Austin Journal of Nephrology and Hypertension

Open Access

Austin Publishing Group

Research Article

Outcomes of Kidney Transplant Recipients on Dual Antiplatelet Therapy

Paul D Bailey[1]*, Hirra Ali[2], Michelle Lubetzky[1] and Liise K Kayler[2]

[1]Department of Medicine, Albert Einstein College of Medicine, USA

[2]Department of Surgery, Montefiore Medical Center, USA

***Corresponding author:** Paul D. Bailey, Department of Medicine, Albert Einstein College of Medicine, USA, Tel: (630) 200-4745; Email: paul.bailey@med.einstein.yu.edu

Received: April 15, 2015; **Accepted:** May 25, 2015; **Published:** May 30, 2015

Abstract

Background: Kidney Transplant (KTX) recipients often have co morbidities requiring anti-platelet therapy with 1 or 2 agents. Whereas a few reports have examined outcomes with one agent, none have evaluated outcomes of KTX recipients on dual antiplatelet agents.

Methods: Consecutive adult kidney-only recipients from 10/11-9/14 taking aspirin alone (ASA, n=135), ASA and Plavix® (DUAL, n=23), or no Antiplatelet therapy (NONE, n=209) at the time of transplantation were assessed for several outcomes post-transplantation.

Results: Of 367 patients, the overall incidence of blood transfusion within 5 days of KTX was 34.6%. Compared to the NONE group, DUAL or ASA alone, were associated with perioperative blood transfusion (27.8%, 52.2%, 42.2%, p<0.01), but not reoperation for bleeding (1.0%, 0.0%, 1.5% p=0.79), delayed graft function (47.9%, 52.2%, 51.1% p=0.81), length of stay > 6 days (31.1%, 34.8%, 36.3% p=0.60), 30-day readmission (26.8%, 21.7%, 33.6% p=0.30), or overall graft failure (7.7%, 4.4%, 7.4% p=0.85), respectively. Despite univariate association, blood transfusion was not significantly associated with ASA (aOR: 1.42, CI: 0.86-2.34), or DUAL (aOR: 1.87, CI: 0.75-4.66) on multivariate analysis.

Conclusion: KTX with single or dual antiplatelet therapy may not carry an increased risk of blood transfusion or other adverse outcomes after other risk factors are accounted for.

Keywords: Bleeding; Renal Transplant; Antiplatelet; Plavix®; Aspirin; Complication; Kidney transplantation; Blood transfusion; Anticoagulation

Introduction

Kidney Transplant (KTX) recipients often have co morbidities that require anti-platelet therapy with 1 or 2 agents most commonly Aspirin® and/or Plavix®. Patients with end-stage renal disease are already at a higher risk of bleeding due to platelet dysfunction and uremia [1]; and bleeding risk is thought to be potentiated with the use of Aspirin® and/or clopidogrel bisulfate (Plavix®) which inhibit platelet function, albeit via different mechanisms. Long term use of Aspirin® leads to a reduction in thromboxane A2 in platelets which inhibits platelet aggregation. Plavix® asserts its action by irreversibly binding to the $P2Y_{12}$ ADP receptor on platelets, inhibiting platelet aggregation and fibrin cross-linking. Patients taking Aspirin® and Plavix® are at increased risk of bleeding because both platelet aggregation and activation pathways are inhibited.

Dual anti-platelet therapy is often considered a contraindication to KTX because of the potential risk of bleeding. Many programs will not transplant patients taking dual anti-platelet therapy until at least one of the anti-platelet agents has been discontinued. This may result in prolongation of waiting time and/or reduced access to transplantation [2]. Alternatively, other programs, will perform kidney transplantation in the setting of dual anti-platelet therapy as long as the anti-platelet agents can be temporarily withheld in the perioperative period despite the potential increased risk of bleeding transfusion [2,3]. Since blood transfusion, in and of itself, has not been shown to be a strong risk factor for adverse outcomes in the transplant population. Most analyses have shown no correlation of blood transfusion with graft survival [4,5], sensitization [4], acute rejection [4], or allograft nephropathy [4], although, one analysis suggested an increased risk of graft failure and patient death [6]. There are no reports of outcomes of KTX recipients on two antiplatelet agents at the time of surgery. The purpose of this study is to examine short-term outcomes of patients receiving single or dual agent anti-platelet therapy at the time of transplantation in terms of blood transfusion, reoperation, readmission and organ function.

Methods

A retrospective cohort study of consecutive adult living- and deceased-donor kidney-only recipients at Montefiore Medical Center between October 3, 2011 and September 3, 2014 was performed to evaluate outcomes between kidney transplant recipients receiving single-antiplatelet therapy with Acetylsalicylic Acid (ASA), dual-antiplatelet therapy with ASA and Plavix® (Dual; clopidogrel bisulfate, Bristol Meyers Squibb, Princeton NJ) or no antiplatelet therapy (NONE) at the time of transplantation. Exclusions were patients with therapeutic levels of warfarin (n=19) or heparin (n=2) at the time of transplant, and those on Plavix® alone (n=7). Our protocol requires that patients on dual therapy who are able to temporarily hold both anti-platelet agents after kidney transplant to be eligible for transplantation. The ASA group was comprised of patients were

Citation: Bailey PD, Ali H, Lubetzky M and Kayler LK. Outcomes of Kidney Transplant Recipients on Dual Antiplatelet Therapy. Austin J Nephrol Hypertens. 2015;2(3): 1040.

Table 1: Recipient, Donor, and Transplant Characteristics by Group.

Characteristic	ASA	DUAL	None	P- Value
% or mean +/- SD	N=135	N=23	N=209	
Recipient, Black race	35.6	34.8	47.4	0.40
Recipient, Male	67.4	78.3	51.2	<0.01
Recipient Age, years	58.8 ±. 9.4	62.9 ±. 6.6	50.5 ±. 14.8	<0.01
Recipient, Diabetes Mellitus	61.5	69.6	28.9	<0.01
Recipient, preemptive transplant	10.4	4.4	12.4	0.47
Recipient BMI kg/m^2	27.9±5.1	26.7±4.5	27.4±5.4	0.45
Prior Solid Organ Transplant	3.7	4.4	12.9	0.02
Thymoglobulin Induction	34.1	34.8	56.5	<0.01
Pre-KTX Hemoglobin < 10 g/dL	18.8	21.7	15	0.53
Cardiovascular Disease	38.5	100	12.4	<0.01
HLA Mismatch >3	79.7	76.3	76.9	0.79
Renal Vein Extension	42.2	65.2	42.6	0.10
Donor Race, Black	17.8	21.7	25.8	0.22
Donor Male	48.9	47.8	56.5	0.34
Donor Age, years	47.9 ±16.7	47.7 ±17.3	41.5 ±.15.6	<0.01
Kidney Type				
Living Donor	14.8	8.7	18.7	0 .07
SCD	52.6	52.2	60.8	
ECD	32.6	39.1	20.6	
Follow-up duration, days	600±340	633±364	610±367	0.92

taking in the majority Aspirin® (n=133; Bayer, Leverkusen, Germany), but also Micropirin® (n=1; Dexcel Pharma Ltd, Daventry UK) or Aggrenox® (n=1; Boehringer Ingelheim Pharmaceuticals, Ingelheim am Rhein, Rhineland-Palatinate)

The primary outcome was at least one blood transfusion during or within 5 days of transplantation. Secondary outcomes were (a) reoperation for bleeding (b) delayed graft function (DGF, defined as dialysis within 1 week post-transplantation)(c)length of stay (LOS)> 6 days (median value), (d) 30 day rehospitalization from day of transplant hospitalization discharge, and (e)overall graft failure following transplantation (defined as allograft nephrectomy, re-transplantation, return to chronic dialysis, or death).

Surgery and Immunosuppression

Through a Gibson incision, allograft renal arteries and veins were generally anastomosed to the external iliac vessels using an end-to-side technique. Right renal veins were typically extended with the donor inferior vena cava by staple or suture closure of the suprarenal cava and left renal vein orifice (renal vein extension). Ureterovesical implantation was performed using an extra vesical technique with or without stent placement depending on surgeon preference. Patients received anti-thymocyte globulin (ATG, 1.5 mg/kg/day for 3 days) or basiliximab (20 mg on the day of surgery and post-transplant day#3) induction treatment, along with tacrolimus, mycophenolate mofetil, and a corticosteroid taper. Corticosteroids were initiated intraoperatively at 500 mg of methylprednisolone, followed by an oral prednisone taper to 5 mg/day by 3 months. Intravenous immunoglobulin (500 mg/kg during transplant surgery and post-operative days 1 and 2) was also administered if positive flow-cytometry cross-match and/or donor-specific antibody. ATG was administered peripherally with 1000 U of heparin included in the formulation. At the discretion of the surgeon, a subgroup of patients received a single dose of 1000 – 3000 U IV heparin during the procedure. Venous thromboembolism prophylaxis was with sequential compression devices only. Desmopressin was not administered to patients on antiplatelet agents.

Covariates

The following recipient covariates were evaluated for inclusion in the multivariable models; recipient age (continuous), sex, race (African-American vs. other), history of diabetes mellitus, induction (basiliximab vs. ATG), panel-reactive antibody (PRA) level > 0%, HLA- A, B, and DR mismatch> 3, body mass index (continuous), pre-operative hemoglobin level > 10g/dL (median), cardiovascular disease (defined as any of prior myocardial infarction, coronary artery bypass graft, coronary angioplasty or stent), prior solid organ transplant, pre-emptive transplant, and renal vein extension. Donor covariates evaluated were age (continuous), sex, race (African-American vs. other) and type [living-donor, Expanded-Criteria Donor (ECD), Standard-Criteria Donor (SCD)]. The appropriate functional form of model covariates was determined by exploratory data analysis in unadjusted models and perceived impact on clinical meaningfulness. ECD was defined as donor age ≥ 60 years or donor age 50-59 with two of the following: history of hypertension, terminal serumcreatinine ≥ 1.5 mg/dl, or death from cerebrovascular accident. SCD was defined as deceased-donor not meeting ECD criteria.

Statistical Analysis

Univariate associations between exposure groups were examined using the Chi-Square tests for categorical variables and t-tests for continuous variables whose distributions approximated normality. The survival distribution for overall graft failure was examined with Kaplan-Meier curves and compared using the log-rank test. Logistic rejection models were fit to estimate the Odds Ratios (OR) and 95% confidence intervals (95%CI) for exposure groups for perioperative blood-transfusion with variables included in the model if associated with the outcome at an α level of 0.05. Time to outcome was defined as time from the date of transplant until date of outcome, censored for loss to follow-up and end of study period (10/31/14).

All statistical analysis was conducted using the SAS system version 9.2 (SAS Institute, Inc., Cary, N.C.). Statistical significance was identified by a p-value of less than 0.05 and all confidence intervals also used a 95% threshold. All p-values are two-sided. The study was approved by the Albert Einstein Institutional Review Board.

Results

Of 367 patients, 209 (57%) were not receiving antiplatelet therapy at the time of transplantation, 135 (36.8%) were receiving ASA only, and 23 (6.3%) were receiving DUAL therapy. The overall incidence of blood transfusion was 34.6% within 5 days of kidney transplantation. Of those who received a blood transfusion 44.5% were given 1 unit, 31.9% received 2 units, 16.0% received 3 units, and 7.6% received 4 or more units.

Compared to the NONE group, the DUAL and ASA recipients

Table 2: Post-transplant Outcomes by Group.

Outcome %	ASA N=135	Dual N=23	None N=209	P-value
Blood Transfusion	42.2	52.2	27.8	<0.01
Reoperationfor Bleeding	1.5	0.0	1.0	0.79
Delayed Graft Function	51.1	52.2	47.9	0.81
Length of Stay > 6 days	36.3	34.8	31.1	0.60
30 Day Readmission	33.6	21.7	26.8	0.30
Overall Graft Failure	7.4	4.4	7.7	0.85

were significantly older (50.5 ±14.8, 62.9 ± 6.6, 58.8 ± 9.4, years p < 0.01),more likely to be male (51.2%, 67.4%, 78.3% p < 0.01), diabetic (28.9%, 69.6%, 61.5% p < 0.01), or have cardiovascular disease (12.4%, 100%, 38.5%, p < 0.01),and less likely to have received a previous solid organ transplant (12.9%, 4.4%, 3.7%, p = 0.02), or receive ATG induction therapy (56.5%, 34.8%, 34.1%, p < 0.01), respectively (Table 1). Also, relative to NONE the DUAL and ASA groups were more likely to receive a kidney from an older donor (41.5 ± 15.6, 47.7 ± 17.3, 47.9 ± 16.7 p <0.01) and somewhat less likely to receive a living donor kidney (18.7%, 8.7%, 14.8% p = 0.07). Other baseline characteristics were similar between the groups (Table 1).

Perioperative blood transfusion was administered in 27.8% of patients in the NONE group, 52.2% of cases in the DUAL group, and 42.2% of cases in the ASA group (p<0.01) suggesting an association of ASA and DUAL with blood transfusion on univariate analysis (Table 2). Antiplatelet therapy, either as DUAL or ASA alone, was not associated with reoperation for bleeding (1.0%, 0.0%, 1.5% p = 0.79), DGF (47.9%, 52.2%, 51.1% p = 0.81), length of stay > 6 days (31.1%, 34.8%, 36.3% p = 0.60), 30-day readmission (26.8%, 21.7%, 33.6% p = 0.30), or overall graft failure (7.7%, 4.4%, 7.4% p = 0.85), respectively. The mean follow-up time was similar between the 3 groups (Table 1). Renal artery or vein thrombosis was not seen in the DUAL group and occurred in 1 patient in the ASA and 2 patients in the NONE groups.

A multivariate analysis was performed to determine if the univariate findings of an association of antiplatelet therapy and blood transfusion remained after assessing for potential confounders. On multivariate analysis including all factors associated with blood transfusion at and alpha level of <0.05, only increasing recipient age (aOR 1.02; 95%CI 1.00-1.05) remained a significant independent risk factor for blood transfusion; whereas, neither ASA (aOR: 1.42, CI: 0.86-2.34), nor DUAL (aOR: 1.87, CI: 0.75-4.66) was associated with blood transfusion relative to NONE (Table 3).

Discussion

We found that kidney transplantation of patients on antiplatelet therapy with one or two agents at the time of transplantation does not confer significantly increased odds of blood transfusion or other outcomes such as reoperation for bleeding, delayed graft function, length of stay, readmission, or organ failure. These findings suggest that restriction of access to transplantation due to pre-transplant antiplatelet therapy usage is not necessary when post-transplant cessation of antiplatelet therapy is allowable.

Kidney transplant recipients often have many co morbidities. Some of these, such as previous ischemic events, coronary stenting, or deep venous thromboembolism, may necessitate Aspirin® or dual

Table 3: Univariate and Multivariate Logistic Regression Model testing for an association of ASA, DUAL and NONE groups for Blood Transfusion.

Characteristic	Univariate		Multivariate	
	Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio	95% Confidence interval
ASA *vs.* None	1.90	1.21-3.00	1.42	0.86-2.34
Dual *vs.* None	2.84	1.19-6.79	1.87	0.75-4.66
Recipient DM	1.97	1.27-3.05	1.34	0.83-2.17
ECD *vs.* Living	2.70	1.34-5.41	1.61	0.65-4.01
SCD *vs.* Living	1.23	0.65-2.34	0.99	0.50-1.96
Donor Age	1.02	1.01-1.04	1.00	0.98-1.02
Recipient Age	1.04	1.02-1.06	1.02	1.00-1.05

antiplatelet therapy [7-10]. Patients on dual anti-platelet therapy for procedures such as coronary artery stinting typically wait 12 months before it is safe to discontinue dual anti-platelet therapy. Although optimal length of dual anti-platelet therapy is not known, a minimum of 6 months is required for drug eluting stents and 4 weeks for bare metal stents is recommended [9,10]. Also, some patients may be on dual anti-platelet therapy permanently such as those with atrial fibrillation or venous thromboembolism who cannot tolerate Coumadin therapy [11]. For those that require permanent antiplatelet therapy, kidney transplantation may not be an option at some centers; however, this practice may not have a strong empiric basis.

The overall incidence of blood transfusion at our center was 34.6% within 5 days of kidney transplantation. These transfusion rates are similar to previously published perioperative KTX transfusion rates of 10% to 51% (3). Whereas none of the previous analyses examined the impact of dual antiplatelet therapy on outcomes, some [3], but not all reports [8], have found increased rates of blood transfusion associated with single antiplatelet agents. Marzouk et al. noted that 33.8% of patients on a single antiplatelet agent (n=136) received transfusions compared to 16.7% of those not taking antiplatelet agents (n=156; p<0.01) [3]. In contrast, Benahmed and colleagues found 21% of 19 patients on clopidogrel or ticlopidine required transfusion compared to 10% (p=0.42) of 39 controls between post-operative days 1-30 [8]. Similarly, Eng and coauthors found lower transfusion rates in 10 patients on clopidogrel (20.0%) and equal rates of transfusion between59patients on Aspirin® (28.8%) and 213 patients not receiving antiplatelet therapy (27.7%) [2].

Our finding that increasing transplant recipient age, but not antiplatelet agent use, is independently associated with blood transfusion suggests that it is the indication for the antiplatelet agents, rather than the antiplatelet agent itself, that confers the majority of the risk of blood transfusion. Older patients may have less cardiac reserve than other patients and are potentially more likely to require transfusion preemptively or to maintain hemodynamic stability. Also, it is recommended that in cases of severe cardiac disease, a lower trigger point for transfusion should be used [12]. Older patients are more likely to receive marginal kidneys. Those willing to accept an older kidney or a kidney from an individual with more co morbidity may be poorer surgical candidates than others able to wait for a more desirable kidney or the quality of the kidney itself may be a risk factor for blood transfusion.

Similar to our findings of a lack of association with antiplatelet agents and reoperation for bleeding, DGF, length of stay, readmission, and graft failure, others have also not found any associations of antiplatelet therapy with several of these endpoints. Eng and colleagues [2] noted reoperation rates of 5.1% in patients on Aspirin® therapy compared to 1.4% of those not receiving antiplatelet agents; there was not a significantly increased relative risk of reoperation (RR: 3.61, CI: 0.84-15.21); however, sample and event sizes were small. These authors also found a similar mean length of stay between these two groups (6.1 ± 3.2, 5.7 ± 3.1 days), respectively. Benahmed and others showed no significant increase in DGF (11% *vs.* 8%, p = 0.65), reoperation (5% *vs.* 5% p = 1), or 1 year acute rejection (5% *vs.* 5%, p = 1) in patients on clopidogrel or ticlopidine compared to none, respectively [8].

Our study is limited by its' design as a retrospective, single center cohort analysis which hampers our ability to ascribe direct causality to any of the significant risk factors identified and limits generalizability. Because recipients are often not randomly selected to receive anti-platelet therapy, it is possible that they are in some unmeasured way systemically less (or more) healthy than recipients of kidneys with only one agent or without anti-platelet therapy. The small sample size of patients on DUAL therapy reduces the power of the analysis to determine a potential association of DUAL therapy and outcomes. Ascertainment of antiplatelet usage was obtained from the patients' preoperative history and physical document and was not able to determine the patient's level of compliance with anti-platelet therapy at the time of transplantation. Lastly, the decision to give a blood transfusion is subjective and triggers for transfusion may vary by physician and institution [13]. Because of the retrospective nature of this study, set criteria for transfusion triggers was not established which leaves the decision for transfusion variable between surgeons and patients.

Discontinuation of anti-platelet therapy in preparation for kidney transplantation is not always possible, especially in the case of deceased-donor transplantation. We found that kidney transplant recipients on one or two antiplatelet agents are not at a significantly higher risk for blood transfusion when compared to those on not taking anti-platelet agents after adjusting for other risk factors for transfusion. Additionally, other outcomes such as reoperation for bleeding, delayed graft function, length of stay, 30-day re-hospitalization, and overall graft survival are not impacted by antiplatelet agent utilization. Our findings suggest that restriction of access to transplantation due to dual pre-transplant antiplatelet therapy usage is not necessary when post-transplant cessation of antiplatelet therapy is allowable.

References

1. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial. 2006; 19: 317-322.
2. Eng M, Brock G, Li X, Chen Y, Ravindra KV, Buell JF, et al. Perioperative anticoagulation and antiplatelet therapy in renal transplant: is there an increase in bleeding complication? Clin Transplant. 2011; 25: 292-296.
3. Marzouk K, Lawen J, Kiberd BA. Blood transfusion in deceased donor kidney transplantation. Transplant Res. 2013; 2: 4.
4. Scornik JC, Schold JD, Bucci M, Meier-Kriesche HU. Effects of blood transfusions given after renal transplantation. Transplantation. 2009; 87: 1381-1386.
5. Connaughton DM, Phelan PJ, Scheult J, Ma'ayeh M, O'Kelly P, Walshe JJ, et al. The impact of peritransplant warfarin use on renal transplant outcome. J Nephrol. 2010; 23: 587-592.
6. O'Brien FJ, Lineen J, Kennedy CM, Phelan PJ, Kelly PO, Denton MD, et al. Effect of perioperative blood transfusions on long term graft outcomes in renal transplant patients. Clin Nephrol. 2012; 77: 432-437.
7. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus Aspirin® in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996; 348: 1329-1339.
8. Benahmed A, Kianda M, Ghisdal L, Nilufer B, Massart A, Lemy A, et al. Ticlopidine and clopidogrel, sometimes combined with Aspirin®, only minimally increase the surgical risk in renal transplantation: a case–control study. Nephrol. Dial. Transplant. 2014; 29: 463-466.
9. Coller JP, Silvan J, Barthelemy O, Range G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomized trial Lanc et 384.9954. 2014; 1577-1585.
10. Steinhuble SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and Sustained Dual Oral Antiplatelet Theray Following Percutaneous Coronary Intervention: a Randomized Controlled Trial JAMA 288.19. 2002; 2411-2420.
11. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S. Effect of clopidogrel added to Aspirin® in patients with atrial fibrillation. N Engl J Med. 2009; 360: 2066-2078.
12. Carless PA, Henry DA, Carson JL, Hebert PP, McClelland B, Ker K. Transfusion thresholds and Other Strategies for Guiding Allogeneic Red Blood Cell Transfusion Cochrane Database Syst Rev. 2010; 6: CD002042.
13. Ejaz A, Spolverato G, Kim Y, Frank S, Pawlik T. Identifying Variations in Blood Use Based on Hemoglobin Transfusion Trigger and Target Among Hepatopancreaticobiliary Surgeons J Am Coll Surg 10.1016. 2014; 219: 217-227.

Austin J Nephrol Hypertens - Volume 2 Issue 3 - 2015
ISSN : 2381-8964 | www.austinpublishinggroup.com

Citation: Bailey PD, Ali H, Lubetzky M and Kayler LK. Outcomes of Kidney Transplant Recipients on Dual Antiplatelet Therapy. Austin J Nephrol Hypertens. 2015;2(3): 1040.