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Heparin dose adjustment required to maintain goal-activated partial thromboplastin time during therapeutic hypothermia☆,☆☆

Ryan T. Fevold, PharmD [a,*], Yuk Ting Lydia Leung, PharmD [a], Adrian C. Garofoli, MD [a], Roger D. White, MD [b,c], Gregory W. Barsness, MD [c], Ross A. Dierkhising, MS [d], Narith N. Ou, PharmD [a]

[a] Department of Pharmacy Services, Mayo Clinic, Rochester, MN, USA
[b] Department of Anesthesiology, Mayo Clinic, Rochester, MN, USA
[c] Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA
[d] Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Purpose: The impact of therapeutic hypothermia (TH) on unfractionated heparin (UFH) management is essentially unknown. The aim of this study was to evaluate the effect of TH on UFH dosing and activated partial thromboplastin (aPTT) response.
Materials and methods: Consecutive patients treated from 2005 to 2011 who received intravenous UFH via a dosing nomogram during TH were included. First, heparin doses and aPTT responses were compared between 2 core temperature groups, less than or equal to 33°C and greater than 35°C. Next, the first aPTT, drawn at 6 hours for temperature less than or equal to 33°C, was assessed. Lastly, a linear model was developed to predict the mean aPTT, based on temperatures and heparin doses.
Results: Of the 156 TH patients, 68 were included. At temperatures less than or equal to 33°C, 76.3% of all aPTT levels and 81.0% of the first aPTTs were above goal range, respectively. Using a linear model, an UFH dose of 12 U/kg per hour predicts an aPTT of 134 seconds at less than or equal to 33°C.
Conclusions: Using guideline-recommended heparin dosing without dose adjustment for temperature changes produced excessive aPTT during the cooling phase for TH patients. Reduction in the UFH dose of 43% to 54% may be required during TH. We recommend frequent aPTT monitoring during the cooling and rewarming phases to attain a desired aPTT range.

1. Introduction

Therapeutic hypothermia (TH) improves neurologic outcomes in cardiac arrest survivors and is a guideline-recommended therapy for patients with return of spontaneous circulation after out-of-hospital cardiac arrest [1]. Hypothermia has been shown to alter the pharmacokinetics and pharmacodynamics of commonly used medications [2]. It is hypothesized that enzymatic reactions, which are often temperature dependent, slow down during TH, resulting in impairment of normal drug metabolism and clearance [3]. However, the impact of TH on unfractionated heparin (UFH) dosing in out-of-hospital cardiac arrest patients is essentially unknown. A small retrospective study by Wahby et al [4] suggests elevated activated partial thromboplastin time (aPTT) values for patients on UFH and reduced heparin dosing requirements during TH; however, no specific dosing adjustment was recommended. In patients undergoing TH for out-of-hospital cardiac arrest and requiring UFH therapy, our institution used a guideline-recommended heparin dosing nomogram with aPTT monitoring [5]. The aim of this retrospective study was to evaluate the effect of TH on guideline-recommended UFH dosing and aPTT response.

2. Materials and methods

A retrospective chart review was performed at Mayo Clinic Hospital–Saint Marys Campus in Rochester, MN, a 1265-bed, tertiary care academic medical center. Patients' electronic medical record (EMR) data were included in our analysis if the patients underwent TH for out-of-hospital cardiac arrest and were admitted to the hospital coronary care unit between December 1, 2005, and December 1, 2011, and they received heparin via a weight-based UFH nomogram (Fig. 1) for longer than or equal to 6 hours with at least 1 aPTT value. A computerized UFH dosing flow sheet was used to obtain information on heparin bolus (units per kilogram) and infusion (units per kilogram per hour); aPTT; and demographic data including sex, age, and dosing weight. Body temperature, UFH indications, and incidence of bleeding were collected using the EMR. The results were assessed during different body temperature stages (≤33°C, 33.1-35°C, and >35°C). Heparin doses and

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* Corresponding author at: Department of Pharmacy Services, 200 First St SW, Rochester, MN 55905. Tel.: +1 507 226 7989.
E-mail address: fevold.ryan@mayo.edu (R.T. Fevold).

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☐ **Intermediate Intensity Heparin Dosing Nomogram**
Orthopedic surgery (except spine) patients: Do not use unless approved by consultant or service.
Neurology patients: Do not use.
All other patients: For atrial fibrillation, acute coronary syndrome, STEMI and Non-STEMI.

Select Only One
☐ Initial loading dose: **60 units/kg* IV push.**
☐ Do not give initial loading dose.

Heparin IV infusion: 25,000 units/250 mL (100 units/mL) at **12 units/kg/hour**.**

aPTT Level	IV push loading dose	Infusion	IV rate change units/hour	Repeat aPTT
less than 39 seconds	60 units/kg	Continue	Increase 4 units/kg/hour	6 hours
39 - 54 seconds	30 units/kg	Continue	Increase 2 units/kg/hour	6 hours
55 - 90 seconds	0	Continue	No change	Next a.m.
91 - 99 seconds	0	Continue	Decrease 1 unit/kg/hour	6 hours
100 - 110 seconds	0	Continue	Decrease 2 units/kg/hour	6 hours
111 - 139 seconds	0	Stop for 1 hour	Decrease 2 units/kg/hour	6 hours after Heparin resumed
140 - 180 seconds	0	Stop for 1 hour	Decrease 3 units/kg/hour	6 hours after Heparin resumed
greater than 180 seconds	0	Stop for 2 hours	Decrease 4 units/kg/hour	6 hours after Heparin resumed

Fig. 1. Heparin order set.

aPTT response times were compared between core temperature groups less than or equal to 33°C and greater than 35°C. For completeness, the transition period of temperature 33.1°C to 35°C was also assessed.

Patients who were initiated on a heparin 12 U/kg per hour with or without a 60 U/kg bolus were included for analysis of first aPTT at 6 hours after UFH initiation if that aPTT occurred at a temperature less than or equal to 33°C. Data of patients who were initiated on a heparin dose of 12 or 18 U/kg per hour were included for all other analyses. The EMRs were excluded if the patients received UFH for shorter than 6 hours, or if aPTT or temperature measurements were unavailable. The study protocol was approved by the Mayo Clinic Institutional Review Board, which waived the need for informed consent.

2.1. Statistical analysis

Each aPTT measured had a corresponding heparin dose and body temperature. Using a mixed effects linear model, with fixed effects for heparin dose, body temperature, and a dose by temperature interaction, equations were constructed to predict mean aPTT at different core temperature stages (≤33°C and >35°C) with 95% confidence intervals (CIs). Random subject effects were included to model the potential correlation between measurements from the same subject. Using the derived equations, the mean aPTT value at an initial dosing regimen of 12 U/kg per hour was estimated for each temperature group. Dose ranges required to maintain an average patient's aPTT within goal range (55-90 seconds) during different core body temperature stages were also calculated. This was done by finding the doses, where the lower and upper confidence limits for the mean aPTT crossed 55 and 90, respectively. The linear model was estimated using SAS version 9.2.

2.2. Definitions

2.2.1. Therapeutic hypothermia protocol

Following the Mayo Clinic TH Protocol, patients were deemed eligible if they remained in a persistent coma after out-of-hospital cardiac ventricular fibrillation arrest with return of sustained spontaneous circulation, and cooling could be initiated within 4 hours of arrest. Using the Arctic Sun Temperature Management System (Medivance, Louisville, CO), patients were cooled to target temperature of 33°C and maintained for 24 hours, then gradually rewarmed to 36.5°C at a rate of 0.25°C per hour [6].

2.2.2. Heparin dosing and monitoring

Heparin dosing was determined through a previously validated computerized weight-based UFH nomogram with an initial infusion rate of 12 U/kg per hour (rounded to the nearest 50 U/h), with or without the initial bolus of 60 U/kg to achieve a plasma heparin level of 0.2 to 0.4 anti-Xa IU/mL (corresponds to an aPTT of 50-70 seconds using reagent Platelin L, 2005-2010 or 55-90 seconds using reagent IL SynthASil, 2011). An alternative dose of 18 U/kg per hour with 80 U/kg bolus was used for acute venous thrombosis to achieve a plasma heparin level of 0.3 to 0.7 anti-Xa IU/mL (corresponds to aPTT 60-90 seconds using Platelin L reagent, 2005-2010 or 70-120 seconds using IL SynthASil, 2011). The laboratory's upper limit of aPTT measurement was 240 seconds. Any aPTT over the threshold was recorded as 240 seconds. Heparin was dosed using actual body weight with no maximum cap on weight, bolus, or infusion rate [7]. Dose adjustments were based on aPTT values checked every 6 hours per nomogram. Once within goal range for 2 consecutive aPTT measurements, frequency of aPTT was reduced to every 24 hours (Fig. 1).

2.2.3. Safety data

Bleeding was defined as the occurrence of any of the following criteria from the initiation of UFH infusion through 24 hours after infusion cessation: (1) nonoperational-related transfusion of at least 1 U of packed red blood cells, (2) a decrease in hemoglobin level of 2 g/dL or greater within 24 hours, (3) bleeding identified by radiographic study (eg, intracranial hemorrhage and retroperitoneal hemorrhage), or (4) bleeding related to heparin therapy documented in the patient's discharge summary [7].

3. Results

Among 156 TH patients, 68 received intravenous UFH via a computerized weight-based nomogram and were included in this study. Mean age was 62 ± 12 years; weight, 90 ± 22 kg; and 74% were male. The most common indication for UFH was acute coronary syndromes (Table 1). Mean baseline aPTT was 29 seconds (n = 49). Included patients had a median of 4 aPTT values (mean, 4) drawn during treatment with UFH. Patients were cooled to target temperature of 33°C (31.9°C-33.0°C).

Table 1
Baseline characteristics

Mean age (y) ± SD	62 ± 12
Sex (% male)	74
Mean weight (kg) ± SD	90 ± 22
UFH indication (%)	
Acute coronary syndromes	74
Prosthetic valve	1
Atrial fibrillation or atrial flutter	9
Venous thromboembolism	10
Other (balloon pump [2], LV failure, atrial myxoma)	6

LV indicates left ventricular.