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Subcutaneous Enoxaparin for Therapeutic Anticoagulation in Hemodialysis Patients☆

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ABSTRACT

Background: Information regarding dosing of low-molecular-weight heparins (LMWH) for therapeutic anticoagulation in hemodialysis (HD) patients is limited. The aim of this study was to retrospectively compare the safety and efficacy of enoxaparin versus unfractionated heparin (UFH) for therapeutic anticoagulation in HD patients.
Materials and Methods: This retrospective chart review evaluated HD patients treated with subcutaneous enoxaparin that were matched based on the indication for anticoagulation with patients treated with intravenous UFH to achieve therapeutic anticoagulation. Primary outcome measures included 30-day incidence of thromboembolic events and major bleeding. Secondary outcomes included rehospitalization within 30 days, length of stay, and mortality.
Results: One hundred sixty-four patients were evaluated, 82 in each group. The average daily dose of enoxaparin used to target therapeutic levels was 0.7 ± 0.2 mg/kg/day (range = 0.4-1). Comparing enoxaparin to UFH, there was no significant difference in major bleeding (6.1% vs 11%, p = 0.4) or thromboembolism (0% vs 2.4%, p = 0.5). Hospital length of stay was shorter in the enoxaparin group (20 ± 53.8 vs 28.9 ± 44.5 days, p = 0.02); there was no significant difference between groups in mortality or readmission. Adjusting for risk factors for bleeding there was a slight but statistically non-significant difference between enoxaparin versus UFH (OR = 0.77, 95%CI: 0.2-3.5, p = 0.73).
Conclusions: These findings suggest that therapeutic dosing of enoxaparin, in doses that ranged from 0.4-1 mg/kg/day, was as safe as intravenous UFH in providing therapeutic anticoagulation in stable patients requiring chronic hemodialysis.

Introduction

Options for full-dose "therapeutic" anticoagulation in patients with chronic renal failure who require hemodialysis (HD) are limited, with few alternatives to the gold-standards of intravenous (IV) unfractionated heparin (UFH) and oral vitamin K antagonists (e.g. warfarin) [1,2]. Nevertheless there are clinical situations when subcutaneously injected low-molecular-weight heparins (LMWH) might be potentially advantageous. These include bridging patients onto or off of warfarin (including perioperative bridging), treating patients with absent or poor venous access, and treating cancer patients with acute venous thromboembolism (VTE) [3]. Although these scenarios are not common, they are not rare. A comparison of HD patients treated with UFH versus LMWH would be useful to better define the incidence of bleeding and thrombotic outcomes in patients managed with these drugs.

Because LMWH have reduced renal clearance, large volumes of distribution, and longer half-lives than UFH, the assumed risk of using

Abbreviations: IV, intravenous; UFH, unfractionated heparin; LMWH, low-molecular-weight heparins; VTE, venous thromboembolism; ACS, acute coronary syndrome; CrCl, creatinine clearance; UCDMC, University of California, Davis Medical Center; ISTH, International Society on Thrombosis and Haemostasis; SAS, Statistical Analysis Software; CAD, coronary artery disease; CVA, cerebrovascular accident; IHD, intermittent hemodialysis; CRRT, continuous renal replacement; SLEDD, slow-extended daily dialysis; PD, peritoneal dialysis.

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these drugs in hemodialysis patients is accumulation, excessive anticoagulation and subsequent bleeding [4–8]. Current practice guidelines also state LMWH should be avoided in HD patients; however, there have been no prospective studies that have directly assessed clinical outcomes of LMWH treatment in this population. Enoxaparin (Lovenox®, Bridgewater, New Jersey, United States of America) has been shown to accumulate in patients treated with therapeutic doses (1.0-1.25 mg/kg) given subcutaneously every 12 hours for non-ST-segment elevation acute coronary syndrome (ACS), with a strong linear relationship between the creatinine clearance (CrCl) and drug clearance [5]. In this study by Becker et al., only 11 of 445 (2.5%) patients in their cohort had impaired renal function, defined as CrCl less than 40 mL/min. Major hemorrhage, a secondary outcome of the study, occurred in 27 of 445 (6.1%) patients, but it is unclear how many of these patients were in the impaired renal function group. Importantly, the enoxaparin dose was not reduced or adjusted for decreased renal function.

A recent study evaluated the use of standard therapeutic doses of dalteparin and tinzaparin for perioperative bridging in HD patients and measured trough anti-Xa levels 20–24 hours after dose administration [8]. Patients in this study had chronic renal failure and were receiving intermittent HD three times per week. This study documented accumulation of tinzaparin and dalteparin at non-adjusted therapeutic doses in these HD patients; however, the trial was neither designed nor powered to make any inferences about the safety or efficacy of treatment using these LMWH preparations, and the authors did not report any clinical outcomes. Routine measurment of plasma anti-Xa levels in HD patients or patients with severe renal insufficiency treated with a LMWH has not been validated as a useful or reliable parameter for monitoring these patients [9].

Use of LMWH to prevent HD circuit thrombosis has been studied, and these drugs are commonly used in HD centers [10]. Reports indicate that use of enoxaparin is safe and effective when single lower doses of 0.4 to 0.7 mg/kg are delivered intravenously prior to the HD session [7,11–16]. In a study comparing enoxaparin to regular UFH, a modified enoxaparin dose of 0.7 mg/kg IV prior to dialysis was shown to be effective in maintaining circuit patency and was associated with a low incidence of significant bleeding; however, use of a LMWH for this indication remains an off-label practice [4,17].

Seeking alternative parenteral anticoagulation, physicians at the University of California, Davis Medical Center (UCDMC) consulted with the inpatient anticoagulation service and began treating select HD patients with a modified, lower dose of subcutaneous enoxaparin ranging 0.4-1 mg/kg daily. Actual dose selection was based principally on assessment of the risk of thrombosis versus the risk of bleeding. This lower "adjusted" treatment dose was used for several different indications including acute VTE, bridging therapy, VTE prophylaxis following orthopedic surgery or multi-trauma, ACS, bridging for cardiac valve replacement, stroke prevention for atrial fibrillation/flutter, hypercoagulable state, and cardioversion/ablation procedures.

Given the paucity of studies in medical literature that have rigorously evaluated therapeutic dosing of enoxaparin (Lovenox®) in HD patients, the aim of this retrospective chart review was to compare the safety and efficacy of therapeutic subcutaneous enoxaparin versus continuous intravenous UFH in patients receiving various forms of HD (e.g. intermittent hemodialysis, continuous renal replacement therapy, slow extended daily dialysis, and ultrafiltration). The primary efficacy endpoint was 30-day thromboembolic event and the primary safety endpoint was the 30-day incidence of major bleeding.

Materials and Methods

Study Design and Patient Population

This single-center retrospective chart review was conducted to evaluate the outcomes associated with use of reduced-dose therapeutic enoxaparin versus continuous infusion IV UFH for anticoagulation in HD patients. Patients were included in the study if they were age 18 years or older, required chronic or acute HD, and received at least one dose of enoxaparin or were started on an UFH continuous infusion. Consecutive patients receiving enoxaparin were matched 1:1 with randomly selected patients treated with IV UFH, based on the indication for anticoagulation. Indications included the following: acute VTE, bridging therapy, VTE prophylaxis following orthopedic surgery or multi-trauma, ACS, bridging for cardiac valve replacement, stroke prevention for atrial fibrillation/flutter, hypercoagulable state, and cardioversion/ablation procedures. Patients were excluded if they were treated with a LMWH other than enoxaparin, received only prophylactic doses of anticoagulation (e.g. enoxaparin 30 mg daily), did not meet matching criteria, or if they had incomplete medical records. The study was approved by the UCDMC Institutional Review Board and requirement for informed consent was waived.

Bleeding Risk Assessment and Monitoring

During chart review, patients were retrospectively assessed for baseline bleeding risk based on the HAS-BLED scoring system [18]. Anti-factor Xa levels were not collected as they were not drawn during hospitalization; patients receiving enoxaparin were monitored with complete blood counts (CBC) and clinical signs and symptoms of bleeding. Patients receiving UFH were monitored using activated partial thromboplastin time (APTT) in addition to CBC and clinical signs and symptoms of bleeding. Baseline international normalized ratios (INR) were also collected.

Outcome Measures

The primary efficacy endpoint was 30-day incidence of a symptomatic thromboembolic event. The primary safety endpoint was 30-day incidence of International Society on Thrombosis and Haemostasis (ISTH)-defined major bleeding, which is fatal bleeding and/or symptomatic bleeding in a critical organ or area (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome) and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or bleeding leading to transfusion of two or more units of packed red blood cells [19]. Secondary outcomes included the 30-day incidence of readmission for any reason, 30-day all-cause mortality, and hospital length of stay. Readmission and mortality as reported in the UCDMC electronic health record (EHR) were the only late outcome measures; all other endpoints occurred during hospitalization.

Statistical Analysis

A sample size calculation to ensure that a 15% difference in major bleeding would be statistically significant indicated that a total of 128 patients would be necessary, assuming 80% power and an $\alpha = 0.05$.

All statistics were performed in Statistical Analysis Software (SAS). Continuous variables were tested using the t-test or Kruskal-Wallis test. Categorical variables were tested using X^2 or Fisher's Exact. Test selection was based on the validity of the normal assumption. A multivariate logistic regression was performed to assess risk factors potentially associated with major bleeding.

Results

Baseline Characteristics

Fig. 1 outlines the entry of patients into the study. A total of 710 patients were identified; 289 had an enoxaparin order and 421 had an UFH order. After exclusion for various reasons (e.g. order not administered, prophylactic dosing, missing order, etc.) 89 enoxaparin treated patients remained to be matched. A total of 164 patients were included