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*Vascular Interventions* *Case Report*

# Argatroban and ultrasound-facilitated thrombolysis with alteplase in a patient with bilateral pulmonary embolism and history of heparin-induced thrombocytopenia: A case report

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## ABSTRACT

A 58-year-old female was admitted to the hospital with bilateral pulmonary embolism (PE) with right heart strain. Her medical history included a previous PE resulting in thrombolysis and inferior vena cava filter placement, heparin-induced thrombocytopenia, morbid obesity, and chronic pain that was treated with an epidural injection 2 weeks prior to admission. This case is unusual due to the need for alternative anticoagulation management during thrombolysis in a patient with a heparin allergy who was at increased risk for bleeding. She was initiated on argatroban to achieve therapeutic aPTTs before receiving both mechanical thrombectomy and alteplase through ultrasound-facilitated catheter-directed thrombolysis. The argatroban was reduced to a flat rate of 0.5 mcg/kg/min during thrombolysis and was subsequently increased to achieve therapeutic aPTTs upon completion of thrombolysis. The patient was transitioned from argatroban to apixaban for lifelong anticoagulation.

**Keywords:** Alteplase, Argatroban, Pulmonary embolism, Thrombectomy

## INTRODUCTION

Submassive pulmonary embolism (PE) is defined as an acute PE with either right ventricular (RV) dysfunction or myocardial necrosis in the absence of hypotension. Systemic thrombolytics are effective in treating the clot burden, but inherently have a high bleeding risk associated with use. As a result, alternative therapies have been explored, such as delivering thrombolysis through an ultrasound-facilitated catheter. The EkoSonic™ Endovascular System (Boston Scientific, Marlborough, MA) has been utilized in the ULTIMA, SEATTLE II and OPTALYSE trials.[1-3] Heparin is typically administered at low doses in conjunction with the thrombolytic. However, there may be instances when heparin should be avoided, such as heparin-induced thrombocytopenia (HIT).

HIT is an immune-mediated reaction that may occur after exposure to heparin products, which could lead to thromboembolic events.[4] Patients who present with HIT begin to display characteristic signs, such as a platelet count decrease of more than 50% from baseline occurring between 5 and 10 days after heparin exposure. HIT causes patients to develop anti-platelet factor 4 (PF4)-heparin antibodies; these antibodies disappear (median, 50–85 days) and typically

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take at least 5 days to regenerate following another heparin exposure.

The recurrence of HIT is unknown so patients should avoid heparin products by receiving alternative anticoagulants if possible. Warkentin and Kelton describe seven patients with history of HIT whom were reintroduced heparin and had no occurrence of new HIT episodes.[5] Potzsch *et al*. reported similar findings in a study of ten patients with history of HIT who were exposed to heparin during a cardiopulmonary bypass procedure.[6] Each patient tested negative for HIT antibodies before the procedure and had no increase in antibodies for up to 10 days following exposure of heparin.

Patients who have a history of HIT may require an anticoagulant for venous thromboembolism treatment and prophylaxis. The American Society of Hematology recommends administration of a non-heparin anticoagulant rather than unfractionated heparin or low molecular weight heparin in patients with remote HIT, defined as no longer having detectable PF4-heparin antibodies.[7] Likewise, the American College of Chest Physicians do not recommend reintroduction of heparin in patients with a history of HIT and acute thrombosis; instead, they suggest the use of therapeutic dose fondaparinux for patients with normal renal function.[8]

With regard to HIT and catheter-directed thrombolysis, there are case reports of using argatroban or bivalirudin in patients with deep vein thrombosis while limited information is available for patients with PE. In addition, there is a lack of published literature for patients receiving catheter-directed thrombolysis with HIT who may have other risk factors that increase their chances of bleeding, such as recent epidural injection.

The use of thrombolytics in patients who recently received lumbar puncture, spinal, or epidural steroid injection is addressed by the American Society of Regional Anesthesia and Pain Medicine. Guidelines suggest avoiding thrombolytic therapy for 10 days following puncture of noncompressible vessels.[9] The timing between entry into the epidural space and thrombolytic administration is imperative to assess since the risk of a spinal hematoma is highest during concomitant use. There are several reports of spinal hematomas associated with epidural injection and thrombolytic use.

We report the case of a patient with history of HIT and recent epidural injection who received argatroban and ultrasound-facilitated catheter-directed therapy with alteplase for bilateral PE.

## CASE REPORT

A 58-year-old Caucasian female presented to the emergency department with acute onset dyspnea. Her medical history included a previous PE, HIT, morbid obesity (BMI≥40 kg/m$^2$), and chronic back pain for which she received an epidural injection 2 weeks prior to admission. Her first PE occurred 7 years prior and required thrombolysis and placement of an inferior vena cava (IVC) filter. She was subsequently placed on warfarin for 3 months and then transitioned to aspirin 81 mg oral daily.

During the current admission, a CT of the chest revealed bilateral pulmonary emboli and right heart strain with a right ventricle to left ventricle size ratio of 1.38. An echocardiogram showed a moderately enlarged right ventricle and reduced RV systolic function. Further imaging revealed a deep vein thrombosis in the right posterior tibial vein. A CT of the abdomen and pelvis was completed to evaluate the integrity of the IVC filter and to assess for iliocaval thrombus. Caval thrombus involving the IVC filter was confirmed. [Table 1] reports laboratory values at baseline and throughout course of admission.

After the diagnosis of PE, the patient was immediately started on argatroban at an initial dose of 2 mcg/kg/min. The baseline aPTT value of 22.7 s was used to establish a goal of 1.5–3 times the baseline (34.1–68.1 s). The first aPTT 2 h after starting argatroban was therapeutic at 60.6 s.

Interventional radiology was consulted for evaluation of catheter-directed thrombolysis. The consideration of thrombolysis was complicated by a recent epidural injection requiring evaluation by a neurosurgeon, who deemed that the patient could safely receive catheter-directed thrombolysis. Hematology was consulted given the history of HIT, IVC filter, and PE requiring outpatient follow-up.

The patient remained on therapeutic argatroban alone until day 4 of admission. After minimal improvement, the patient preceded with mechanical thrombectomy of the IVC and placement of EKOS catheters for catheter-directed thrombolysis of the pulmonary arteries. Primary suction thrombectomy was performed of the IVC thrombus including the thrombus within the IVC filter utilizing the CATD Indigo® System (Penumbra, Alameda, California). Before the procedure, >50% of the filter volume was affected by the clot, which was then reduced to <30% of the filter volume after thrombectomy. Pulmonary arteries pressures were confirmed to be elevated at 50/18 mmHg with a mean of 33 mmHg. Two EKOS 12 cm infusion length catheters were positioned into the left and right lower lobar pulmonary arteries, and alteplase was infused through each catheter at 0.5 mg/h (total dose 1 mg/h) for approximately 18 h. The procedure was completed with no complications.

During thrombolysis, argatroban was reduced from the therapeutic rate of 2 mcg/kg/min to a flat rate of 0.5 mcg/kg/min. A reduced, flat rate was decided upon due to the increased risk of bleeding from the recent epidural

**Table 1:** Laboratory values throughout course of admission.

| Key Events | Day 1 (admission) | Day 4 (thrombectomy and ultrasound-facilitated thrombolysis) | | | | Day 5 |
|---|---|---|---|---|---|---|
| | Argatroban started | Prior to procedure | Immediately after procedure (argatroban reduced) | Six hours after procedure | Twelve hours after procedure | Argatroban increased |
| Hemoglobin (10.8–15.5 g/dL) | 13.4 | 11.7 | 12.7 | 12.4 | 11.8 | 11.2 |
| Platelets (140–440 thou/mm$^3$) | 212 | 195 | 469 | | | |
| aPTT (22.1–33.9 s) | 22.7 (baseline), 60.6 | 43.5 | 33.4 | 26.2 | 43.9 | 62 |
| Fibrinogen (231–480 mg/dL) | | 378 | 469 | 490 | 431 | |

injection. The rate of 0.5 mcg/kg/min was anticipated to result in lower aPTT values, but still provide levels above the patient's baseline. After the reduction of the argatroban, aPTT values were drawn approximately 6 and 12 h later, which resulted as 26.2 and 43.9 s, respectively. A further argatroban dose reduction would have been considered if aPTT values resulted above approximately 55 s. Thrombolysis continued until the following morning and the venous sheaths were removed. Argatroban was increased to the previous therapeutic rate of 2 mcg/kg/min, which again achieved aPTT values within the patient's goal within approximately 2 h of the rate increase.

On day 7, the patient's IVC filter was removed since it still contained clot and posed a risk of inciting rethrombosis. The following day, the hematologist transitioned the patient to apixaban 10 mg oral twice daily for 7 days, followed by 5 mg oral twice daily indefinitely. The patient was discharged without any complications.

## DISCUSSION

The SEATTLE II study was a prospective, single arm, multicenter trial that studied the safety and efficacy of catheter-directed therapy using EKOS in patients with acute submassive PE.[2] Patients received 24 mg of tissue-plasminogen activator with a unilateral catheter (1 mg/h for 24 h) or bilateral catheter (1 mg/h/catheter for 12 h). Patients received intravenous unfractionated heparin with a target aPTT of 40–60 s while thrombolysis was infusing. Results showed decreased RV dilation and thrombus burden as well as minimal intracranial hemorrhage.

The OPTALYSE trial also selected heparin as their anticoagulant of choice during thrombolysis; heparin was infused at a reduced rate of 300–500 units/hour with no target aPTT.[3] Unfortunately, the literature is sparse for non-heparin anticoagulants in combination with catheter-directed therapy in patients with PE. To the best of our knowledge, there is only one published case report of pulmonary artery thrombolysis with argatroban in a patient with a history of HIT.

Bethea *et al*. discuss a female who was initiated on argatroban 2 mcg/kg/min intravenously (aPTT goal 50–90 s) upon diagnosis of a PE.[10] The argatroban was held for 12 h before being transferred to the catheterization laboratory, where ultrasound-emitting thrombolysis catheters were placed. Alteplase was initiated through the catheters for 20 h and the argatroban rate was adjusted to maintain a lower aPTT goal of 35–55 s (observed values ranged from 38.5 to 52.2 s). Once the alteplase infusion completed, argatroban was then increased to reach a goal aPTT of 50–90 s. The patient experienced hemodynamic improvement and was later transitioned to warfarin prior to discharge. With our patient, we used a more conservative approach to argatroban dosing by administering a reduced, flat rate. The lower rate was selected due to her recent epidural injection and increased risk for bleeding. Our patient's aPTT during thrombolysis achieved lower aPTTs (ranging from 26.2 to 43.9 s) when compared to the patient reported by Bethea *et al*. This approach required less bleed risk while still producing a positive outcome in our patient.

## CONCLUSION

Argatroban and ultrasound-facilitated thrombolysis can be combined to successfully treat a patient with submassive PE and a history of HIT and recent epidural injection. Further studies are warranted to confirm safety and efficacy of our approach.

### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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