Use of enoxaparin in the setting of warfarin induced calciphylaxis in an ESRD patient with a mechanical heart valve
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Abstract

Calciphylaxis creates a challenge in anticoagulation therapy for patients with mechanical heart valves and ESRD as warfarin cannot be used. We describe our approach in using enoxaparin as an alternative for anticoagulation in a patient with a mechanical heart valve and ESRD who developed calciphylaxis from warfarin.

Keywords: calciphylaxis, warfarin, enoxaparin, mechanical heart valve, anticoagulation, ESRD

Key Clinical Message

A treatment option in patients with ESRD, mechanical heart valves and calciphylaxis from warfarin is dose adjusted enoxaparin with anti-factor Xa monitoring to effectively and safely prevent thromboembolic events without an increased risk of bleeding

Introduction

Patients with mechanical heart valves require life-long anticoagulation due to an increased risk of thromboembolism. Mechanical valves in the mitral position are associated with a higher thromboembolism risk compared with valves in the aortic position. [1,2] According to the American College of Cardiology, the current anticoagulation recommendations for a patient with a mechanical heart valve is a vitamin K antagonist such as warfarin. [3] However, the management of anticoagulation is complicated in the setting of calciphylaxis, as its development requires discontinuation and permanent contraindication of warfarin. Calciphylaxis is a serious complication in patients with end stage renal disease (ESRD) and has a high mortality rate, with an occurrence of about 1-4% in ESRD patients. [4] There are no clear guidelines on alternatives to warfarin for mechanical heart valves in ESRD patients. We report a case describing the use of enoxaparin for long-term anticoagulation in a patient with a mechanical mitral valve, atrial fibrillation and ESRD.

Case Report

A 75-year-old female with history of atrial fibrillation and mechanical mitral valve replacement being anticoagulated with warfarin, hypertension, heart failure, and ESRD on renal replacement therapy (RRT) was admitted for management of purulent and malodorous bilateral lower extremity ulcers. She was started on broad-spectrum intravenous antibiotics, warfarin was interrupted, and she underwent surgical debridement of the ulcers. Following the procedure, she was restarted on warfarin. Her hospital course was further complicated by the development of severe pain, tissue induration and necrotic infiltration of the previous debridement incision sites. Warfarin was discontinued and she underwent repeat excisional debridement of the affected areas followed by vacuum assisted closure of the lesions. She was subsequently started on intravenous heparin infusion following the repeat debridement procedure. Pathology of the debrided tissue demonstrated calciphylaxis with necrosis, thrombosis and acute and chronic inflammation of the skin and soft tissue with ulceration. Given that warfarin is contraindicated in the presence of calciphylaxis, after discontinuation of vacuum assisted wound therapy, the patient was started on enoxaparin at a dose of 0.7 milligrams (mg)daily. Anti-factor Xa level was monitored with the target level being between 0.5 and 1. Anti-factor Xa level was monitored six hours after administration of the third dose of enoxaparin and was found to be 0.5. After initiation of enoxaparin therapy, her wounds demonstrated marked improvement and we did not observe any bleeding events using this dosing regimen. She was subsequently transferred to another institution for hyperbaric oxygen therapy.

Discussion

Calciphylaxis or calcific uremic arteriolopathy is a rare systemic disease which can occur in patients receiving RRT. It causes calcification of arterioles, thrombosis and ischemia. Certain risk factors such as hyperparathyroidism, diabetes, and warfarin have been identified. [5] Warfarin is a vitamin K antagonist that affects two forms of vitamin K: vitamin K1 and vitamin K2. [6,7] While vitamin K1 is responsible for activation of hepatic clotting factors, vitamin K2 is involved in inhibition of calcium deposition in the vasculature. [6,7] Warfarin has been thought to provoke calcification by interfering with vitamin-K dependent carboxylation of matrix G1A, an 84 amino acid protein synthesized in the kidney, cartilage, lung, heart, and vascular smooth muscle and is responsible for inhibiting the mineralization of tissues. [7] Inhibition of the matrix G1A protein has been shown to cause vascular calcification in rat models, and could potentially explain vascular calcification seen in patients receiving long-term warfarin therapy. [4,7,8] Susceptibility to vascular calcification may also depend on genetic variation and differences in gamma-carboxylation at the glutamate residues. [4]

Anticoagulation with vitamin K antagonists has been the gold-standard for prevention of thromboembolism in patients with prosthetic valve replacement. Direct oral anticoagulants have not been studied in patients with mechanical prosthetic valves so they are currently not approved for use in this patient population. The RE-ALIGN trial evaluated warfarin compared to the direct thrombin inhibitor dabigatran as anticoagulation therapy in patients with either aortic and mitral valve replacement. The trial was terminated prematurely as treatment in the dabigatran cohort was associated with increased thromboembolic and bleeding events. [3] The use of low molecular weight heparin (LMWH) has been evaluated in this context and is supported by consensus guideline statements. [4,8] In highly thrombogenic states such as the presence of mechanical heart valves or atrial fibrillation, treatment dosing of anticoagulation may also be preferred. [9] Additionally, recommended options for therapeutic anticoagulation in patients with ESRD requiring RRT have traditionally been limited to unfractionated heparin and oral vitamin K antagonists, [10] however there is limited data regarding the use of LMWH for anticoagulation in patients RRT. Pon et al. reported the results of using lower doses of subcutaneous enoxaparin at 0.4-1mg per kilogram (kg) daily (average dose 0.7 ± 0.2mg/kg/day) given prior to RRT with monitoring of anti-factor Xa levels for a variety of indications including thromboprophylaxis in patients with cardiac valve replacement. [10] Based on the safety results of this study, we decided to pursue low dose enoxaparin dosing at 0.7mg/kg daily with anti-Xa level monitoring.

Measuring anti-factor Xa levels in ESRD has been traditionally used to minimize bleeding while maximizing thromboembolic reduction. Peak concentrations are usually checked about 4-6 hours after administering the third dose of enoxaparin. [11] Trials such as the Thrombolysis in Myocardial Infarction (TIMI) 11A study showed maintaining peak anti-factor Xa concentrations between 0.5-1 resulted in fewer bleeding events. [12] According to the American College of Chest Physicians, if LMWH is chosen for patients with creatinine clearance (CrCl) $\leq$30 milliliter (mL) per minute then anti-factor Xa monitoring along with dose reduction should be considered. [12] As available literature is limited in patients requiring RRT, trials such as ESSENCE and TIMI 11B showed increased risk for major bleeding in patients with CrCl $\leq$30 mL/minute receiving therapeutic doses of enoxaparin. In a meta-analysis by Lim and associates, enoxaparin at a therapeutic dose was associated with a further increase in major bleeding in non-RRT patients with a CrCl <30mL/minute due to elevated anti-factor Xa levels but this was not observed when enoxaparin was empirically dose reduced. [13] This is thought to be due to the accumulation of LMWH products as they are renally cleared. These studies, however, did not include patients requiring RRT so recommendations are inferred using the data from the population of patients with CrCl $\leq$30 population not requiring RRT. Because data and research trials including patients on RRT and the use of enoxaparin are extremely limited, no clear guidelines are available and our approach was based on these studies.

Conclusion

Thus, our case represents another treatment option in patients with ESRD, mechanical heart valves, and complications from warfarin use such as calciphylaxis. Our patient is high risk as she has two indications for anticoagulation: atrial fibrillation

and a mechanical heart valve. As there are no guidelines for renal dose adjustments, our approach was adapted from previous literature published on this topic. The dosing and monitoring of anti-factor Xa levels is crucial to effectively and safely prevent thromboembolic events in this patient population without causing major bleeding. Larger clinical trials are needed to establish the dosing and long-term risks and benefits with enoxaparin use in patients requiring RRT.

We have no conflicts of interest to disclose.

Author Contributions
NP: contributed to literature search, manuscript preparation and editing, PG: contributed to manuscript preparation, editing and review, SC: contributed to literature search and manuscript preparation, EP: contributed to manuscript editing and review

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Figures

Figure 1. Bilateral lower extremity necrotic ulcers after debridement