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Use of systemic bivalirudin with catheter-directed thrombolysis in a patient with heparin-induced thrombocytopenia: A case report

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Abstract
In patients with submassive pulmonary embolism, the use of catheter-directed thrombolysis (CDT), using low-dose alteplase is associated with improvement in overall hemodynamics. The data for use of CDT in patients with heparin-induced thrombocytopenia are limited. We report a case of CDT in a patient with HIT using bivalirudin anticoagulation. Data of the use of bivalirudin and argatroban for systemic anticoagulation with CDT are limited.

KEYWORDS
bivalirudin, catheter-directed thrombolysis, heparin-induced thrombocytopenia

1 | INTRODUCTION
In North America, venous thromboembolism is the third most common cardiovascular disorder [1]. In patients with submassive pulmonary embolism (PE), the use of catheter-directed thrombolysis (CDT) with low-dose alteplase, in conjunction with low-dose systemic anticoagulation, is associated with improved outcomes such as decreased right ventricular dilation, reduced pulmonary hypertension, and decreased anatomic thrombus burden [2]. The use of lower-dose thrombolytics in CDT has been observed to cause less bleeding compared to high-dose systemic thrombolytic therapy [2,3]. The evidence for effectiveness of CDT is in patients treated with unfractionated heparin (UFH) and without a diagnosis of heparin-induced thrombocytopenia (HIT). There are limited reports of the use of DTIs, especially bivalirudin, in patients undergoing CDT [4–6]. We report a case of CDT using systemic anticoagulant with low-dose bivalirudin in a patient with recurrent deep vein thrombosis (DVT) and PE due to HIT.

2 | CASE PRESENTATION
A 60-year-old (weight, 118 kg; body mass index, 32 kg/m²) obese male with a history of hypertension and recent diagnosis of metastatic pancreatic cancer presented to an outside hospital in January of 2017 with a left lower extremity DVT. He was bridged with therapeutic dose enoxaparin to warfarin targeting an international normalized ratio (INR) of 2–3. Two weeks later, he represented to the outside hospital with a new right upper extremity and right lower extremity DVT despite therapeutic INR. A computed tomographic pulmonary angiogram (CTPE) revealed a new PE. He was transitioned to fondaparinux 10 mg subcutaneously once daily given his body weight. Ten days later, he was re-admitted in the setting of new shortness of breath. He reported strict adherence to fondaparinux. New CTPE was performed demonstrating a new PE in the left pulmonary artery and increased thrombus burden in right lower lobe pulmonary arteries. UFH infusion was initiated targeting activated partial thromboplastin time (aPTT) goal of 60–80 sec. Thrombophilia panel including, anticardiolipin antibodies, antinuclear antibodies, factor V leiden, and prothrombin gene mutation were all negative. Protein S, protein C, and antithrombin levels were not sent given that the patient was on anticoagulation. He was transferred to Brigham and Women’s Hospital for further management. On hospital day 3, the platelet count declined from 150,000 to 77,000 K/uL, with a reported baseline of 208 K/uL. The calculated “4-T’s” pretest HIT probability score was 6 indicating high probability of HIT (2 points for
platelet fall from baseline of greater than 50%, 2 points for prior heparin exposure within the past 30 days, 1 point for suspected thrombosis, and 1 point for thrombocytopenia due to other causes) [7]. Our institutional protocol necessitates discontinuation of all heparin products and further workup for HIT diagnosis in patients with 4-T's score of equal or greater than 4. Peripheral smear showed no schistocytes. Heparin was discontinued, and a bivalirudin infusion was initiated at 0.15 mg/kg/hr using actual body weight with an aPTT goal of 60–80 sec.

The heparin-platelet factor-4 (PF-4) IgG antibody test result was positive with an optical density of 0.9 (>0.4 is considered positive at our institution) [7]. In preparation for placement of a tunneled central access catheter, bivalirudin was discontinued for 3 hr. Three hours after central access catheter placement, he was started on fondaparinux 12.5 mg subcutaneously daily as fondaparinux is standard management for patients with HIT, acceptable renal function, and low bleeding risk at our institution. The dose was escalated given the development of recurrent thrombosis on standard intensity fondaparinux as dose escalation has been demonstrated in small studies to be effective [8,9]. Anticoagulation was interrupted for a total of 6 hr. The next day, he became hypotensive and hypoxic. A repeat CTPE showed a significant increase in pulmonary clot burden and right heart strain (Figure 1). The emboli were more central and larger compared to the previous CTPE. He was deemed to be not a surgical candidate for embolectomy due to stage IV pancreatic cancer complicated by HIT. Bivalirudin was restarted at 0.2 mg/kg/hr with aPTT goal of 60–80 sec. A multidisciplinary decision was made to use CDT with continuation of systemic bivalirudin during CDT at a lower rate. The bivalirudin infusion was reduced by half to 0.1 mg/kg/hr targeting an aPTT of 50–60 sec. CDT using alteplase infusion was initiated without a bolus at 0.5 mg/hr through two sheaths through left and right pulmonary artery catheters via right internal jugular vein introducer. Alteplase infusion was continued for 20 hr. The aPTT during CDT ranged from 68.5 to 61.5 sec. Fibrinogen was 498 mg/dL (baseline 514 mg/dL) during the alteplase infusion. Following CDT completion, the goal aPTT target was increased from 60 to 80. The patient significantly improved post procedure with decreased symptoms and improved oxygen saturation. The patient remained hemodynamically stable throughout. No bleeding events were observed requiring blood products during or following the CDT. Despite successful CDT therapy with bivalirudin therapy, the patient subsequently expired six days later due to aspiration pneumonia (Figure 2).

3 | DISCUSSION

We report the use of bivalirudin for systemic anticoagulation in a patient with HIT treated with CDT. Data are limited on the simultaneous use of alteplase and DTIs in patients undergoing CDT. Three case reports
describe the concomitant use of DTIs in patients undergoing CDT. Argatroban was used in two case reports. Maldonado reported the successful use of argatroban in a 73-year-old male with lower extremity limb and graft ischemia and acute renal allograft vein occlusion [4]. Argatroban was used given that its pharmacokinetic and pharmacodynamic properties are minimally affected by renal function. Argatroban infusion without a bolus was initiated at 0.75 mcg/kg/min just prior to CDT with a targeted goal aPTT of 50–75 sec. CDT with alteplase was initiated at 0.5 mg/hr without a bolus. The patient received a total of 48 hr of alteplase and 11 days of argatroban therapy. The patient was then successfully transitioned to warfarin after regaining baseline renal function and functioning bilateral extremities.

Turba et al. reported another successful case using argatroban in a patient with acute lower extremity arterial thrombosis in a 77-year-old male undergoing CDT [5]. Argatroban infusion without a bolus was initiated at 0.75 mcg/kg/min just prior to CDT with a targeted goal aPTT of 50–75 sec. CDT with alteplase was initiated at 0.5 mg/hr without a bolus. The patient received a total of 48 hr of alteplase and 11 days of argatroban therapy. The patient was then successfully transitioned to warfarin after regaining baseline renal function and functioning bilateral extremities.

Martinez and Burnett report on the use of bivalirudin in a 48-year-old female with small subsegmental embolus at the right lung base, distended inferior vena cava filter (IVC), iliac veins, bilateral external iliac, common femoral, femoral, popliteal, peroneal, and posterior tibial veins [6]. Bivalirudin was used as it was the preferred agent at the institution. Alteplase was started at 0.5 mg/hr without a bolus through each of the sheaths. Bivalirudin was initiated at 0.06 mg/kg/hr through each catheter, with a goal aPTT of 45–75 sec. The total dosage of bivalirudin was then halved and infused into both sheaths. CDT with bivalirudin was continued for 36 hr. The IVC filter and sheaths were successfully removed without incident. Patient was then transitioned to bivalirudin intravenously and was discharged on warfarin. No bleeding was reported in these three cases.

Our patient had extensive clot burden in the setting of active cancer and a positive PF4 test. Thrombosis progressed despite multiple anticoagulation regimens at standard dose, including warfarin and fondaparinux. The hypercoagulable state due to pancreatic cancer in the setting of briefly holding anticoagulation for the central access catheter placement was a contributing factor in progression of PE, although contribution from HIT cannot be excluded. The use of CDT with systemic bivalirudin in this cancer patient with HIT was successful at treating submassive PE.
Treatment with bivalirudin was a successful adjunct to CDT in this case. Although the aPTT remained slightly above goal throughout the CDT, there was no evidence of bleeding during or after the procedure. He showed significant improvement clinically and hemodynamically following CDT. The unfortunate deterioration in his condition was thought to be caused by aspiration pneumonia and underlying metastatic pancreatic cancer, and not recurrent thrombosis.

4 | CONCLUSION

Data surrounding the use of DTIs for systemic anticoagulation with CDT are limited. This case demonstrates that the use of systemic bivalirudin with a reduced aPTT goal during CDT can be a viable treatment option in patients with HIT.

CONFLICT OF INTEREST

Nothing to report.

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