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Original research

Weight based heparin dosing for thromboembolic disease is associated with earlier anticoagulation in surgical patients

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HIGHLIGHTS

- Weight based heparin is associated with improved outcomes.
- The risk of bleeding from weight based heparin in surgical patients is unclear.
- The weight based heparin group achieved earlier therapeutic anticoagulation.
- Weight based heparin did not increase the incidence of hemorrhagic events.
- Heavier patients were most susceptible to under-dosing.

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ABSTRACT

Introduction: Achievement of early therapeutic anticoagulation with unfractionated heparin (UFH) is associated with improved outcomes in thromboembolic disease. Weight based UFH expedites time to therapeutic anticoagulation. Treatment with UFH is challenging in surgical patients due to their high propensity for bleeding. We sought to test the hypothesis that an initial weight based UFH infusion in surgical patients increases the percentage of patients who achieve early therapeutic anticoagulation without increasing the risk of hemorrhagic events. **Methods**: Using a non-concurrent retrospective cohort study design, adult surgical patients receiving UFH for venous thromboembolism (VTE) at a tertiary care center were included. Two groups were identified: the weight based (WB) and the under-dosed (UD) heparin groups. For our primary outcome, we compared percentage of patients in each group that achieved a therapeutic PTT within 24 h. Secondary outcomes included the incidence of supra-therapeutic PTT levels, hemorrhagic events, and complications associated with VTE. **Results**: 73 subjects met study criteria, which included 8 subjects in the WB group and 65 in the UD group. The demographic, baseline laboratory, admitting service and type of VTE were similar between the 2 groups. The percentages of WB and UD subjects who achieved a therapeutic PTT within 24 h were 75% and 28%, respectively ($p < 0.01$). There was no difference in the incidence of supratherapeutic PTT or hemorrhagic events. **Conclusion**: Surgical patients who received an initial weight based UFH infusion achieved earlier therapeutic anticoagulation compared to under-dosed UFH without increasing the occurrence of supratherapeutic PTT levels or hemorrhagic events.

1. Introduction

Hospitalized patients in the post-operative state are among those at highest risk for venous thromboembolism (VTE), the most common preventable cause of hospital mortality [1]. Without chemoprophylaxis, the risk of deep vein thrombosis (DVT) in surgical patients with major trauma and spinal cord injury exceeds

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50% [2]. However, adequate prevention and treatment of VTE in this population can be challenging given the increased risk of bleeding from surgery and trauma. These factors are further amplified in surgical patients admitted to the intensive care unit (ICU) due to coexisting coagulopathy, thrombocytopenia, and presence of renal dysfunction [3].

The standard treatment options for VTE in the acute setting include unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Use of UFH in surgical patients is more advantageous in the peri-operative and peri-procedural setting due to its short half-life, the availability of a reversal agent, and its extra-renal elimination [4]. Weight based UFH treatment initiated with a loading dose of 80 units/kg followed by an infusion at 18 units/kg per hour has been shown to expedite the time to achieve goal activated partial thromboplastin time (PTT) and reduce recurrent VTE [5,6]. Additionally, achievement of goal PTT within 24 h in patients with acute pulmonary embolism (PE) is associated with a 66% reduction in 30-day mortality [7].

Several risk factors for bleeding related to UFH treatment have been outlined [8]. One of these risk factors includes the intensity of UFH dosing [9]. Limited data is available describing the benefits and risks of weight-based UFH dosing in surgical patients. We sought to assess and compare the effectiveness and safety of weight based (WB) versus under-dosed (UD) UFH infusion in surgical patients with VTE.

2. Material and methods

2.1. Patient population and data collection

Using the Partners Healthcare System Research Patient Data Registry (RPDR), a comprehensive clinical and administrative database at our tertiary academic medical center, we identified all patients aged 18 years or older with ICD9-CM diagnoses of DVT and PE who received an UFH infusion for at least 24 h from June 1, 2010 to May 31, 2011. DVT and PE diagnoses were confirmed by review of ultrasound or computed tomography, respectively.

Patient demographics, co-morbidities, pre- and post-infusion laboratory values, and VTE-related complications were collected from medical records. The following data were additionally captured: dates of hospital and ICU admission, time of initiation and discontinuation of UFH, and dates of ICU and hospital discharge. The admitting surgical service and type of surgery performed were also recorded from the operative report. The bolus dose, initial rate of infusion, and duration of UFH administration were obtained from the electronic medical record. Concurrent blood product administration and the simultaneous use of medications that could potentiate bleeding such as clopidogrel, aspirin, non-steroidal anti-inflammatory drugs, and warfarin were also recorded.

2.2. WB vs. UD groups

The standard template for VTE treatment at our institution recommends initiating UFH with a loading dose of 80 units/kg followed by a rate of 18 units/kg per hour, based on the nomogram established by Raschke et al. [5]. UFH infusions were titrated using a standardized sliding scale to a goal PTT between 60 and 84 s. Our standard lab monitoring protocol is to draw PTT prior to UFH initiation, 6 h after initiation of therapy, and 6 h after any dosage adjustment. Once infusion rates were stable and patients were maintained in the therapeutic range, PTT was monitored twice daily.

In our study, the WB group included patients who received an initial UFH infusion at a rate of at least 18 units/kg per hour rounded to the nearest 50 units based on patient's actual body weight. The UD group included patients who received an initial UFH infusion less than 18 units/kg per hour.

2.3. Primary and secondary endpoints

The primary endpoint of the study is the percentage of patients who achieved a therapeutic PTT within 24 h. Secondary endpoints included the incidence of supratherapeutic PTT levels, the incidence of hemorrhagic events, and complications associated with VTE that occurred during each subjects' hospital admission.

Hemorrhagic events were defined as acute non-operative blood loss of at least 2 g/dL of hemoglobin that required both cessation of UFH and blood transfusion. Non-operative bleeding was defined as any hemorrhagic event that occurred 24 h after the operation. If the UFH infusion was held at least 6 h before and 24 h after surgery and the patient experienced a hemorrhagic event within 24 h of the operation, this was deemed to be due to operative bleeding. VTE complications included DVT conversion to PE, stroke, patient transfer to an ICU, cardiac arrest, and death.

2.4. Statistical analysis

Data analysis was performed using Microsoft Office Excel 2011 (Microsoft Corporation, Redmond, WA, USA) and STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Demographic data were presented as mean ± standard deviation for continuous variables. Statistical significance for continuous variables were analyzed using a 2 independent sample *t*-test and categorical variables were calculated using a Fisher's exact test. Ordinal data was analyzed with the Wilcoxon–Mann–Whitney test. An alpha-error of 0.05 or less was considered to be statistically significant. The modified Thompson tau technique was used to detect outliers for UFH duration and total administered packed red blood cells (pRBC).

This retrospective non-concurrent case–control study was approved by the Partners Institutional Review Board (IRB number: 2013P001282, MGH).

3. Results

During the study time period, 590 patients requiring UFH were assessed, of which 73 met the inclusion criteria. Of the 517 patients excluded, 483 were initiated on UFH for a non-VTE indication, 17 received UFH less than or equal to 24 h, 16 were non-surgical patients and 1 was identified as an outlier. Eight subjects received weight based UFH compared to 65 subjects in the UD group. Patient demographics of each group are described in Table 1. The 2 groups were equal at baseline with the exception of subjects in the UD group having a significantly higher mean body weight at 90 kg compared to 65 kg in the WB group ($p = 0.02$).

Twenty-five percent of subjects in each group received an initial UFH bolus dose ($p = 1.0$). Of the subjects who received a bolus dose, 2 subjects in each group received a weight based bolus ($p = 0.06$). In these subjects, the mean time to achieve target PTT was 28.9 ± 15.9 h compared to 47.2 ± 38.6 h ($p = 0.38$) in subjects who received an under-dosed bolus and 50.5 ± 47.2 h in the non-bolused subjects ($p = 0.37$). Fifty percent of subjects who were administered an appropriate weight based bolus developed a supratherapeutic first PTT compared to 7% of subjects who had an under-dosed bolus ($p = 0.04$) or no bolus ($p < 0.01$).

The mean initial infusion rate in the WB group was 21.4 ± 4.47 units/kg compared to 8.94 ± 3.54 units/kg ($p < 0.01$). The mean initial PTT in the WB group was 61.4.5 ± 37.2 s vs. 44.1 ± 26.3 in the UD group ($p = 0.09$). The percentage of subjects in each group