Catheter-Directed Thrombolysis with Direct Intra-Catheter Administration of Argatroban and Alteplase for Extensive Deep Vein Thrombosis in a Patient with Heparin-Induced Thrombocytopenia

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INTRODUCTION

Proximal deep vein thrombosis (DVT) has traditionally been treated with medical therapy in patients without contraindications to systemic anticoagulation. In recent years, catheter-directed thrombolysis (CDT) has emerged as a potential interventional management option, which allows for the direct intra-thrombus administration of pharmacologic agents. Current clinical practice guidelines state CDT is a reasonable therapy in certain clinical settings, such as acute iliofemoral DVT associated with impending limb-threatening thrombosis, provided the patient has a low risk of bleeding complications and good expected functional status.1–9

CDT involves direct intra-thrombus administration of weight-based recombinant tissue plasminogen activator (rTPA); alteplase is recommended at a rate of 0.01 mg/kg/hr, not to exceed 1 mg/hr.10 Proposed advantages of CDT include the ability to achieve high intra-thrombus concentrations of drug, lower overall exposure to thrombolytic doses as compared to systemic thrombolysis, and decreased risk of developing post-thrombotic syndrome (PTS) and venous ulceration. Interventionalists also have the option of implementing adjunctive mechanical therapy during the procedure to further enhance clot dissolution and/or removal.11–13 An anticoagulant agent, typically unfractionated heparin (UFH), is often administered concomitantly. Depending on each institution’s CDT protocol, UFH may be given intravenously or via direct intra-catheter infusion at the target site. Unfortunately, if a patient has confirmed or suspected heparin-induced thrombocytopenia (HIT), an alternative non-heparin anticoagulant may have to be considered.

Currently, the clinical evidence investigating the use of direct thrombin inhibitors (DTI) during CDT for acute proximal DVT is not well-defined. Furthermore, there is even less efficacy and safety data regarding the direct administration of DTIs at the target site during CDT, as well as a lack of formal dosing recommendations in this scenario. Herein, we present the case of a patient with HIT and an extensive iliofemoral DVT treated with CDT using direct intra-catheter administration of both argatroban and alteplase.

CASE REPORT

A 61-year-old female with a history of hypertension, hyperlipidemia, and acute cholecystitis was admitted after an incidental finding of a right renal mass with inferior vena cava (IVC) invasion. She underwent a right radical nephrectomy and IVC tumor thrombectomy and was discharged 6 days later on prophylactic subcutaneous enoxaparin 40 mg daily. Her platelet count upon discharge was 277 x 10³/µL. After 16 days of prophylactic enoxaparin, she began experiencing pain and swelling in her right lower extremity, which extended from her calf to her thigh. She was re-admitted and a venous ultrasound showed the presence of an extensive deep vein thrombosis (DVT) with occlusions involving the lower IVC, right common iliac, internal iliac, external iliac, common femoral, superficial femoral, popliteal, and peroneal veins.

Thrombocytopenia with Argatroban and Alteplase

No bleeding complications occurred and an argatroban-to-warfarin bridge was subsequently completed. To our knowledge, this is the first case report to describe direct intra-catheter administration of both argatroban and alteplase during CDT for a patient with HIT who developed an extensive iliofemoral DVT with distal involvement. If clinicians are to opt for direct intra-catheter argatroban administration, we advise individualizing pharmacotherapy with close monitoring of coagulation parameters.

Key words: Argatroban, tissue plasminogen activator, heparin-induced thrombocytopenia, catheter-directed thrombolysis, endovascular procedures

Intravenous (IV) UFH was administered, with a bolus of 80 units/kg and an initial infusion rate of 18 units/kg/hr. Notable laboratory results upon admission included a platelet count of 64 x 10^9/L and a serum creatinine of 2.02 mg/dL. With a calculated 4 T’s score of 6, suggesting a high probability of HIT, the UFH infusion was discontinued and IV argatroban was initiated at 1 mcg/kg/min. The heparin anti-platelet factor 4 enzyme-linked immunosorbant assay returned positive, with an optical density elevated at 0.786 (reference range <0.400). The patient was diagnosed with HIT with thrombosis (HITT) and the argatroban infusion was continued to target an activated partial thromboplastin time (aPTT) of 50-70 seconds.

Given the widespread iliofemoral DVT with distal extension, the decision was made to implement CDT, with the goal of reducing acute symptoms and the chronic effects of PTS. This approach was chosen over suction thrombectomy and balloon angioplasty were performed below the vein down to the peroneal vein. However, a high clot burden and re-look venography. Patency was observed from the common femoral extremity thromboses were discovered, affecting the IVC and IVC interruptions for 18 hours, at which point the patient underwent an angio-dedema of the target site given the extensive nature of the DVT. The available protocol for the combined administration of argatroban and rtPA via the popliteal sheath.[20] Of note, none of the patients included in this study were diagnosed with HIT. For patients with unilateral DVT, intra-catheter rtPA was infused at 1 mg/hr and argatroban was infused at 0.5-1 mcg/kg/min through the sheath’s side port for 20-24 hours. For patients with bilateral DVT, rtPA was infused at 0.75-1 mg/kg/hr through each catheter and argatroban was infused at 0.3-0.75 mcg/kg/min through each side port. For all cases, the argatroban infusion rate was adjusted to target an aPTT of 50-90 seconds. Complete thrombus resolution, from the popliteal vein up to the IVC, was observed in 30 patients (91%) during the follow-up venography, which took place 20-30 hours after the intervention. No bleeding events or iatrogenic pulmonary embolism were reported.

Martinez et al. described a trauma patient who developed HIT after UFH and low-molecular-weight heparin exposure.[20] Extensive lower extremity thromboses were discovered, affecting the IVC and IVC filter, bilateral external iliac, common femoral, femoral, popliteal, posterior tibial, and peroneal veins. During the CDT procedure, 2 thrombolytic infusion catheters were placed via the bilateral iliac veins, which extended up to the IVC. Alteplase 0.5 mg/hr and bivalirudin 0.06 mg/kg/hr were initiated through each sheath, for a combined total dose of 1 mg/hr and 0.12 mg/kg/hr, respectively. The bivalirudin infusion was adjusted to maintain an aPTT of 45-75 seconds and the dose per sheath ranged from 0.06-0.072 mg/kg/hr (total dose: 0.12-0.144 mg/kg/hr). After 24 hours, a venography showed improvement in IVC and iliac venous flow, but residual clot remained in the IVC filter and narrowing was still observed in the left common iliac vein. Thus, the intra-catheter alteplase and bivalirudin infusions continued for an additional 12 hours, for a total of 36 hours. At that point, a repeat venography showed satisfactory resolution of all thromboses in the
IVC and iliac vein. A small residual thrombus was still noted in the IVC filter, but the filter was subsequently removed. The authors do not report on the status of distal vein occlusions.

Turba et al. reported the case of a patient diagnosed with HIT who underwent CDT for lower extremity arterial thromboses. The patient had developed occlusions of the left distal superficial femoral, popliteal, posterior tibial, anterior tibial, and peroneal arteries. Intra-arterial rtPA was initiated at 1 mg/hr through the infusion catheter. Argatroban was concomitantly administered via the arterial sheath with an initial bolus of 350 mcg/kg followed by an infusion 25 mcg/kg/min, titrated to an aPTT 2-3x above baseline. The intra-arterial infusions continued for 14 hours, at which point a follow-up angiogram showed the previously occluded arterial segments were now patent. No intra-or post-operative complications were reported.

To our knowledge, this is the first case report to describe direct intra-catheter administration of both argatroban and alteplase during CDT for a patient with HIT who developed an extensive iliofemoral DVT with distal involvement. The patient was already receiving an IV argatroban infusion at 1 mcg/kg/min prior to the intervention, allowing us to derive a decreased intra-catheter dose of 0.8 mcg/kg/min during and after the procedure to target a slightly lower aPTT. Although continuing the IV argatroban during the procedure was discussed as an option, clinicians felt direct intra-catheter administration would have the advantage of achieving higher intra-thrombus concentrations of the anticoagulant. In addition, this method of direct administration theoretically avoids bypass of the drug around occluded veins via collateral circulation.

There was concern for suboptimal results since the intra-catheter argatroban and alteplase infusions ran for only 8 and 18 hours, respectively, which is a shorter duration than what has been described in previous literature and protocols. However, the majority of vessels were patent on follow-up venography, from the common femoral down to the peroneal veins. A high clot burden was still observed in the common iliac vein. This was not surprising, given the extensive nature of the DVT, the shorter duration of CDT, and the fact that the common iliac is the furthest up from the popliteal access site where the intra-catheter infusions were delivered. The CDT therapy was able to dissolve enough of the clot burden so that suction thrombectomy could be safely performed to remove the remaining occlusion.

Although this case suggests CDT with direct intra-catheter administration of argatroban and alteplase was effective in significantly reducing the clot burden without any major complications, the available clinical evidence is not sufficient enough to devise a formal treatment or dosage recommendation. The chosen intra-catheter argatroban dose in our case was individualized and derived from previous patient-specific data. If clinicians are to opt for this direct route of administration, they should individualize pharmacotherapy and dosages with close monitoring of coagulation parameters and potential adverse reactions.

CONCLUSION

A patient with HIT who developed an extensive iliofemoral DVT with distal involvement was treated with CDT using direct intra-catheter infusions of both argatroban and alteplase without any major complications.

Conflicts of interest

The authors have no conflicts of interest to disclose.

REFERENCES