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Derivation and Validation of Age- and Body Mass Index-Adjusted Weight-Based Unfractionated Heparin Dosing

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Abstract

Unfractionated heparin dosing is unpredictable and subject to numerous pharmacokinetic changes including distribution and metabolic changes associated with obesity and age. Weight-based dosing is commonly used to better predict the dose for a patient when targeting a therapeutic range. A dosing equation that adjusts weight-based doses for age and body mass index may improve therapeutic dose prediction. We conducted a 2-phase observational study with a derivation and validation period to develop an equation to adjust weight-based unfractionated heparin for age and body mass index to target a therapeutic activated partial thromboplastin time of 60 to 80 seconds. The first phase retrospectively identified patients who acheived therapeutic anticoagulation and utilized linear regression to determine a predictive equation for weight-based dosing that adjusts for age and body mass index. The second phase prospectively identified patients in an observational manner and compared the dose of unfractionated heparin on which they became therapeutic against both the weight-based dose and the predicted dose adjusted for age and body mass index. The correlation between predictive age and body mass index adjusted dose and actual therapeutic dose was 0.703 compared to the correlation between the empiric weight-based dose and actual therapeutic dose which was 0.532 ($P = .05$). Age and body mass index adjusted weight-based dosing significantly improved therapeutic dose prediction for unfractionated heparin. Further study in a prospective, randomized trial is warranted for validation of this approach in a real world setting.

Keywords

heparin, anticoagulants, venous thromboembolism, cardiology

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Introduction

Unfractionated heparin (UFH) is commonly utilized in the inpatient setting for its rapid onset of action, reversibility, and ease of titration. However, pharmacokinetic and pharmacodynamic properties of the agent make accurate dosing predictions difficult. Variables such as heparin neutralizing proteins, macrophage elimination mechanisms, endogenous antithrombin III levels, clot burden, volume of blood distribution, obesity, and age contribute to the unpredictable nature of drug dosing.[1] Furthermore, the activated partial thromboplastin time (aPTT), which is traditionally used for monitoring UFH, is subject to variation in manufacturer and institutional assay.[2,3] Some institutions choose to use the chromogenic antifactor Xa assay, and currently there is debate regarding which should be the standard of care with practice varying by institution.[4]

In the early 1990s, the shift from fixed-dose regimens toward weight-based dosing regimens improved empiric dosing predictions by eliminating up to 30% of dosing variability.[5] Although this signified a substantial improvement, accounting for other contributing factors with adjustments may be useful in

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better predicting therapeutic UFH doses to improve both efficacy and patient safety. Delays in achieving a therapeutic dose are associated with worse outcomes, and higher doses are associated with bleeding.[6-8] Therefore, accurate initial prediction of the therapeutic dose is essential to optimize clinical outcomes and prevent adverse events. We hypothesized that adjusting weight-based UFH dosing for age and body mass index (BMI) would improve the predictive value of dose initiation. The purpose of this analysis was to derive an equation for UFH dose initiation using historical data and internally validate it in an institution-specific, observational fashion.

Providers at the study institution have the option to utilize a standard UFH titration nomogram including a goal of 60 to 80 seconds for certain indications. The 60 to 80 seconds target is utilized for venous thromboembolism (VTE), stroke prevention in atrial fibrillation, and any indication where the covering provider deems this titration strategy and target aPTT appropriate. The aPTT assay utilizes a silica activator (PTT Automate, Diagnostica Stago Inc, Parsippany, New Jersey) run on the STA-R Evolution (Diagnostica Stago Inc). The average time to achieve therapeutic aPTT at this institution with the nurse-driven nomogram is 11.7 hours,[9] and the overall rate of nomogram compliance is 84.6%.[10] Detailed information regarding the institution nomogram and UFH practices is published elsewhere.[9,10]

Methods

We conducted a 2-phase evaluation that included a derivation (phase I) and validation group (phase II). Patients were retrospectively identified in the electronic health record for the phase I group from September 1 to 30, 2015. Patients who achieved therapeutic anticoagulation of UFH utilizing the institutional weight-based, nurse-driven titration nomogram were included in the analysis. Therapeutic anticoagulation was defined as having 2 consecutive aPTT values within a goal range of 60 to 80 seconds on the same UFH dose. This goal range was selected from the institutional UFH practice because it is the most common strategy utilized and allows for consistency of results. For the phase II group, patients were identified in a prospective, observational manner. Inclusion criteria was the same for the phase II group. Patient data were collected beginning in October 2015 until a prespecified number of 100 patients were identified for this pilot analysis. Patients who received UFH for less than 24 hours were started on UFH at an outside hospital, and those who received UFH with alterations to the institutional nomogram were excluded. Unfractionated heparin infusions were titrated to an aPTT goal of 60 to 80 seconds based on the standard institutional nurse-driven titration nomogram.[9] Phase II was performed in both an Intention-to-Treat (ITT) and Per-Protocol (PP) manner. The phase II-PP group excluded all patients who received UFH for an indication other than VTE, stroke prevention in atrial fibrillation, acute coronary syndrome (ACS), stroke, or cancer-associated indications.

The phase I group was utilized to develop a linear regression equation (henceforth referred to as the predictive equation) that used age and BMI adjustments to the standard weight-based regimen to predict the final dose of UFH to achieve a therapeutic aPTT. The predictive equation was then used to calculate a dose for patients in the phase II group (ITT and PP) that would be predictive of the dose upon which they would become therapeutic. Patients in the phase II group were dosed according to the standard of care, weight-based institutional nomogram targeting a goal aPTT of 60 to 80 seconds. Simultaneously, the predictive equation was used to determine the BMI- and age-adjusted dose (predictive dose) to compare to the standard dose. The following definitions are used throughout the study:

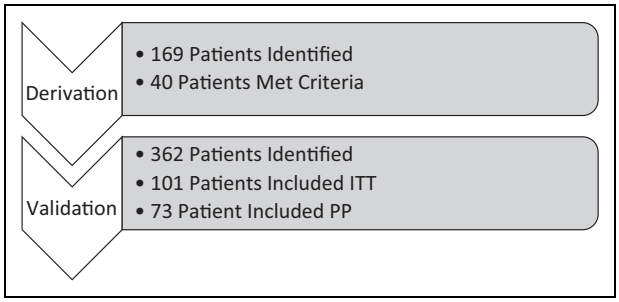

Figure 1. Patient inclusion for phase I (derivation) and phase II (validation) groups.

- Therapeutic dose: The dose of UFH (units/kg/h) on which a patient had 2 consecutive aPTT values in target therapeutic range (60-80 seconds).
- Empiric dose: The weight-based dose of UFH (units/kg/h) on which therapy for a patient was initiated.
- Predictive dose: The predictive, weight-based dose of UFH (units/kg/h) adjusted for age and BMI.

The dose of UFH on which the patient eventually achieved a therapeutic aPTT was recorded and documented as the therapeutic dose. The major study end point was to compare the correlation between the standard weight-based dose (*empiric*) versus the therapeutic dose against the correlation between the age- and BMI-adjusted dose (*predictive*) versus the therapeutic dose. The major end point was performed in an ITT approach including all patients regardless of UFH starting dose. A secondary analysis of the PP population was performed as well as a minor end point to assess consistency of results with regard to indication for UFH use.

Statistical methods performed included a multiple linear regression model with 1-way analysis of variance (ANOVA) for the predictive equation derivation and 2-tailed Fisher transformation for the major end point analysis. Statistical analyses were performed using IBM SPSS v.25.0 (IBM Corp, Armonk, New York).

Results

The phase I, phase II-ITT, and phase II-PP groups enrolled 40, 101, and 73 patients, respectively (Figure 1). The phase I group did not include 65 patients for not achieving at least 2 consecutive aPTT values in the therapeutic range on the same UFH dose and 104 patients for meeting exclusion criteria. In the

Table 1. Baseline Patient Characteristics.[a]

Characteristic	Derivation Group (N = 40)	Validation Group (N = 101)—Intention-to-Treat	Validation Group (N = 73)—Per-Protocol
Age (years)	65.5 (28-85)	65 (20-91)	65.5 (30-91)
Male	26 (65.0)	53 (52.4)	42 (57.5)
Weight (kg)	92.67 (29.7)	80.4 (21.9)	82.3 (21.9)
BMI (kg/m^2)	29.9 (7.8)	27.5 (7.5)	28.0 (7.7)
Creatinine	1.68 (1.9)	1.62 (1.4)	1.61 (1.3)
Medical history			
VTE	6 (15.0)	24 (23.8)	21 (28.7)
Active cancer[b]	9 (22.5)	18 (17.8)	12 (16.4)
ACS	4 (10.0)	11 (10.9)	10 (13.7)
HIT	0 (0)	1 (1.0)	1 (1.4)
Stroke	2 (5.0)	6 (5.9)	4 (5.5)
Home anticoagulation	18 (45.0)	48 (47.5)	35 (47.9)

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; HIT, heparin-induced thrombocytopenia; VTE, venous thromboembolism.
[a]Data presented as median (range), mean (SD), or n (%).
[b]Cancers included ovarian, pancreatic, lymphoma, liposarcoma, chronic lymphocytic leukemia, bladder, renal cell carcinoma, acute leukemia, lung, and multiple myeloma.

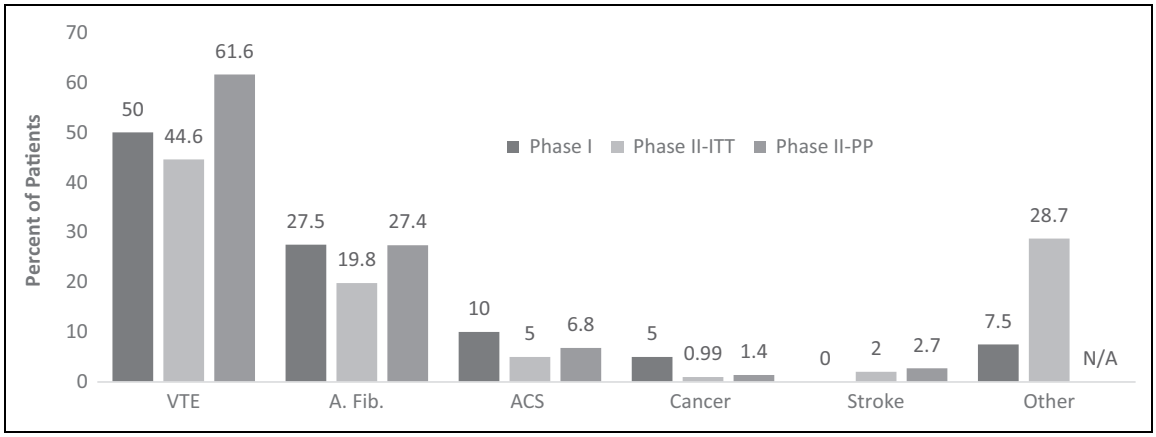

Figure 2. Indications for unfractionated heparin (UFH) use during derivation (phase I) and validation (phase II) phases.

phase II group, 186 patients were not included for failure to achieve 2 consecutive aPTT values in therapeutic range on a consistent UFH dose and the remaining 75 met exclusion criteria. All patients were titrated to a goal aPTT of 60 to 80 seconds. Baseline characteristics are reported in Table 1. History of VTE was somewhat more common in the Validation Group while proportion that was male and weight were higher in the derivation group. Venous thromboembolism was the most common indication for UFH in all groups (Figure 2). The phase II-PP group notably has a higher proportion of patients with VTE as the primary indication for UFH due to the exclusion of patients with an indication other than VTE, stroke prevention in atrial fibrillation, ACS, cancer, or stroke.

The predictive equation derived from the phase I group to adjust the weight-based UFH starting dose is: $\text{Dose}_{\text{units/kg/hr}} = -0.275(\text{BMI}_{\text{kg/m·m}}) - 0.143(\text{Age}_{\text{years}}) + 33.06$, where the predicted weight-based dose is a linear function. The overall fit of the model includes an R^2 of 0.303 and significance for each variable (BMI, $P = .005$; age, $P = .01$). Overall model significance was determined using 1-way ANOVA ($P = .001$). Additional information regarding statistical derivation of the predictive equation is found in Supplementary Appendix 1.

In the phase II-ITT group, the predictive dose demonstrated a higher correlation with the therapeutic dose than the empiric dose with the therapeutic dose (Pearson correlation $r = 0.703$ vs $r = 0.532$; $P = .05$; Figure 3). The variability in dosing also improved from the empiric dose to the predictive dose with the R^2 values demonstrating improvement from 28.3% to 49.4%, respectively. For the minor end point of analysis in a PP population, the predictive dose demonstrated a trend toward higher correlation with the therapeutic dose than did the empiric dose, but did not maintain statistical significance (Pearson correlation $r = 0.696$ vs 0.532; $P = .057$).

Discussion

The results of this analysis demonstrated that including adjustments for age and BMI into a weight-based predictive UFH

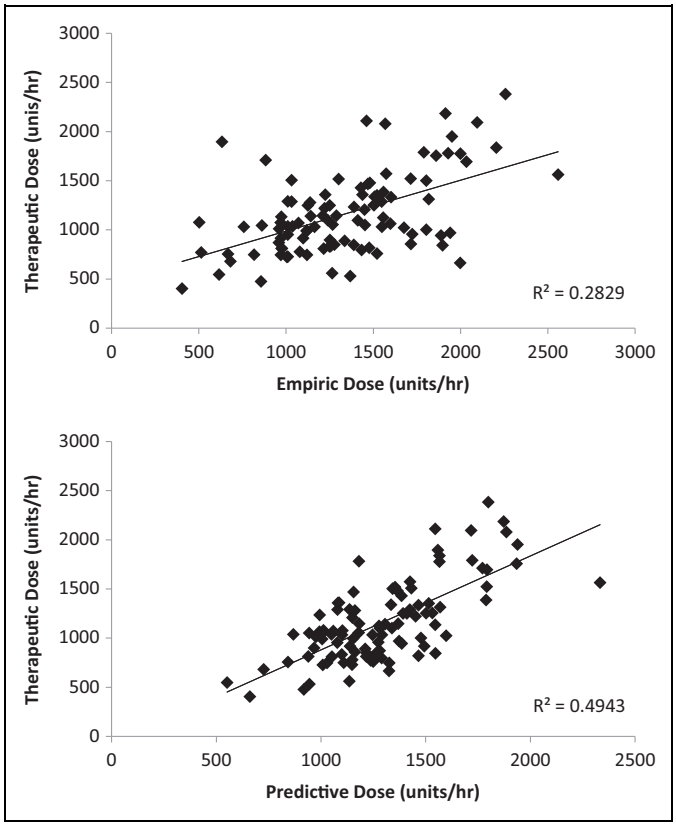

Figure 3. Major end point outcome: correlation of therapeutic versus empiric dose and therapeutic versus predictive dose in Intention-to-Treat (ITT) group.

dosing equation had a significantly higher correlation with the actual therapeutic dose than did the empiric, weight-based dose. Previous studies demonstrated that weight-based dosing accounts for approximately 30% of dosing variability leaving 70% of the variability unaccounted for, making accurate initial dosing difficult.[5] Ultimately this leads to delayed time to therapeutic aPTT which has been correlated with adverse events such as recurrent VTE.[6] Our evaluation was consistent with this finding as the R^2 value for the weight-based UFH patients in the phase II-ITT group was 0.282. By adjusting for age and BMI, predictive weight-based dosing improved to account for almost 50% of UFH dose variability. This represents a significant improvement and demonstrates the potential for improved patient care. The phase II-PP population demonstrated consistent results with the phase II-ITT analysis but was unable to maintain statistical significance likely due to the smaller sample size. However, the consistent trend of superior predictive dose correlation with the therapeutic dose suggests that this finding occurred regardless of UFH indication.

Previous analyses have investigated the impact of obesity on UFH dosing and demonstrated inconsistent conclusions.[11-13] One study demonstrated that both increasing BMI and age were predictors of supratherapeutic aPTT during UFH therapy.[12] Utilizing these easily obtained variables, we hypothesized that UFH dosing could be improved with adjustment. Our hypothesis is that because the volume of distribution of UFH is largely relegated to the blood volume, the decrease in vasculature of adipose tissue will lead to lower UFH requirements per kilogram as BMI increases. The findings from our analysis appear to support this hypothesis. Making a dose adjustment for BMI increased the predictive value of the initial dosing regimen. Furthermore, as patients' age, adipose tissue tends to predominate over muscle potentially resulting in lower volume of UFH distribution which may explain why an age adjustment is also required. This hypothesis appears to be consistent with our findings. Further, no significant hemorrhagic or thromboembolic complications were observed during this study.

Our analysis is limited by its observational nature and represents mathematical correlation rather than clinical causation. A low proportion of patients with BMI >35 kg/m^2 makes extrapolation to severely obese patients difficult. The aPTT test has many limitations due to its variability in manufacturer and individual patient characteristics.[14] Some clinicians prefer use of the chromogenic antifactor Xa assay for its more standardized results. Among patients with active cancer, the specific cancer types are not uniform and therefore likely underwent varying therapies for their diseases which may have affected the variability of UFH dosing. This is hypothesis generating and further study is warranted based on these results. There is the potential for improved UFH dosing that may result in faster time to reach therapeutic anticoagulation with a lower risk of supratherapeutic aPTT levels and subsequent bleeding complications. A prospective analysis should address the utility of a formula to adjust UFH dosing taking into account age and BMI. A large prospective trial to further validate this approach and assess for clinical outcomes is warranted. Further analysis may include the use of the chromogenic antifactor Xa assay as a comparator.

Authors' Note

Dr Connors reports consulting for Bristol Meyer Squibb and serving on Scientific Advisory Boards for Bristol Meyer Squibb and Boehringer Ingleheim. Dr Sylvester reports participating on a scientific advisory board for Bristol Myers Squibb/Pfizer. Ethical approval to report this study was approved by the institutional review board of Brigham and Women's Hospital. Informed consent was waived do to observational nature and minimal patient risk.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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