Hemorrhagic Complications of Enoxaparin and Aspirin in Patients with Kidney Transplants

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Study Objective. To evaluate the frequency of early posttransplant hemorrhagic complications in patients with kidney and kidney-pancreas transplants who received thromboprophylaxis with enoxaparin and aspirin.

Design. Retrospective chart review.

Setting. University-based tertiary care center.

Patients. Thirteen patients who had received enoxaparin within 10 days of kidney or kidney-pancreas transplantation.

Intervention. Medical records were reviewed, and data from patients who had received low-dose aspirin 81 mg once/day and enoxaparin within 10 days of transplantation were collected.

Measurements and Main Results. Major bleeding events were defined as intracranial or retroperitoneal bleeding, or a decrease in hemoglobin of greater than 2 g/dl that was confirmed on repeat evaluation. Nine (69%) of the 13 patients had confirmed major bleeding events and required blood transfusions. Six of the nine patients had elevated serum creatinine levels.

Conclusion. The combination of enoxaparin and low-dose aspirin early after kidney or kidney-pancreas transplantation was associated with a high frequency of hemorrhagic events. Further evaluation is needed to determine the safety of enoxaparin in combination with aspirin after transplantation.

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Thrombotic events after kidney transplantation can have devastating consequences and ultimately result in graft loss. Allograft thrombosis occurs in 0.4–7% of adult kidney transplant recipients.[1, 2] The antithrombotic agents aspirin, warfarin, heparin, and low-molecular-weight heparin (LMWH) have been used to prevent and treat thrombotic complications after kidney transplantation.[3, 4] Few published data exist, however, regarding LMWHs, particularly enoxaparin, for thromboprophylaxis in patients with kidney transplants.

The practice at our institution for over 10 years has been to administer aspirin 81 mg once/day as prophylaxis for allograft thrombosis during the first few months after transplantation. To further decrease the risk of thrombosis, enoxaparin was given to patients who were deemed at increased risk of thrombotic complications. We report our experience with enoxaparin and aspirin in patients with kidney and kidney-pancreas transplants.

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Table 1. Data from Thirteen Patients Administered Enoxaparin after Kidney or Kidney-Pancreas Transplant

Age (yrs)	Weight (kg)	S_{cr} (mg/dl)	Platelet Count[a] (x 10^3/mm^3)	INR	aPTT (sec)	Dose (mg b.i.d.)	Enox Started (POD)	No. of Inpt Days Enox Given	Major Bleed	Hgb Drop (g/dl)	Blood Given (units)	Reexploration Indication
37	41	0.5	142	0.8	24.8	30	2	6	No	None	3	None
59	73	1.1	195	NA	NA	30	2	≥ 1[b]	No	None	None	None
42	82	0.7	219	1.1	26.9	30	3	1	No	NA	1	None
63	52	1	155	1.1	31.3	30	3	5	No	None	None	None
30	110	6.4	122	NA	NA	30	5	≥ 30[b]	Yes	2.2	7	None
40	54	7.4	143	1	20.5	30	1	5	Yes	2.3	4	Bleed around graft
40	71	1.1	88	NA	NA	30	4	6	Yes	3.4	5	Hematoma right kidney after biopsy, 10 x 15 cm
38	52	4.6	81	3	37.3	30	1	5	Yes	3.7	5	Bleed around graft, clots in bladder
23	51	1.1	110	1	26.3	30	1	2	Yes	3.6	6	Perinephric hematoma, 10 x 5 x 5.7 cm
52	65	1.3	NA	1.3	26.2	30	0	3	Yes	3.3	8	Large right retro-peritoneal hematoma[c]
47	70	8.9	254	2.1	49	30	1	6	Yes	2.9	7	Hematoma around allograft
26	76	4.4	225	1.2	25.7	70	0	≥ 10[b]	Yes	2.5	1	None
67	71	2.4	108	1.1	33.9	70	7	8	Yes	3.2	2	None

Enox = enoxaparin; Inpt = inpatient; Hgb = hemoglobin; INR = international normalized ratio (normal range = 0.9–1.1); POD = postoperative day; aPTT = activated partial thromboplastin time (normal range = 20–35 sec) ; S_{cr} = serum creatinine at the time of enoxaparin initiation (normal range= 0.8–1.3 mg/dl); NA = not available.
[a]Normal range = 156–369 x 10^3/mm^3.
[b]Enoxaparin continued after hospital discharge.
[c]Upper pole of kidney.

Methods

The study was conducted in a tertiary care university hospital. A search of electronic medical records identified patients who received a kidney or kidney-pancreas transplant between October 1, 1998, and August 1, 1999, and who were treated with enoxaparin within 10 days of the transplant. This represents the total use of enoxaparin in this population.

The following data were collected from the patients' inpatient medical records: age, height, and weight at the time of transplantation; date of transplant surgery; indication for enoxaparin; enoxaparin dosage and inpatient length of treatment; concomitant drugs, documented bleeding events; and number of blood transfusions. In addition, laboratory data were evaluated: hemoglobin, hematocrit, platelets, serum creatinine levels; international normalized ratio, prothrombin time, and activated partial thromboplastin time. If available, antifactor Xa levels were evaluated.

Occurrence of bleeding events also was noted. Major bleeding events were defined as documented intracranial or retroperitoneal bleeding, or a decrease in hemoglobin of greater than 2 g/dl (confirmed on repeat evaluation). These bleeding events were considered drug-related adverse events unless another probable cause, such as a bleeding disorder or a documented surgical complication, was identified.

Results

Patient demographics and laboratory test results are summarized in Table 1. Mean ± SD patient age was 43 ± 14 years. Subcutaneous enoxaparin was administered within 10 days of transplantation: 2 patients received 1 mg/kg (70

mg) twice/day, and 11 patients received 30 mg twice/day. All patients received low-dose aspirin 81 mg once/day. Patients received immunosuppressive therapy with tacrolimus, mycophenolate mofetil, and prednisone; one patient received only tacrolimus and prednisone. Patients did not receive warfarin or any agent other than aspirin and enoxaparin that could cause bleeding complications.

None of the 13 patients developed thrombotic complications immediately after their surgery. Nine patients (69%) had a confirmed major bleeding episode while receiving enoxaparin. Six of these patients began receiving enoxaparin within 1 day of transplantation, and the bleeding event occurred within the first 6 days of receiving enoxaparin. Three of the 13 patients had kidney-pancreas transplants; one of these three had a major bleeding event. Bleeding events were similar among patients who were operated on by different surgical teams. To manage bleeding complications in the nine patients, all patients received blood transfusions, and six patients had reexploratory surgery and wound drainage. After identification of a bleeding event, enoxaparin was discontinued in seven of the nine patients. A hemoglobin level was not measured in one patient, who thus was classified as not having a major bleeding event. Antifactor Xa levels were not measured in any of the patients. One patient died several months after transplantation due to complications unrelated to any enoxaparin-induced hemorrhage. At their most recent follow-up visits, the 12 surviving patients had functioning grafts, and the mean serum creatinine level was 1.8 ± 0.8 mg/dl.

After our study was completed, the use of enoxaparin in combination with aspirin was discontinued in this patient population at our institution.

Discussion

The use of enoxaparin has increased dramatically in recent years. Many clinical trials have explored new treatment indications. Limited published data exists, however, regarding enoxaparin in patients with kidney transplants.

One study reported the results of administering dalteparin 2500 or 5000 U postoperatively to 120 kidney transplant recipients. No significant bleeding events, defined as a "necessity for surgical intervention" or requiring a transfusion of more than 2 units of blood, were found.[4]

In our study, we found that major bleeding complications occurred at a rate of 69% in patients receiving enoxaparin after kidney or kidney-pancreas transplantation. This was much higher than the historic 5% bleeding rate (defined as a need for reexploration or postoperative transfusion) in this transplant population at our institution. There are two possible reasons for this discrepancy. First, all our patients were receiving aspirin, which has been given to patients after transplantation for many years without a significant increase in morbidity. Perhaps the combination of aspirin and enoxaparin increased the risk of bleeding. The influence of aspirin, enoxaparin, and combination therapy on bleeding time were assessed in one study[5]; patients had not undergone transplant. The bleeding time was 2- to 3-fold longer after combination therapy with aspirin and enoxaparin compared with either agent alone.[5] Another study, also not done in transplant recipients, found that while combination therapy of the LMWH reviparin and aspirin had no effect on plasma anti-Xa activity and Heptest (clotting assay that is sensitive to both anti-Xa and anti-IIa activity, as well as inhibition of the extrinsic pathway by LMWH-stimulated release of tissue factor inhibitor) results, bleeding time was longer in patients who received the combination therapy compared with patients who received either agent alone.[6]

The second reason for the bleeding rate discrepancy may be due to enoxaparin's renally dependent elimination, leading perhaps to an accumulation of the agent during the early posttransplant period. One study showed that elimination of enoxaparin after a single dose is twice as long in patients with renal insufficiency compared with patients with normal renal function.[7] Another study found that the frequency of bleeding complications after enoxaparin treatment was significantly higher in patients with renal insufficiency (serum creatinine of 2.0 mg/dl or greater) compared with patients with normal renal function (30% vs 2%, $p<0.001$).[8] In our evaluation, all four patients without bleeding complications had serum creatinine levels of 1.1 mg/dl or below (normal range 0.8–1.3 mg/dl). The estimated creatinine clearance for this group was 47–99 ml/minute, as calculated by the Cockcroft-Gault method.[9] Three of the nine patients who experienced a major bleeding event while receiving enoxaparin and aspirin had normal serum creatinine levels and creatinine clearances above 30 ml/minute.

Study Limitations

Due to the retrospective nature of our study, determining how the risk of allograft thrombosis was assessed was difficult. In addition, we undertook this study because we had noticed that patients who began enoxaparin postoperatively were having bleeds, so we assessed only patients receiving enoxaparin. There was no control group. Thus, we were unable to compare patient coagulability and the frequency of major bleeding events in patients receiving only aspirin compared with those receiving combination therapy. Another limitation is the absence of antifactor Xa levels. Finally, only a small number of patients were studied because use of this combination therapy was stopped after our analysis.

Conclusions

The use of enoxaparin in combination with low-dose aspirin within 10 days of kidney or kidney-pancreas transplantation was associated with a high frequency of hemorrhagic events. The usual twice-daily dosages of LMWH may be excessive in these transplant recipients and may result in drug accumulation. Prospective studies are needed to evaluate further the safety of enoxaparin in combination with aspirin after kidney and kidney-pancreas transplantation, as well as to define appropriate dosage regimens in these patients.

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