Hosp Pharm 2013;48(11):936–941,957

www.hospital-pharmacy.com
doi: 10.1310/hpj4811-936

Original Article

Evaluation of Bleeding Rates in Renal Transplant Patients on Therapeutic Intravenous Heparin

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Abstract

Background: It is unknown whether coagulation properties differ between renal transplant and nontransplant patients.

Objective: To assess whether renal transplant patients on intravenous (IV) heparin, titrated to therapeutic activated partial thromboplastin times (aPPT; 56-93 seconds), experienced a higher rate of bleeding compared to nontransplant patients.

Methods: Twenty-nine renal transplant and 29 nontransplant patients receiving IV heparin for a deep vein thrombosis, pulmonary embolism, atrial fibrillation, or acute coronary syndrome were randomly identified through a retrospective chart review.

Results: Renal transplant patients had higher bleeding rates on IV heparin therapy compared to nontransplant patients (31% vs 6.9%, respectively; $P = .041$). Renal transplant patients experienced a drop in hemoglobin of at least 1 g/dL or the need for a transfusion more often then nontransplant patients (69% vs 45%, respectively; $P = .111$), although the difference was not statistically significant.

Conclusions: Further research is necessary to identify the factors contributing to increased rates of bleeding in renal transplant patients on IV heparin and to determine the ideal aPTT to appropriately balance anticoagulation in renal transplant patients.

Key Words—aPTT, bleeding, heparin, renal transplant

Hosp Pharm—*2013;48(11):936–941,957*

In patients who need anticoagulation, it is a challenge to provide the optimal balance between enough anticoagulant to prevent the formation of a thrombus and too much, which may cause a bleeding event.[1] As many as 10% of adult patients experience thrombotic events following renal transplantation.[2] Most thrombotic events occur in the initial 48 hours after surgery, but they can occur up to 14 days after renal transplantation.[2] It is especially important in this population to achieve that balance in anticoagulation therapy, because immediate graft loss may occur if patients experience thrombosis of the renal artery or vein.[2] Heparin may be used in the perioperative phase in an attempt to prevent thrombotic events, especially in patients with hypercoagulable states.[3-5]

In the general population, major bleeding occurs in up to 7% of patients who receive therapeutic intravenous (IV) heparin.[1,6] Because one of the risk factors for heparin-induced bleeding is recent surgery, it would be expected that there would be increased bleeding risk in the early postoperative transplantation period.[6]

Patients with chronic renal failure may have impaired hemostasis. Platelet production may be disturbed due to the accumulation of protein biodegradation products. Bleeding tendencies may be further increased due to clotting factor deficiencies and vascular defects. Conversely, in uremic patients, clotting factors VII and XIII and fibrinogen may be increased, leading to an increased thrombosis risk. The clotting inhibitors protein C and S, antithrombin III, and heparin cofactor II

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activity may also be impaired. Unfortunately, complete improvement in hemostasis does not occur after successful renal transplantation.[7]

A previous study by Mathis et al[2] evaluated bleeding events due to therapeutic IV heparin in renal transplant patients to prevent perioperative thrombosis. They found no link between the immunosuppressive agents used in the study (primary agents: cyclosporine, mycophenolate, prednisone; alternatives: tacrolimus and rapamycin) and risk of bleeding. However, there was a trend toward increased rates of bleeding in patients who received antibiotic prophylaxis for surgery for longer periods of time ($P = .053$); cefotetan was used more frequently in patients who experienced bleeding ($P = .091$).

A literature search regarding bleeding rates in renal transplant patients found trials in the early postoperative transplantation period, with bleeding occurring in 60% to 64.3% of patients.[2,5,8] No literature was found regarding bleeding rates in renal transplant patients who were receiving therapeutic IV heparin at any time beyond the early transplantation period. The perceived increase in susceptibility to bleeding in renal transplant patients receiving IV heparin (any time after transplantation) led to our assessment of renal transplant patients' bleeding rates on IV heparin, titrated to a therapeutic activated partial thromboplastin time (aPTT; 56-93 seconds; 1.5 to 2 times normal, institution specific) compared to nontransplant patients.

MATERIALS AND METHODS

Study Design

A retrospective chart review at a single center, 601-bed teaching hospital was conducted to identify bleeding events in renal transplant and nontransplant patients who received therapeutic IV heparin between December 1, 2007, and December 31, 2010. The transplantation had to occur prior to heparin use. Saint Barnabas Medical Center has one of the largest renal transplant programs in the United States and performs nearly 200 renal transplants per year.

A billing database was used to identify renal transplant recipients and nonmatched, randomly selected, nontransplant recipients on IV heparin infusions with deep vein thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation (Afib), or acute coronary syndrome (ACS). Patients with all transplantation types (ie, cadaveric, living) were included. Patients younger than 18 years of age, recipients of solid organ transplants other than renal, patients with bleeding complications within 24 hours of admission, and patients with an international normalized ratio (INR) greater than 4 within 24 hours of admission were excluded. The discharge electronic medical record and the transplant electronic medical record were used to confirm the use of IV heparin and identify a potential link to bleeding. Institutional review board approval was obtained.

Heparin Protocol

Saint Barnabas uses 2 heparin protocols: an ACS (without thrombolytics) and Afib protocol and a DVT, PE, and aggressive anticoagulation protocol. Both protocols require a stat baseline aPTT, prothrombin time (PT), and a complete blood count (CBC) with differential prior to beginning heparin. A weight-based heparin loading dose (80 units/kg for the DVT/PE protocol and 60 units/kg for the ACS/Afib protocol) and the corresponding suggested initial infusion rate (18 units/kg/h for the DVT/PE protocol and 12 units/kg/h for the ACS/Afib protocol) are provided on both protocols. After initiation of the heparin infusion, aPTT and CBC with differential are to be drawn within 6 hours. Nurses manage the dose heparin drip rate adjustments. When aPTT results are available, nurses send an order to pharmacy to adjust the heparin drip rate according to the protocol to achieve the institutionally defined therapeutic goal of 56 to 93 seconds. The aPTTs are ordered every 6 hours until 2 consecutive aPTT results are within the therapeutic window. At this point, aPTTs may be drawn daily.

Outcomes

The primary outcome was bleeding rates in renal transplant patients compared to nontransplant patients receiving IV heparin titrated to a therapeutic aPTT. Bleeding events were defined as a positive magnetic resonance imaging or computed tomography scan for a bleed, a procedure (eg, endoscopy, colonoscopy) that identified a gastrointestinal or head bleed, or other positive symptoms of bleeding (eg, hematuria, hematoma, or melena). The secondary outcome was a drop in hemoglobin (Hgb) of at least 1 g/dL within 2 consecutive days or evidence of transfusion history. A drop in Hgb was chosen as a surrogate marker for bleeding, because renal transplant patients tend to receive fewer blood transfusions than nontransplant patients in order to minimize the chance of receiving cross-reacting antibodies. The 48-hour time period was defined to accommodate potential fluctuations in the Hgb. Chart reviews via electronic medical records were conducted to record each patient's Hgb and aPTT values during heparin administration and to identify evidence of transfusions during heparin administration up to 48 hours after heparin discontinuation. The 48-hour time frame was chosen to account for any time lag between

discontinuation of heparin and evidence of bleeding requiring transfusions.

Statistical Analysis

A sample size of 27 in each group was needed to achieve 80% power in identifying a 25% difference in the bleeding events between the 2 groups ($\alpha = 0.05$). Bleeding rates in renal transplant patients on therapeutic IV heparin at any time after transplantation are unknown. Taking into account a bleeding rate of up to 7% in the general population, we sought to identify a 25% difference in the bleeding rates between the renal transplant and nontransplant groups.[1,6] The Fisher exact probability test was performed for the primary outcome, and the chi-square test was performed for the secondary outcome. For all other nominal data, the chi-square test was performed. Student *t* test was performed for normally distributed data, and Mann-Whitney test was performed for non-normally distributed categorical data.

RESULTS

Twenty-nine renal transplant and 29 nontransplant patients were identified. Baseline characteristics are shown in **Table 1**. The average age of the renal transplant patients was significantly younger than nontransplant patients (58.6 vs 70.8 years; $P = .002$). A similar number of renal transplant and nontransplant patients received heparin for an ACS and/or a PE. The most common indication for a heparin infusion in the renal transplant patients was a DVT, and Afib was the most common indication in nontransplant patients. Transplant patients had a similar length of stay compared to nontransplant patients (16 vs 10.4 days, respectively; $P = .0784$).

Upon initiation of therapeutic heparin, a heparin bolus was administered in 45% (13/29) of renal transplant patients and 59% (17/29) of nontransplant patients ($P = .431$). Evaluation of heparin results are shown in **Table 2**. The average aPTTs in both groups were within the institutionally defined therapeutic goal of 56 to 93 seconds. The average aPTT of 72.6 seconds in renal transplant patients was similar to the average aPTT of 78.1 seconds in nontransplant patients. The average of the highest aPTT values for each patient was similar between renal transplant and nontransplant patients. Renal transplant patients received heparin for a longer duration (7 vs 4.7 days, respectively; $P = .0183$) and had more aPTTs drawn than nontransplant patients ($P = .002$).

Thirty-one percent of renal transplant patients experienced bleeding events compared to 6.8% of nontransplant patients ($P = .041$). This corresponds to a number needed to harm of 5 (95% CI, 4.94-43.4), indicating that for every 5 renal transplant patients receiving therapeutic IV heparin, 1 patient experienced a bleeding event. Further, the incidence of bleeding was 44.1 per 1,000 heparin days in renal transplant patients compared to 14.7 per 1,000 heparin days in nontransplant patients. In addition, renal transplant patients experienced a drop in Hgb of at least 1 g/dL or the need for a transfusion more often then nontransplant patients (69% vs 45%, respectively; $P = .111$).

The DVT/PE heparin protocol was used in 4 of 9 renal transplant patients who bled, and the ACS/Afib protocol was used in the remaining transplant and nontransplant patients who bled.

Of the 9 renal transplant patients who bled, 6 experienced a hematoma, 4 experienced hematuria, and 1 experienced melena (some patients experienced more than 1 bleeding event). The bleeding event in both of the nontransplant patients was hematuria.

Twelve of the renal transplant patients received a deceased donor renal transplant; 6 received a living, unrelated renal transplant; 10 received a living related donor renal transplant; and transplant type was unknown in 1 patient. Fourteen patients received heparin within

Table 1. Baseline characteristics

Characteristics	Transplant patients (n = 29)	Nontransplant patients (n = 29)
Mean age (range), years*	58.6 (24–75)	70.8 (35–96)
Male, %	55	45
Heparin indication[a], %		
Acute coronary syndrome	17	17
Atrial fibrillation	28	62
Deep vein thrombosis	52	17
Pulmonary embolism	24	21
Mean length of stay (range), days	16 (3-51)	10.4 (2-57)

[a]Some patients received heparin for more than one indication.
*$P = .002$

Table 2. aPTT in renal transplant and nontransplant patients receiving heparin

Changes	Transplant (n = 29)	Nontransplant (n = 29)
Average aPTT, seconds	72.6 ± 43.1	78.1 ± 50.6
Average highest aPTT/patient, seconds	157.4 ± 59.8	147.3 ± 74.4
Patients with ≥1 supratherapeutic aPTT, %	86	69
Mean supratherapeutic aPTTs/patient, seconds*	2.86 (range, 0–7)	1.79 (range, 0–11)
Mean of total aPTTs/patient, seconds*	14.1 (range, 2–52)	7.6 (range, 1–47)
Average heparin duration, days	7 ± 4.5 (range, 2–25)	4.7 ± 4.5 (range, 1–26)

Note: Student *t* test was performed for normally distributed categorical data, and Mann-Whitney was performed for non-normally distribute categorical data. To calculate percent of patients with at least one supratherapeutic aPTT, the Fisher exact probability test was performed.
*$P < .05$.

the first year of their transplant, 10 within 1 to 5 years of transplantation, 4 within 6 to 10 years of transplantation, and 1 at more than 10 years after transplantation (**Table 3**). Six patients received heparin during their admission for renal transplantation, and 3 of these patients experienced bleeding.

There were several confounders that could have influenced bleeding rates, including home anticoagulant or antiplatelet therapy, concomitant anticoagulants or antiplatelets at time of heparin infusion, and surgery. None of the patients in either group received a concomitant anticoagulant or antiplatelet other than warfarin, aspirin, or clopidogrel. Enoxaparin was used in a similar number of renal transplant and nontransplant patients after discontinuation of warfarin therapy. There was no statistically significant difference in any of the confounding variables regarding anticoagulant or antiplatelet medications or surgery (**Table 4**), although twice as many patients in the renal transplant group had surgery compared to the nontransplant group (55.1% vs 27.6%, respectively; $P = .062$). All of the transplant patients were on corticosteroid therapy, and none of the nontransplant patients were on corticosteroids ($P < .001$). Patients in the renal transplant group had a lower Hgb and higher serum creatinine (SCr) at initiation of heparin therapy compared to nontransplant patients ($P = .048$ and .0007, respectively). Further, one of the renal transplant patients who bled was on concomitant warfarin and had a supratherapeutic INR of 6.2 at the time of the bleed.

Of the 9 renal transplant patients who bled, 3 were on concomitant warfarin alone, 2 were on concomitant warfarin and aspirin, and 1 was on concomitant aspirin alone. Of the 2 nontransplant patients who bled, both were on concomitant warfarin.

DISCUSSION

Renal transplant patients appear to bleed at a higher rate than nontransplant patients receiving IV heparin, titrated to a therapeutic aPTT. One reason for the increased bleeding in renal transplant patients may be related to the common nature of acquired coagulation defects in end-stage renal disease, with more than 10% of patients awaiting a renal transplant having antiphospholipid antibodies.[3] A potential selection bias that could have contributed to the higher rate of bleeding in renal transplant patients is related to DVT being the most common indication for heparin compared to ACS in the nontransplant patients. This is supported by 4 out of 9 renal transplant patients requiring the DVT/PE protocol, whereas neither of the 2 nontransplant patients who bled required the DVT/PE heparin protocol. The DVT heparin protocol provides for more aggressive anticoagulation than the ACS protocol, which theoretically could increase bleeding risks. Although there were some patients who had hypercoagulable/acquired thrombophilia, the presence of an ACS, DVT, PE, or Afib was required for inclusion.

The lack of a statistically significant difference in average aPTT values between the 2 patient groups strengthens the primary endpoint toward being related to coagulation differences in renal transplant patients. Further, in a study in which 10 out of 16 renal transplant patients received heparin to prevent renal allograft thrombosis, the patients who bled tended to have similar aPTT levels compared to those who did not bleed.[5]

Although elevated aPTT results have been associated with potential bleeding complications, this link

Table 3. Time since renal transplant

Time since renal transplant, years	No. of patients
< 1	14
1–5	10
6-10	4
>10	1

Table 4. Confounders with potential to increase bleeding rates on intravenous heparin therapy in renal transplant and nontransplant patients

	Transplant (n = 29)	Nontransplant (n = 29)
Home anticoagulant or antiplatelet	12 (41.4%)	16 (65.5%)
Concomitant		
Warfarin	18 (62.1%)	20 (69%)
Aspirin	6 (20.7%)	10 (34.5%)
Clopidogrel	2 (6.9%)	6 (20.1%)
Corticosteroid	29 (100%)	0
Enoxaparin	8 (27.6%)	6 (20.7%)
Surgery during heparin therapy	16 (55.1%)	8 (27.6%)
Mean hemoglobin at heparin initiation, g/dL	10.8	12
Mean liver function		
AST	44.7 (range, 15-174)	44.5 (range, 15-178)
ALT	42.3 (range, 10-260)	44.2 (range, 8-271)
Total bilirubin	0.63 (range, 0.2-1.8)	0.68 (range, 0.2-1.5)
Mean SCr*	2.12 (range, 0.6-6.86)	1.4 (range, 0.43-8.91)

Note: Values given as n (%), unless otherwise noted. Chi-square analysis was completed for home anticoagulant or antiplatelet therapy, concomitant medications, and presence of surgery. Student *t* test was used for all laboratory values with a normal distribution, and Mann-Whitney test was used for all laboratory values with a non-normal distribution. ALT = alanine aminotransferase; AST = aspartate aminotransferase; SCr = serum creatinine.
*$P = .007$.

is controversial because bleeding has been shown to occur in patients who had aPTTs within the therapeutic window.[1,9] Further, in a study by Landefeld et al, patients' age and patient-specific comorbidities were related to a greater risk of bleeding from heparin compared to the maximum PT or aPTT.[9,10] The increased risk of bleeding in renal transplant patients whose average highest aPTT and therapy average aPTTs were similar to nontransplant patients supports the idea that there is some other confounder in renal transplant patients that increases their bleeding risks. The statistically higher number of total PTTs per patient and higher supratherapeutic aPTTs in renal transplant patients may be a function of the longer duration of heparin therapy compared to nontransplant patients.

A literature search did not provide any evidence for a relationship between immunosuppressive agents and an increased bleeding risk. Although all of the renal transplant patients were on corticosteroids as an immunosuppressant and none of the nontransplant patients received corticosteroids ($P < .001$), a direct link cannot be made at this time between corticosteroids and increased bleeding risks.

Cefotetan contains the side-chain N-methylthiotetrazole (NMTT), which is also present in several other beta-lactam antibiotics that have been associated with abnormal prothrombin levels, hypoprothrombinemia, and occasionally clinically significant bleeding. The increased bleeding risk seen by Mathis et al is postulated to be related to a reaction that occurs when the NMTT side chain is cleaved that is essential for vitamin K-dependent clotting factor synthesis.[11] It is not possible to comment on this phenomenon in our study, because antibiotic use was not evaluated. Further research is necessary to determine whether there is a relationship between the increased bleeding events in renal transplant patients on therapeutic heparin receiving antibiotics with a NMTT side chain.

The relationship between aPTT ratio and bleeding was evaluated by Mathis et al[2] in 28 patients receiving therapeutic heparin within 24 hours of renal transplantation. Bleeding was associated with 12.8% of all aPTT ratios that were 2 to 2.4 times above normal. An optimal aPTT ratio of 1.5 to 1.9 times above normal was suggested for renal transplant patients receiving therapeutic heparin to prevent thrombosis while limiting bleeding events. An aPTT of 1.5 to 2 times above normal was the goal range sought in renal transplant patients with hypercoagulable states receiving heparin for prevention of renal allograft thrombosis.[3,8] However, a literature search did not yield any information regarding appropriate aPTT goals in renal transplant patients receiving heparin at any time other than immediately after transplantation. It is therefore important to identify the appropriate aPTT range for renal transplant patients receiving IV heparin at any time

after transplantation to achieve a balance in anticoagulation without increased bleeding rates.

The longer duration of heparin in renal transplant patients may be related to differing coagulation properties and may require a longer bridging therapy for patients who require chronic anticoagulation with warfarin therapy. Although renal transplant patients experienced a drop in Hgb of at least 1 g/dL or had the need for a transfusion more often then nontransplant patients, the difference was not statistically significant. Anemia is more common in older patients, which could have influenced the secondary endpoint toward no difference when one may exist. The statistically significant older age of nontransplant patients compared to renal transplant patients is a potential study limitation. The retrospective chart review nature of this trial is also a limitation, because bleeding could have been missed if documentation was not appropriate. Inclusion of Hgb drops as one of the secondary endpoint measures was necessary to capture potential bleeding in transplant patients who may not have received a transfusion. However, this addition may have influenced the results in either group toward no difference due to day-to-day variations in a patient's Hgb potentially being greater than the defined cutoff of 1.

Ideally, anticoagulants and antiplatelets are discontinued prior to surgery to reduce the risk of bleeding. Unfortunately, transplant patients who receive organs from deceased donors often do not have enough advanced notice to appropriately discontinue therapy prior to transplantation. Of the 3 renal transplant patients who received heparin during their transplant admission and bled, 2 were on warfarin at home. There is no institution-specific protocol for reversing anticoagulation or antiplatelet therapy prior to transplantation, but physicians use fresh frozen plasma as deemed necessary. Eng et al[12] reported that in renal transplant patients who pre-operatively received anticoagulation or antiplatelets, there was no increased change in hemoglobin, length of stay, or number of patients requiring transfusions compared to patients not receiving such therapy.

One limitation of the research is that it did not control for confounders that may increase bleeding risks. The 2 study arms were well matched regarding the anticoagulant and antiplatelet confounders that may have increased bleeding rates. However, 3 of the 9 renal transplant patients who experienced bleeding were receiving therapeutic heparin during their renal transplant admission, a time period that has been shown to correlate with high bleeding rates on IV heparin.[2,5] The inclusion of renal transplant patients who were in the early postoperative phase could have contributed to the statistical significance in bleeding rates. Half (3 out of 6) of transplant patients who received heparin during the early postoperative phase of their admission experienced bleeding, which is similar to previous studies reporting bleeding rates in 60% to 64.3% of renal transplant patients in the early postoperative phase.[2,5,8] Also, transplant patients have a statistically significant lower Hgb at initiation of heparin therapy, which may have affected bleeding rates.

Renal transplant patients appear to bleed more often at a therapeutic aPTT compared to nontransplant patients. A prospective trial involving renal transplant patients at any time, other than immediately post transplantation, would be advantageous to identify potential risk factors that increase bleeding risks on IV heparin and the appropriate aPTT goals. The prospective trial should control for potential bleeding confounders to help identify whether renal transplant patients have an increased bleeding risk compared to nontransplant patients.

ACKNOWLEDGMENTS

Financial support/disclosures: No funding was received for this study. All of the authors are affiliated with Saint Barnabas Medical Center. Two of the authors are also affiliated with Rutgers, The State University of New Jersey.

Conflict of interest: The authors have no conflicts of interest to disclose.

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