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Full Length Article

Safety and efficacy of starting warfarin after two consecutive platelet count rises in heparin-induced thrombocytopenia

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ABSTRACT

Introduction: Current guidelines on the treatment of heparin-induced thrombocytopenia (HIT) recommend warfarin initiation when platelet levels recover to 150×10^9/L or more. However, many patients may not achieve this platelet level or may have slow platelet recovery. The aim of this study is to determine if initiating warfarin when platelets start trending upward instead of at a specific level is safe and effective in patients diagnosed with HIT.
Materials and methods: Two groups of patients diagnosed and treated for HIT in a tertiary care hospital were assessed for HIT-related outcomes: 28 patients had warfarin initiated after platelets recovered to 150×10^9/L or more and 30 patients had warfarin initiated prior to platelet recovery.
Results: There was no significant difference between the rate of thrombosis, venous limb gangrene, or limb amputation. Three patients died during the data collection period, all deemed to be unrelated to HIT by independent investigators. The average hospital length of stay was 22.2 ± 12.7 days and 38.8 ± 19.1 days for patients who started warfarin at platelets less than 150×10^9/L and platelets greater than or equal to 150×10^9/L respectively ($P = 0.0002$).
Conclusions: The data suggests that the absolute platelet level at which warfarin is initiated does not affect the rate of thrombosis or mortality but may shorten overall hospital length of stay and associated costs. Therefore, it may be more important to observe an upward trend in platelets rather than striving to achieve an absolute platelet level before starting warfarin in patients with HIT.

1. Introduction

Heparin-induced thrombocytopenia (HIT) is a relatively uncommon immune mediated process typically characterized by a substantial decrease in platelet levels after exposure to heparin. HIT can cause paradoxical thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), thromboembolic stroke, and myocardial infarction; which can result in limb amputation or death [1–4]. More than 50% of patients with HIT are at risk of thrombosis if it is not recognized and treated with an alternative non-heparin anticoagulant, such as argatroban, bivalirudin, or fondaparinux [4–7]. In addition, it is recommended that patients requiring prolonged anticoagulation are transitioned to an oral anticoagulant, such as a vitamin K antagonist (VKA) [1,7–9]. The 2012 CHEST guidelines recommend starting VKA after platelets have recovered to 150×10^9/L (Class 1C recommendation) and to overlap VKA therapy with a non-heparin anticoagulant for at least 5 days and until the international normalization ratio (INR) is within the target range.

The central question for this analysis is: when should warfarin therapy be initiated in the treatment of HIT? Health care providers are often conservative in warfarin initiation and dosing because of early reports of complications, such as venous limb gangrene (VLG), related to excessive dosing and stopping the alternate anticoagulant prior to reaching INR targets. Additionally, acutely ill patients may have multiple drivers suppressing platelet counts that can lead to prolonged infusions of expensive parenteral direct thrombin inhibitors or prolonged hospital stays while waiting for platelet recovery, defined by as equal or greater than 100×10^9/L or 150×10^9/L by different studies [2,3,7,10]. To our knowledge, there are no data to support waiting for these platelet values to transition from initial intravenous to oral anticoagulation therapy. Furthermore, as health care costs increase and reimbursement becomes more stringent, identifying factors that can shorten hospital stay and cost of therapy while providing a high quality of care is crucial for sustainable practice. Considering that many patients' platelets may never fall below or recover to 150×10^9/L during HIT, more data is needed to guide treatment for these patients. At the University of California Davis Medical Center (UCDMC), warfarin initiation prior to platelet recovery was a management approach started shortly after parenteral direct thrombin inhibitors (DTI) were available. The potential benefits of starting warfarin therapy prior to recovering to a certain platelet level

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are shorter length of stay in the intensive care unit and hospital, which may reduce health care costs and improve clinical outcomes. Our use of bivalirudin in the management of HIT has previously been described with a very low rate of thrombosis [11]. We then sought to explore our practice of initiating warfarin based on platelet trends instead of reaching a pre-determined number. The purpose of this analysis is to determine if initiating warfarin when platelets start trending upward is safe and effective in patients diagnosed with HIT.

2. Materials and methods

2.1. Analysis design and patients

This retrospective, single-center, observational analysis was approved by the UCDMC Institutional Review Board. The electronic medical record (EMR) was screened between October 2014 to October 2015 for patients hospitalized at our institution with a diagnosis of HIT between January 1, 2008 and September 30, 2014, started on bivalirudin or fondaparinux, and transitioned to warfarin. Exclusion criteria were age less than 18 years, pregnant or breast feeding, cognitively impaired, prisoners, taking warfarin for another indication at the time of HIT diagnosis, and contraindication to warfarin. Patients were assessed for 30 days from diagnosis of HIT. This time frame was chosen because most cases of thrombosis related to HIT management is expected to occur by 30 days. The primary endpoint was incident of new symptomatic thrombosis. Secondary endpoints included all-cause mortality, VLG, all-cause limb amputation, and hospital length of stay (HLOS). The safety endpoint was clinically significant bleeding.

2.2. Definitions

A confirmed HIT diagnosis was defined as having a positive serotonin-release assay (SRA), positive heparin enzyme-linked immunosorbent assay (ELISA) test with optical density (OD) greater than or equal to 0.4 and 4Ts score of four or higher, or a positive heparin ELISA test with OD greater than or equal to 1.4 regardless of the 4Ts score. An OD cutoff of 1.4 was chosen based on a greater than 50% association with a strong-positive SRA [12]. A negative SRA was considered confirmation that the patient did not have HIT and heparin products could be restarted per physician preference. A 4Ts score of four points or higher was considered intermediate to high risk of true HIT based on previous studies [13]. New thrombosis was defined as a venous or arterial thrombosis or progression of a pre-existing thrombosis occurring after the patient received 12 h of therapeutic doses of bivalirudin or fondaparinux. Clinically significant bleeding was defined as any bleeding event requiring a hold in anticoagulation as determined by the primary medical team. VLG was defined as ischemic limb necrosis with active DVT and assessable arterial pulses [14].

2.3. Management of HIT

At UCDMC, when HIT is suspected, the primary team usually consults the Inpatient Pharmacy Anticoagulation Service or Hematology Oncology Consult Service. If the patient is determined to have a moderate to high risk of having HIT based on the 4Ts score and clinical assessment, a heparin ELISA test is sent, all heparin products are discontinued, and bivalirudin or fondaparinux is initiated. All diagnoses of acute thrombosis at the time of suspected HIT were included in the 4Ts score calculation. For the majority of patients, bivalirudin is preferred for initial alternative anticoagulation due to the high acuity of illness, including organ failure, and potential for fondaparinux-induced HIT [15]. Fondaparinux may be used for more stable patients with lower acuity, lower potential consequences of HIT, lack of intravenous access, or a more stable overall condition. Once the heparin ELISA test results are obtained, the consulting and primary teams determine whether it is necessary to send a confirmatory SRA. The HIT ELISA test used at UCDMC has been assessed internally and found to have an extremely low potential for false negative values. The SRA may take a few days to result and is more costly than ELISA. As such, SRAs are not routinely sent unless there is clear need for further clarification. At UCDMC, patients with suspected or confirmed HIT are not routinely screened for DVT due to the concern of identifying subclinical thrombosis and inappropriate treatment with anticoagulation. Institutions in the United States may be hesitant to perform routine DVT screening because identification of any thrombosis, including subclinical thrombosis, would count against the institution in national benchmarks and may not change therapy. The 2008 CHEST guidelines for treatment of HIT recommended routine screening for DVT [16]. However, the recommendation carried a low evidence grade of 1C and was not sustained in the 2012 guidelines. The Inpatient Pharmacy Anticoagulation Service supports initiating warfarin after two consecutive platelet rises but the primary team determines when warfarin is initiated. All bivalirudin, fondaparinux and warfarin doses targeted therapeutic anticoagulation as defined by the primary and consulting teams.

2.4. Laboratory testing for HIT

The PF4-IgG ELISA method (Immucor GTI Diagnostics, Inc. Waukesha, WI) was used during this study period. SRAs were sent to an outside laboratory (Blood Center of Wisconsin, Milwaukee, WI, USA). The SRA was considered to be positive if there was equal to greater than 20% release of serotonin with low dose heparin and less than 20% release in the presence of high concentration heparin. The SRA has a sensitivity of 88% to 100% and specificity of 89% to 100% for HIT [3].

2.5. Data collection

All data collection was performed retrospectively via our institution's electronic medical record. Data points included age, sex, body mass index, admitting service, indication for heparin, date of HIT diagnosis, heparin ELISA and SRA results, and 4Ts score. The 4Ts score was determined retrospectively by a researcher with a portion adjudicated by a second researcher. Platelet levels at nadir, at the time of bivalirudin or fondaparinux initiation and discontinuation, at time of warfarin initiation, and at discharge were also collected. Bleeding events requiring a hold in anticoagulation and any venous thromboembolism (VTE) event up to 30 days after discharge were described. VLG, limb amputation, mortality and cause of death were documented.

2.6. Statistical analysis

A one-sample non-inferiority power analysis was performed based on the incidence of thrombosis in a comparable single center study [1]. However, the power analysis was not applicable for the resulting data because it was done based on the assumption that all patients had warfarin initiated prior to platelet level of 150×10^9/L. Approximately half the collected patients were treated according to guideline recommendations, thus the patients were analyzed as two separate groups. Students' *t*-tests were used to derive standard deviations of the data.

3. Results

3.1. Demographics

Patients were screened for inclusion if bivalirudin or fondaparinux was ordered during a hospitalization within the study period. A total of 598 patients were identified and 540 were excluded based on presence of at least one exclusion criteria. The top three reasons for exclusion were unconfirmed HIT diagnosis (61.1%), never started warfarin therapy (18.3%), or never administered bivalirudin or fondaparinux (10.7%). Other reasons for exclusion included age less than 18 years