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Effect of Subcutaneous Unfractionated Heparin Prophylaxis on Activated Partial Thromboplastin Time: A Retrospective Evaluation★,★,★,★,★,★,★

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Abstract

Study Objective—Characterize the incidence of elevated aPTT results in patients treated with prophylactic, subcutaneous unfractionated heparin (UFH).

Design—Retrospective, cohort analysis.

Setting—Single-center, university hospital.

Measurements—Evaluation of 257 patients with activated partial thromboplastin time (aPTT) testing both prior to and following subcutaneous (SC) unfractionated heparin (UFH) therapy.

Main Results—Evaluated patients received UFH 5000 units every 8 hours. Baseline aPTT values were within the normal range (mean $\pm$ SD, 32.0 $\pm$ 8.5 seconds). After initiation of UFH, aPTT values increased (mean $\pm$ SD, 37.6 $\pm$ 15.2 seconds). After 24 hours of SC UFH, mean aPTT

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values (mean $\pm$ SD, 38.6 ± 15.5) exceeded the normal laboratory range (23.3–35.7 seconds). An elevated aPTT result after UFH was associated with baseline aPTT, length of therapy, and weight-based UFH dose. A significant association was not identified between aPTT elevation and age, race, sex, history of liver disease, type of admission, or transfusion of blood products.

Conclusions—Treatment with UFH resulted in a small, but significant, increase in aPTT.

Keywords

Unfractionated heparin; Venous thromboembolism prophylaxis; Activated partial thromboplastin time

1. Introduction

The estimated annual incidence of venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is 17 cases per 100,000 patients in the general population; however, the incidence of VTE is increased over 260-fold in hospitalized patients [1–2]. The risk of VTE also increases with age (especially age greater than 70 years), comorbid conditions (malignancy, history of VTE, pregnancy, congestive heart failure), reduced mobility, and recent surgery or trauma [3,4]. Based on this information, the American College of Chest Physicians (CHEST) recommends pharmacologic prophylaxis using subcutaneous (SC) unfractionated heparin (UFH) or low molecular weight heparins (LMWH) [1]. Since the twice daily (BID) LMWH regimen often utilized for surgical VTE prevention is contraindicated in patients with indwelling neuraxial catheters due to an increased risk of epidural hematoma development [5], SC UFH is often chosen for VTE prophylaxis in patients with indwelling neuraxial catheters.

Neuraxial catheters have been repeatedly shown to improve postoperative pain and patient outcomes following major abdominal and thoracic surgery [6–7]. However, this patient population is also at high risk for VTE and requires pharmacologic prophylaxis [1]. While large case series have reported utilization of SC UFH with indwelling neuraxial catheters without complications [8], the landmark study supporting the use of BID SC UFH for VTE prevention also reported statistically significant increases in activated partial thromboplastin time (aPTT) ($P < .001$) following SC UFH administration [9]. Unfortunately, the exact aPTT values were not published. Additionally, thrice daily dosing (TID) of SC UFH, which is preferred by many surgeons for postoperative VTE prophylaxis, was not examined. Subsequent publications have commented on the unknown effect TID dosing may have on aPTT [5].

We hypothesized that SC UFH administered TID will only slightly prolong aPTT to values that remain in our institution's normal laboratory range (23.3–35.7 seconds), which would help evaluate the safety of TID SC UFH with concomitant neuraxial catheter use. The primary objective of this study was to determine the incidence of elevated aPTT results in hospitalized patients treated with 5000 units TID SC UFH for VTE prophylaxis. Secondary objectives were to evaluate the impact of body mass index (BMI) on aPTT values and incidence of VTE in patients receiving prophylactic UFH.

2. Materials and Methods

This retrospective, single-center, institutional review board-approved study was conducted on a cohort of medical and surgical patients admitted to a large academic medical center between July 2011 and January 2012. Subjects included were age 18 and older that received doses of SC UFH for VTE prophylaxis and had aPTT testing performed both prior to and during SC UFH therapy. Exclusion criteria encompassed patients without documented height or weight and patients who received therapeutic intravenous UFH at any point during the specified admission.

Patient charts and information stored in a clinical data warehouse were reviewed to obtain all pertinent data. Data were collected and confirmed by 3 investigators. Collected demographic information included age, gender, race, height, weight, and length of stay. Data regarding UFH administration included dose, frequency, number of days of heparin therapy, and aPTT laboratory values. Pertinent ICD-9 diagnosis codes for liver dysfunction, bleeding complications or coagulopathies, and procedure codes related to administration of blood products during the admission were also examined. Incidence of VTE was also evaluated using ICD-9 diagnosis codes. Concomitant antiplatelet use was not assessed; however, patients with ICD-9 diagnosis codes for long-term anticoagulation with a vitamin K antagonist were excluded.

The baseline aPTT was defined as the aPTT value immediately preceding initiation of UFH therapy. All subsequent aPTTs drawn during active UFH therapy were included in the comparative analysis, with statistical adjustment for repeated measures in the same patient. The time between the baseline aPTT and subsequent aPTT values were measured in number of hours.

2.1. Statistical Analysis

Prior to data collection, a power analysis was conducted and determined that a sample size of 200 patients would be required for a power of 80% to detect a difference of 3 seconds between the baseline and treatment aPTT values. Descriptive statistics were determined for unique study subjects. Since multiple aPTT measures were recorded on each subject, univariate associations between aPTT and each variable in the data were examined using linear mixed models with a random subject effect to account for correlation of repeated measures of aPTT within each subject. All variables with *P* values less than 0.20 were considered in a multivariable mixed linear regression model.

All analyses were conducted in SAS v. 9.3 (SAS Institute, Cary, NC). *P* values less than 0.05 were considered significant.

3. Results

Inclusion criteria were met by 935 patients. Of those, 658 were excluded, leaving 257 patients in the final analysis (Fig. 1). Patient demographic data and aPTT measurement data are presented in Table 1. Receipt of blood products was not associated with aPTT elevation within the total cohort. Mean baseline aPTT measurements were within normal ranges

(mean $\pm$ SD; 32.0 ± 8.5 seconds) for our institutional values (23.3–35.7 seconds). After receiving one or more doses of SC UFH, the mean aPTT increased to 37.6 seconds (SD, ± 15.2 seconds) slightly greater than laboratory normal values (Table 1). After 24 hours of SC UFH therapy, aPTT values were further elevated (mean $\pm$ SD; 38.6 ± 15.5 seconds; Table 1).

Univariate analysis found baseline aPTT, total weight-based heparin dose, length of heparin therapy, and BMI to be associated with an increase in aPTT following administration of SC UFH (Table 2). In the multivariable model, all of those associations remained statistically significant. BMI was not considered in the multivariable model due to its co-linearity with total weight-based heparin dose. There was not an association between aPTT elevation and history of liver disease, age, race, sex, or medical versus surgical or admitting service. Further analysis of aPTT results after greater than 24 hours of SC UFH therapy ($n = 160$) found that weight-based heparin dose was associated with aPTT increase in the univariate but not multivariate model. Additionally, BMI was no longer associated with a change in aPTT in the univariate model for patients receiving UFH therapy for greater than 24 hours.

4. Discussion

Our data suggest that TID SC UFH elevates aPTTs values above normal laboratory ranges. These results appear to correlate with the findings of Gallus et al. [9] using BID SC UFH that led to the widespread use of low-dose heparin for VTE prophylaxis; however, the exact aPTT measures from the Gallus et al. trial have not been published [9].

Since there appears to be a small, but measureable increase of aPTT, the safety of maintaining indwelling neuraxial catheters during TID SC UFH use remains an unanswered question. The American Society for Regional Anesthesia and Pain Medicine guidelines recommend the preferential use of BID UFH SC and note that the risk of TID UFH should be “assessed on an individual basis” with daily regular evaluation for new or progressive neurodeficits [5]. However, there is not evidence that TID dosing is more dangerous as the degree of aPTT elevation with BID or TID dosing has also not been described for comparison. Notably, 23 of our subjects had an indwelling neuraxial catheter. All patients with neuraxial catheters had normal baseline aPTT (< 33 seconds) at the time of catheter placement and none developed epidural hematomas. Nine of these subjects did have a documented aPTT level elevated above our institution’s normal range (23.3–35.7 seconds) at some point during heparin therapy.

Other studies have tried to address the safety of TID SC UFH in the presence of a neuraxial catheter. Pace et al. also retrospectively examined this question in a review of 3253 patients with epidurals in which 1594 patients received BID UFH and 714 patients received TID dosing [10]. Ten subjects on BID therapy and 20 patients on TID therapy were noted to have elevated aPTT values (>35 seconds) on the day of epidural removal. They concluded that routine measurement of aPTT values at the time of epidural catheter removal was not supported as less than 3% of patients had abnormal values, which were of unknown clinical significance. Davis et al. reviewed 928 thoracic surgery patients with indwelling epidurals and noted aPTT to be prolonged over 40 seconds in 115 patients (12%) [11]. However, they

also stated that further investigation was needed. Both studies reported zero epidural hematomas.

Our investigation differs from other studies as we were interested in examining the degree of change of aPTT (if any) after SC UFH for VTE prophylaxis. Prior studies have noted SC UFH to increase the risk of bleeding [12–13] and cause patients to have unpredictable changes in or even to reach therapeutic aPTT values [9]. After SC UFH administration, our mean aPTT values exceeded normal laboratory values (23.3–35.7 seconds). However, values did not approach therapeutic anticoagulation, defined as aPTT 1.5 to 2.5 times baseline (61–105 seconds) and our mean aPTT increased only 5.6 seconds (approximately 1.2 times baseline). This generalized finding indicates that the change in aPTT is often small, consistent with the low reported incidence of neuraxial complications with concomitant SC UFH. However, any aPTT elevation after UFH administration may raise questions about the safety of using TID dosing in patients with neuraxial catheters [5]. Further, many physicians would consider an aPTT of 50 seconds, one standard deviation above the mean, to be a contraindication to maintaining an indwelling epidural catheter.

In addition to the BID versus TID dosing, another interesting difference between our study and the work by Gallus et al. is that the average patient weight was substantially greater in our study [9]. The Center for Disease Control reports that 35.7% of Americans are classified in the “obese” BMI category as of 2011, which is more than twice the 16% of Americans who met those criteria in 1974 [14–15]. Our initial data evaluation noted a significant association between weight-based heparin dose and BMI with aPTT change, supporting prior findings that standard-dose SC UFH administered to patients with a higher BMI may not result in the same degree of anticoagulation as normal weight counterparts [16]. However, this association was lost when only subjects receiving at least 24 hours of SC UFH therapy were examined. After greater than 24 hours of heparin therapy, mean aPTT values were greater than our normal laboratory aPTT range (23.3–35.7 seconds), regardless of BMI.

As this study was conducted retrospectively, there are inherent limitations to interpretation of the results. Specifically, patients were not randomized nor were providers blinded, and it is not possible to confirm why UFH was used in place of other anticoagulants such as LMWH. Additionally, we are unable to define a temporal relationship between SC UFH administration and change in aPTT since the time between lab draws and medication administration varied between subjects.

Our results indicate many future directions to explore. Future prospective studies should attempt to confirm or refute the mean aPTT change (5.6 seconds) from baseline patient values prior to UFH SC therapy. Additionally, future reports need to characterize which patients are more likely to achieve an elevated aPTT after treatment with low-dose SC UFH for VTE prophylaxis and may have an increased risk of neuraxial hematoma development. Finally, to better assess the clinical significance of this aPTT elevation, studies should report the degree of aPTT elevation that occurs with BID SC UFH as this was not quantified by Gallus et al. [9].

In conclusion, this retrospective cohort study found that aPTT times were elevated from baseline following low-dose SC UFH administration for VTE prophylaxis. While this increase was not therapeutic, mean aPTT values were elevated above our normal laboratory range.

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Fig. 1. Patient Enrollment. (aPTT: activated partial thromboplastin time; UFH: unfractionated heparin).

Table 1

Patient Demographic and aPTT Measurement Data

Age (Years)	58.3 ± 14.7
Male	157 (61.1)
Race	
Caucasian	152 (59.1)
African American	98 (38.1)
Other	7 (2.8)
Length of stay (Days)	13.3 ± 13.4
Height (cm)	172.5 ± 11
Weight (kg)	88.5 ± 26.2
BMI (kg/m ²)	29.7 ± 8.7
History of hepatic disease	45 (17.4)
PRBC Transfusion	65 (25.3)
Surgical Admitting Team	129 (54.9)
Indwelling Neuraxial Catheter	23 (8.9)
aPTT (Seconds)	
Baseline	32.0 ± 8.5
After any SC UFH administration	37.6 ± 15.2
After 24 hours SC UFH administration	38.6 ± 15.5

PRBC = packed red blood cells. Data are presented as n (%) or mean ± SD.

Table 2

Variables Associated with a Change in aPTT

	Total SC UFH therapy n = 257		24 h SC UFH n = 160	
	Univariate Analysis <i>P</i> value	Multivariate Analysis <i>P</i> value	Univariate Analysis <i>P</i> value	Multivariate Analysis <i>P</i> value
Baseline aPTT	<0.001	<0.001	<0.001	<0.001
Total Heparin Dose per kg	0.004	0.002	0.036	0.061
Age	0.148	0.079	0.206	0.145
Race	0.638	0.379	0.839	0.611
Sex	0.934	0.459	0.235	0.629
Length of Heparin Therapy	0.039	0.034	0.367	0.283
History of Hepatic Disease	0.133	N/A	0.172	N/A
BMI	0.006	N/A	0.133	N/A
Medical vs. Surgical Admission	0.252	N/A	0.268	N/A

BMI = Body Mass Index.