased rejection episodes. Data on the effect of these factors on the outcome of children after renal transplant are rare.[15]

Platelet activation is a link in the pathophysiology of diseases prone to thrombosis and inflammation. Evidence, particularly derived from prospective studies and a meta-analysis, suggest a correlation between an increase in MPV and the risk of thrombosis. High MPV associates with a variety of established risk factors, cardiovascular and cerebrovascular disorders, and low-grade inflammatory conditions prone to arterial and venous thromboses.[22]

In our study, a higher MPV found in the hemodialysis group than in either the peritoneal dialysis group or the nondialysis group before transplant was thought to be associated with increased thrombocyte turnover because of chronic platelet activation during hemodialysis treatment. At the end of the first posttransplant month, a

significant increase was observed in platelet, hemoglobin, and hematocrit levels of the patients. In contrast, MPV levels were found to be decreased significantly when compared with pretransplant levels. These findings suggest that kidney transplant may reverse not only the metabolic disorders caused by chronic renal failure but also by hematologic abnormalities.

None of the 34 renal transplant patients had any thrombotic events and/or graft loss during the posttransplant period. Before transplant, 5 of them (14.7%) had arterio-venous fistula thromboses were detected by color Doppler sonography, and 1 (2.9%) had his second renal transplant because of focal segmental glomerulosclerosis. These patients were evaluated with regard to inherited and acquired thrombophilias (deficiency of antithrombin 3, protein C and S, factor V Leiden, prothrombin and MTHFR gene mutations, anticardiolipin antibodies, homocysteine levels) before transplant, but none were consistent with these thrombophilic conditions. The only common finding of these patients was the presence of high MPV levels before transplant.

Despite the great advantages of antirejection therapy, a prothrombotic state generated by the use cyclosporine and high doses of OKT3 can be responsible for the thromboembolic events after transplant.[13] Several investigators have reported a dramatic increase in the incidence of renovascular thrombosis among cyclosporine-treated renal transplant recipients when compared with recipients treated with prednisone and azathioprine only.[23-25] Interestingly, a prospective multicenter study showed no significant difference regarding the occurrence of renovascular thrombosis under cyclosporine versus azathioprine.[26] In our study, 18 of 34 patients (52.9%) had been receiving cyclosporine and 16 of them (47.1%) had been receiving tacrolimus. There was no relation between the 2 immunosuppressive regimens and MPV levels of the patients, and there existed no renovascular thrombosis under these therapies.

High C-reactive protein levels are known to be good indicators in the presence of chronic inflammation for dialysis patients with chronic renal failure.[27] The correlation between MPV and inflammation has especially been studied in patients with several chronic inflammatory diseases.[28-30] On the other hand, especially in chronic inflammatory situations, C-reactive protein is high, while MPV is low, and this is mentioned as an indicator of disease activation.[31,32] In accord with the literature, a negative correlation was seen in our study between MPV and C-reactive protein (r=-0.53), which suggests to us that chronic inflammatory situation because of chronic renal failure has resolved after kidney transplant.

To the best of our knowledge, our study is the first to identify MPV as a risk factor for the tendency to thrombotic complications and/or hemorrhagic diatheses after kidney transplant. The only limitation to our study was the lack of a second group comprising patients with renovascular thrombosis after transplant. Therefore, we did not have a chance to compare MPV levels of each group. In conclusion, platelet numbers increased and MPV levels decreased after pediatric renal transplant, but the potential for increased thrombosis was not observed.

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