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Heparin-Dependent Platelet Factor 4 Antibodies and the Impact of Renal Function on Clinical Outcomes:

A Retrospective Study in Hospitalized Patients

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Abstract

Patients who develop thrombocytopenia and heparin-dependent platelet factor 4 antibodies while on or shortly after receiving a heparin product are often considered for alternative anticoagulation to minimize the occurrence of life and limb-threatening events. We retrospectively reviewed the hospital records of 97 patients with heparin-dependent platelet factor 4 antibodies (at least 65 of whom were felt by the primary team to have HIT) to determine the influence of renal performance on alternative anticoagulant selection and associated clinical events. For GFR >30, approximately 30% of patients who did not receive alternative anticoagulation had documentation of concern for HIT versus 60% of patients in the GFR <30 group. We found that a smaller proportion of patients with severe renal insufficiency, GFRs < 30 mL/min/1.73 m² were treated with an alternative anticoagulant - this despite their high incidence of thromboembolic events and comparable rates of HIT. Overall, rates of hemorrhage did not differ between patients when compared to those without renal insufficiency. However, there was a higher percentage of hemorrhagic events for patients with GFR < 30 mL/min/1.73 m² on alternative anticoagulants. This study demonstrates that patient's with GFRs < than 30 mL/min/1.73 m² need to be assessed for overall hemorrhagic risk at the time of starting an alternative anticoagulant and need to be monitored closely to avoid hemorrhagic events.

Keywords

heparin-induced thrombocytopenia; platelet factor 4 antibodies; renal insufficiency

Introduction

Heparin-dependent Platelet Factor 4 (PF4) antibody determination represents the diagnostic cornerstone among patients suspected of having heparin-induced thrombocytopenia (HIT). In this clinical setting early management includes heparin cessation and thromboprophylaxis with an alternative, non-heparin anticoagulant.¹

While the benefit of a proactive approach to use of an alternative anticoagulant is well documented in HIT, treatment decisions are often influenced by a variety of patient- and clinician-related factors, including the perceived risk of hemorrhagic complications with systemic anticoagulant therapy.

The following single-center study was undertaken to determine the impact of renal function on clinical outcomes in hospitalized patients with positive heparin-dependent platelet factor 4 antibodies.

Methods

The study population consisted of all hospitalized patients at Duke University Medical Center with positive (absorbance at 405nm; OD $\geq$ 0.4) heparin-dependent PF4 antibodies by commercial (GTI Inc., Brookfield, WI, USA) enzyme-linked immunosorbent assay (ELISA) from January 1st, 2005 to December 31st, 2005. Institutional Review Board approval was obtained and our coagulation laboratory database was queried to identify these patients. For this report, only patients 18 years of age or older with a positive confirmatory step were included. The confirmatory step is performed concurrently with the PF4 ELISA and is positive if there is a greater than 50% decrease in absorbance in the presence of additional heparin. Platelet activation assays for confirming HIT, such as the serotonin release assay, are not used at our institution.

Both hospital charts and computerized patient data were reviewed. A database was created to collect data on demographics, glomerular filtration rate (GFR), heparin exposure (which included unfractionated heparin by intravenous and/or subcutaneous administration and/or heparin flush and/or enoxaparin), non-heparin anticoagulation usage including direct thrombin inhibitor (DTI, ie, lepirudin, argatroban, or bivalirudin) or other alternative anticoagulant (eg, fondaparinux), and documentation of concern for HIT in the chart or dictated discharge summary. Endpoint measures included thromboembolic events, hemorrhagic events, and mortality during the hospitalization. Age was calculated by using date of birth and the admit date. For this study, the MDRD GFR Calculator found on the National Kidney Foundation™ (by Stephen Z. Fadem, M.D.) website was used.² The equation for the MDRD GFR is as follows:

$$GFR \left(\text{mL/min/1.73m}^2 \right) = 186 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$$

Descriptive analysis using mean and standard deviation (SD) for continuous variables and percentages for categorical variables was used to compare patients with a GFR <30, GFR 30 to 59, and GFR >59. To evaluate for data entry error, 10% of the data points were re-assessed.

Results

Figure 1 captures the overall flow of this retrospective study and shows that of the 97 patients included in the study, the distribution was fairly even between patients with a GFR >59 (N=36), GFR 30 to 59 (N=29), and GFR <30 (N=32). In most cases, an anti-heparin/platelet factor 4 antibody test was sent due to a fall in patient's platelet count and known exposure to heparin, although HIT was not ultimately considered in almost a third of these individuals. Of the 37 patients who had a thrombotic event, 29 patients had the thrombotic event prior to the anti-heparin/platelet factor 4 antibody test being sent. In the 47 patients who received alternative anticoagulation, 36 patients had heparin discontinued prior to or on the day that the positive anti-heparin/platelet factor 4 antibody test was sent, 10 patients had heparin discontinued within 8 days of the positive test being sent, and in one case the date heparin was discontinued is unclear. In the 50 patients who did not receive an alternative anticoagulant, 26 patients had heparin discontinued prior to or on the day that the positive anti-heparin/platelet factor 4 antibody test was sent, 14 patients had heparin discontinued within 14 days of the positive test being sent, 6 patients remained on either unfractionated heparin (intravenous or subcutaneous administration) or enoxaparin, and 4 cases were unclear. Among the 50 patients who did not

receive an alternative anticoagulant in the form of a direct thrombin inhibitor or fondaparinux, 8 patients were started on coumadin, 4 patients had still been on heparin at the time that coumadin was started.

Table 1 shows the overall study population demographics and percentage alternative anticoagulant usage. In this cohort of 97 patients, 37 patients had a thrombotic event and 60 did not. In all GFR groups, 87% to 95% of patients who received alternative anticoagulant had documentation of concern for HIT in the chart or dictated discharge summary. In patients with GFR >30, approximately 30% of patients who did not receive alternative anticoagulation had documentation of concern for HIT in the chart or dictated discharge summary versus 60% of patients in the GFR <30 group.

Table 2 breaks down demographics and endpoint measures by GFR group. Overall length of hospitalization, length of stay after a positive anti-heparin/platelet factor 4 antibody test, and duration of alternative anticoagulation was less for patients with GFR >59 and was most for patients with GFR 30 to 59. A lower percentage of patients with a GFR < 30 were treated with an alternative anticoagulant at 31% compared to patients with GFR > 30 (76% for GFR 30-59 and 42% for GFR >59). Of note patients with a GFR<30 had a high incidence of thromboembolic events at 41% (versus 33% for GFR >59) and a lower alternative anticoagulation usage in patients with a thromboembolic event at 62% (versus 75% for GFR >59 and 100% for GFR 30-59). Of the 37 thrombotic events, 14 were venous thromboembolic events (extremity deep vein thrombosis and/or pulmonary embolus), 6 strokes, 9 extremity arterial thrombosis, 5 cardiac events (1 left ventricular thrombus, 2 coronary artery thrombosis, 1 saphenous vein thrombosis, 1 coronary artery stent thrombosis), 1 splenic and renal infarcts, 1 heparin-induced skin necrosis, and 1 TIPS shunt thrombosis.

From Table 3, the differences in morbidity and mortality are given by GFR and by treatment with or without alternative anticoagulation usage. In the GFR <30 group treated with an alternative anticoagulant, all received either argatroban or bivalirudin. In the GFR 30-59 group treated with an alternative anticoagulant, most received argatroban or bivalirudin, but almost a fifth received lepirudin. Among the 5 patients with hemorrhage while on an alternative anticoagulant in the GFR < 30 group and 4 patients in the GFR 30-59 group, 3 patients in each group had to discontinue the alternative anticoagulant due to hemorrhage. In the GFR ≥ 59 group, 47% patients were treated with argatroban, 40% with lepirudin, and 1 patient (6.5%) each with bivalirudin and fondaparinux. Among the 3 patients with hemorrhage while on an alternative anticoagulant in the GFR ≥ 59 group, all 3 had to discontinue the alternative anticoagulant due to hemorrhage. Of the 12 hemorrhagic events on an alternative anticoagulant therapy, all were noted to have bleeding complications and with a hemoglobin drop ranging from 1.8 to 3.5 g/dL within a 24 hour period (mean 2.3, SD 0.5).

Discussion

As shown in Table 3, most patients who received an alternative anticoagulant (87% to 90%), the primary team had documented the concern for HIT in the chart or discharge summary. However, for patients with GFR <30 and concern for HIT, 60% of patients did not receive an alternative anticoagulant. This suggests that GFR may impact on the decision to use an alternative anticoagulant.

There are several other clinically relevant observations from this study. For patients with GFR>30, only a bit more than half were initiated on an alternative anticoagulant drug for a thromboembolic event. Second, for patients with GFR<30 who had a thromboembolic event, a lower percentage were on an alternative anticoagulant. Finally, patients with GFR<30 were

at higher risk than patients with $GFR > 30$ of having both a thromboembolic event as well as having hemorrhagic events while on an alternative anticoagulant.

There have been several reports that the dosing guidelines for lepirudin need to be lowered to avoid hemorrhage³⁻⁵, especially in patients with renal insufficiency.⁶⁻⁷ Other's have shown that with close monitoring, patients with renal insufficiency have been treated successfully with both argatroban⁸ and with bivalirudin.⁹

Our study shows that patients with $GFR < 30$ and positive anti-heparin/platelet factor 4 antibodies offer a greater challenge when making treatment decisions when compared to patients with $GFR > 30$ due to the concern of hemorrhage. Depending on the degree of renal insufficiency, patients may be at risk of bleeding due to uremia.¹⁰ In addition to uremic bleeding, patients may also be on anti-platelet drugs. Given the risk of hemorrhage, alternative anticoagulant drugs with the shortest half-lives and the optimal management in patients with renal insufficiency should be further explored for safety and efficacy.

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Figure 1.
Overall Flow of Retrospective Study

Table 1

Anti-Heparin/PF4 Antibody and Confirmatory Step Test Positive: Demographics and Use of Alternative Anticoagulant (N=97)

<i>Variables</i>	
Age (yrs, mean $\pm$ SD)	64 $\pm$ 14
Number of Female	54 (56%)
Number of African American	31 (32%)
Number felt to have HIT by primary team	* 65 (67%)
No Alternative Anticoagulant	50 (52%)
Argatroban	29 (30%)
Lepirudin	10 (10%)
Bivalirudin	7 (7%)
Fondaparinux	1 (1%)

* unclear in additional 5 patients

Table 2

Anti-Heparin/PF4 Antibody and Confirmatory Step Test Positive: Demographics and Differences in Treatment and Outcomes for Patients with Renal Insufficiency

<i>Variables</i>	GFR $\geq$ 59 N=36 (37%)	GFR 30-59 N=29 (30%)	GFR < 30 N=32 (33%)
Age (yrs, mean $\pm$ SD)	59 $\pm$ 13	69 $\pm$ 12	65 $\pm$ 15
No. of Female	15 (42%)	17 (59%)	22 (69%)
No. of African American	11 (31%)	6 (21%)	14 (44%)
Services Patients Admitted to: • Cardiology • Cardiovascular Surgery • Medicine • Other Surgical Services	4 4 18 10	9 15 3 2	4 14 9 5
GFR with 1st positive PF4 panel	102 $\pm$ 41	44 $\pm$ 8	16 $\pm$ 7
Platelet Count with 1st PF4 panel (mean $\pm$ SD)	98,083 $\pm$ 53,534/ μ L	83,966 $\pm$ 44,897/ μ L	101,437.5 $\pm$ 73,078/ μ L
Hemorrhagic event	10 (28%)	9 (31%)	11 (34%)
Alternative Anticoagulant usage	[†] 15 (42%)	22 (76%)	10 (31%)
Overall Length of Stay in the hospital (days, mean $\pm$ SD)	20 $\pm$ 17	[*] 35 $\pm$ 28	24 $\pm$ 16
Length of Stay after 1st positive PF4 panel (days, mean $\pm$ SD)	12 $\pm$ 11	24 $\pm$ 26	16 $\pm$ 15
Duration of Alternative Anticoagulation	9 $\pm$ 5	12 $\pm$ 12	11 $\pm$ 8
Death	3 (8%)	6 (21%)	13 (41%)
Thromboembolic event	12 (33%)	12 (41%)	13 (41%)
Alternative Anticoagulant usage among patients with a thromboembolic event	9/12 (75%)	12/12 (100%)	8/13 (62%)
Thromboembolic event among patients who died	1/3 (33%)	4/6 (67%)	9/13 (70%)

[†] Fondaparinux was received by 1 patient

^{*} One patient was hospitalized for 142 days

Table 3
Anti-Heparin/PF4 Antibody and Confirmatory Step Test Positive: Differences in Outcomes for Patients with Renal Insufficiency by Treatment

Variables	GFR ≥ 59 N=36 (37%)		GFR 30-59 N=29 (30%)		GFR < 30 N=32 (33%)	
	† Alternative Anticoagulant N=15 (42%)	No Alternative Anticoagulant N=21 (58%)	Alternative Anticoagulant N=22 (76%)	No Alternative Anticoagulant N=7 (24%)	Alternative Anticoagulant N=10 (31%)	No Alternative Anticoagulant N=22 (69%)
Documented in chart or discharge summary concern for HIT	13/15 (87%)	* 7/21 (33%)	* 21/22 (95%)	2/7 (29%)	* 9/10 (90%)	** 13/22 (60%)
Argatroban usage	7 (47%)	-	14 (64%)	-	8 (80%)	-
Lepirudin usage	6 (40%)	-	4 (18%)	-	0 (0%)	-
Bivalirudin usage	1 (6.5%)	-	4 (18%)	-	2 (20%)	-
Platelet Count with 1 st PF4 panel (mean±SD)	114,933 ± 69,934	100,333 ± 60,770	79,455 ± 39,223	98,143 ± 60,936	133,500 ± 105,327	86,864 ± 49,163
Hemorrhagic event during hospitalization	5 (33%)	5 (24%)	9 (41%)	0 (0%)	6 (60%)	5 (23%)
Hemorrhagic event while on Alternative Anticoagulant	3 (20%)	-	4 (18%)	-	5 (50%)	-
Thromboembolic event	9 (60%)	3 (14%)	12 (55%)	0(0%)	8 (80%)	5 (23%)
Thromboembolic event before or ‡ after Alternative Anticoagulant discontinued	9/9 (100%)	-	‡ 12/12 (100%)	-	6/8 (75%)	-
Death	2 (13%)	1 (0.5%)	6 (27%)	0 (0%)	5 (50%)	8 (36%)

† Fondaparinux was received by 1 patient (6.5%)

‡ Alternative Anticoagulant discontinued in 1 patient the day before a thrombotic stroke and subsequent death

* data unknown for one patient

** data unknown for two patients