Prevalence of Heparin-Induced Thrombocytopenia in Patients Receiving Continuous Veno-Venous Hemodialysis with Extracorporeal Heparin Exposure

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Introduction:

Heparin is a clinically important anticoagulant therapy. One of the adverse effects of heparin exposure is heparin-induced thrombocytopenia (HIT). HIT is an immune-mediated, potentially life-threatening adverse effect of heparin treatment. Antibodies against heparin and platelet factor 4 (HIT antibodies) are induced by heparin administration, and can stimulate platelets and endothelial cells, resulting in an excess production of thrombin, inducing thrombocytopenia and thromboembolic events. HIT is clinically diagnosed by a drop in platelet count to less than 100,000/μL or a 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation other than HIT. A positive laboratory test for HIT antibodies supports the clinical diagnosis. The development of HIT can be either delayed-onset, typically 5 to 14 days after the initial administration of heparin, or rapid-onset, occurring soon after the re-administration of heparin in a patient with prior heparin exposure and HIT antibodies.

In one study HIT in the ICU setting was very uncommon (0.3-0.5%)[1], whereas thrombocytopenia from other causes is very common (30-50%). Other studies have shown that the general prevalence of HIT is 0.5-5%, depending on the clinical setting[2]. Thirty to 50% of HIT patients suffer from thromboembolic events, and the mortality of HIT is 10 to 20%.

The assay for the HIT antibody in serum has high sensitivity (high negative predictive value) but specificity is low. A false-positive detection of HIT antibody could potentially lead to adverse events. A false diagnosis of HIT may prompt replacement of heparin by an alternative anticoagulant, which can lead to bleeding. Heparin alternatives are also expensive and may require closer monitoring. Also, when patients receive the diagnosis of HIT, heparin is no longer a feasible anticoagulation therapy for the patient.

In an ICU setting there are many patients with acute renal failure (ARF) and tenuous hemodynamic status that require continuous veno-venous hemodialysis (CVVHD). A subset of these patients often have multi-organ system dysfunction and have contraindications of systemic administration of heparin, but do continue to receive heparin through the CVVHD extracorporeal circuit. The prevalence of HIT in unknown in this population of patients on CVVHD with only extracorporeal heparin exposure.

Hypothesis:

The prevalence of HIT in patients receiving CVVHD whose only exposure to heparin is via the extracorporeal circuit of the CVVHD apparatus is significantly lower than the prevalence of HIT in patients receiving CVVHD who have either intravenous or

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[1] Selleng K. Heparin-Induced Thrombocytopenia in Intensive Care Patients. *Crit Care Med*. 2007; 35(4):1165-1176.

[2] Warkentin TE. Heparin-induced thrombocytopenia: a ten-year retrospective. *Annu Rev Med.* 1999; 50: 129–147.

subcutaneous exposure to heparin. We hypothesize that the difference of prevalence between these two groups will be significant enough that the clinical course of thrombocytopenic patients on CVVHD with only extracorporeal heparin exposure may be altered.

Methods:
The primary outcome measured will be the diagnosis of HIT as measured by a positive serum assay for the heparin associated antibody.

Study type: observational
Study design: retrospective, longitudinal, cohort study

Statistical analysis will be performed with chi square analysis. A comparison of proportions will be done, where:
Group 1: Patients in an ICU on CVVHD receiving only extracorporeal heparin through the HD circuit
Group 2: Patients in an ICU on CVVHD receiving subcutaneous or intravenous heparin

Null hypothesis: There is no difference in the prevalence of HIT in the two groups. As only one degree of freedom, the diagnosis of HIT, will be considered, to reject the null hypothesis with a p-value <0.05 (with a 95% probability that this did not occur by chance) chi square result will need to be greater than 3.8

Distribution of Chi square Probability

	Probability			
degrees of freedom	0.10	0.05	0.01	0.001
1	2.7	3.8	6.6	10.8
2	4.6	6.0	9.2	13.8
3	6.3	7.8	11.3	16.3
4	7.8	9.5	13.3	18.5
5	9.2	11.1	15.1	20.5
6	10.6	12.6	16.8	22.5
7	12.0	14.1	18.5	24.3
8	13.4	15.5	20.1	26.1
9	14.7	16.9	21.7	27.9
10	16.0	18.3	23.2	29.6

Power calculations for Chi-square:
If the prevalence of HIT overall is 0.5% - 5%, the prevalence of HIT in patients whose only exposure to heparin is via a dialysis circuit will be less then 1 %. We also estimate that the number of patients in group and 1 and 2 are not equal, with a 3:1 ratio of patients on CVVHD who are receiving heparin compared to patients on CVVHD that are only receiving heparin via the dialysis circuit.

Thus when p1= 0.01 (1% HIT Ab positive), and p2= 0.05 (5% HIT Ab positive), with a ration of Group2/Group 1 = 3
N= 241 in Group 1, N= 724 in Group 2
If there are 400 CVVHD patients treated at Columbia University Medical Center in one year, and if 25% of them develop thrombocytopenia with a presumed diagnosis of HIT, and have the HIT Ab sent, the retrospective data will need to extend over a 10 year course.

When p1= 0.001 (0.1% HIT Ab positive), and p2= 0.05 (5% HIT Ab positive), with a ration of Group2/Group 1 = 3
N= 148 in Group 1, N= 443 in Group 2
If there are 400 CVVHD patients treated at Columbia University Medical Center in one year, and if 25% of them develop thrombocytopenia with a presumed diagnosis of HIT, and have the HIT Ab sent, the retrospective data will need to extend over a six year course.

When p1= 0.001 (0.1% HIT Ab positive), and p2= 0.01 (1% HIT Ab positive), with a ration of Group2/Group 1 = 3
N= 937 in Group 1, N= 2810 in Group 2
If there are 400 CVVHD patients treated at Columbia University Medical Center in one year, and if 25% of them develop thrombocytopenia with a presumed diagnosis of HIT, and have the HIT Ab sent, the retrospective data will need to extend over a 40 year course.

After initial data collection analysis, it will be determined in a multi-center study will be necessary to accumulate the number of patients needed to achieve acceptable power

Subject Selection:

Inclusion criteria: Adult male and females who meet the criteria below

1. Patients who are >= 18 years of age
2. Patients should be in an ICU setting of CUMC receiving CVVHD
3. Patient have the clinical diagnosis of HIT, with a HIT Ab result

Exclusion criteria:

1. Patients who have documented history of HIT
2. Chronic thrombocytopenia, platelets < 100,000/µL

3. Hematopoietic malignancy
4. Patients who have received anti-neoplastic agents

Miscellaneous:
Informed consent: This study would qualify for a waiver of informed consent as there is no risk to the patients and there would be no distribution of confidential information

Location: If larger numbers than expected will be needed to power this study, a multi-center study may be required. Other centers of recruitment must use CVVHD routinely in their ICUs. The study should be limited to centers that use CVVHD as oppose to CVVH as the difference in the mechanism of CVVH and CVVHD may affect heparin exposure to patients. Furthermore, it must be protocol to send a HIT Ab assay when there is presumed HIT or there is suspicion for HIT at the other centers for recruitment.