Bivalirudin during thrombolysis with catheter-directed tPA in a heparin refractory patient: A case report.

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Abbreviation	Full Term
VTE	Venous thromboembolism
UFH	Unfractionated heparin
HIT	Heparin induced thrombocytopenia
DTI	Direct thrombin inhibitor
tPA	Tissue plasminogen activator
ECHO	Echocardiogram
aPTT	Activated partial thromboplastin time
IVC	Inferior vena cava
PF4	Platelet factor 4
PE	Pulmonary embolism

Abstract

Venous thromboembolism (VTE) has increasing significance in hospitalized pediatric patients. Patients that have life or limb threatening thrombotic events require thrombolysis in addition to anticoagulation (AC). In patients who show signs of heparin resistance or heparin induced thrombocytopenia (HIT) it is imperative to identify alternative therapeutic options. We

present a child in whom bivalirudin was used for systemic AC during catheter directed thrombolysis along with tissue plasminogen activator (tPA, Alteplase®) for the treatment of a near-occlusive organ threatening thrombus. We also review the currently available literature on the use of combination therapy of an intravenous direct thrombin inhibitor with alteplase.

Introduction

The incidence of pediatric venous thromboembolism (VTE) has increased over the last decade[1] and patients are prescribed anticoagulation therapy to prevent extension and recurrence.[2] Unfractionated heparin (UFH), low-molecular-weight heparins, and vitamin K antagonists are the mainstay of anticoagulation in children.[1–3] In patients with heparin resistance, difficulty in achieving therapeutic heparin levels or in those who develop heparin induced thrombocytopenia (HIT), alternative options need to be identified. Bivalirudin, a direct thrombin inhibitor (DTI), that inhibits circulating and clot-associated thrombin, is an effective anticoagulant in children.[3,4] However, patients who develop limb or organ threatening thromboses may require additional thrombolytic treatment. We present a child in whom bivalirudin was used for systemic anticoagulation during catheter-directed thrombolysis using tissue plasminogen activator (tPA, Alteplase®) and review the current literature on the use of combination therapy of an intravenous DTI and alteplase.

Case Report

A 2-year-old male with Down syndrome and artificial heart valves on warfarin presented with shock. An echocardiogram (ECHO) showed moderate right ventricular dilation with increased pressures, but no signs of thrombus or vegetation. Blood work revealed an international normalized ratio of 7, and he received Vitamin K and fresh frozen plasma. Warfarin was discontinued, and he was started on UFH [goal activated partial thromboplastin time (aPTT) of 48-78 seconds].

Five weeks later, a repeat ECHO revealed an echogenic density in the hepatic inferior vena cava (IVC) with near complete occlusion and extension of the thrombus into the right renal vein. Given the development of an organ threatening thrombus while on high doses of UFH (>50 units/kg/hr) there was suspicion for development of HIT. Bivalirudin was started at 0.3 mg/kg/hr with a goal aPTT of 1.5 – 2 times his baseline (30 seconds). After 12 hours, catheter-directed alteplase was initiated at 0.03 mg/kg/hr and bivalirudin dose was reduced by 50% with a goal aPTT of 45-60 seconds. ECHO after 24 hours of catheter-directed alteplase showed worsening of thrombus, and alteplase was increased to 0.06 mg/kg/hr for an additional 48 hours; bivalirudin was increased to a maximum of 0.3 mg/kg/hr to maintain a goal aPTT of 45-60 seconds. After 48 hours, ECHO showed decreasing thrombus with improved IVC flow. Throughout treatment the patient's laboratory parameters including fibrinogen, plasminogen, and platelet counts were monitored and remained within normal limits and there were no bleeding complications. Platelet factor 4 (PF4) screen was negative indicating no evidence of HIT. With thrombus stabilization, alteplase was discontinued and bivalirudin was titrated to maintain a goal aPTT of 45 – 60 seconds. Unfortunately, the patient passed away 4 weeks later due to persistent candidal sepsis.

Discussion

The American College of Chest Physicians recommends thrombolysis in children with organ or limb threatening VTE.[5] The concomitant use of heparin at 5-10 units/kg/hr has been recommended to

prevent new clot formation as clot lysis releases thrombin during thrombolysis.[2] In patients with heparin resistance or HIT, choosing an alternative anticoagulant becomes imperative. DTIs have been used an alternative to UFH in patients with HIT. Bivalirudin is a commercially available DTI that has been used in pediatric patients with VTE and cardiac catheterization.[3,4] Its use during thrombolysis has been limited, although there are few reports of use of DTI with thrombolytic therapy in adult patients (Table 1).

Badreldin et al.[6] reported a case of bivalirudin and alteplase in an adult male with HIT and recurrent DVTs with new unstable pulmonary embolism (PE). Martinez and Burnett[7] reported an adult female with extensive thrombosis of the bilateral lower extremities and IVC dilatation who developed HIT. Lausin et al.[8] used systemic bivalirudin during catheter-directed thrombolysis with alteplase for an adult male patient with PE. Patients were prescribed DTI with 50% reduction in dosing during thrombolytic therapy and with variable target aPTTs. All had improvement in thrombus size and no bleeding events during thrombolytic therapy.

There is a strong need for alternative options for systemic anticoagulation in critically ill patients requiring thrombolytic therapy when heparin is contraindicated. It is unclear why our patient was refractory to heparin, as his PF4 screen was negative and antithrombin level was only mildly low at 67%; although likely multifactorial due to critically ill condition. In children, the recommended dose of tPA is highly variable. Recommendations vary with some using a low dose (0.01-0.06 mg/kg/hr) to high dose (0.1-0.5 mg /kg/hr).[2] Our patient was successfully treated with alteplase at 0.03 – 0.06 mg/kg/hr while receiving systemic anticoagulation with bivalirudin at a 50% dose reduction. In our review, this is the first pediatric patient where combination therapy (DTI and alteplase) has been reported.

Conflict of Interest Statement

Authors K. Regling, M. Callaghan, and M. Rajpurkar have no disclosures to acknowledge.

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TABLE 1 Summary of reported cases using DTIs during thrombolytic therapy.

Study	No. treated	DTI Used	Bolus dose (µg/kg)	Maintenance dose (µg/kg/min)	Administration route for tPA	Goal aPTT (sec)	Total tPA dose (mg/hr)	Duration of tPA therapy (hours)
Present case	1	Bivalirudin	0	0.15 mg/kg/hr	Peripheral IV	45 – 60	0.03 – 0.06 mg/kg/hr	72
Badreldin[6]	1	Bivalirudin	0	0.1 mg/kg/hr	Peripheral IV	50 – 60	1	20
Martinez[7]	1	Bivalirudin	0	0.12 – 0.144 mg/kg/hr	Iliac venous sheath	45 – 75	1	36
Lausin[8]	1	Bivalirudin	0	0.05 mg/kg/hr	Peripheral IV	37 – 44	2	12
Bethea[9]	1	Argatroban	0	0.65	Central catheter	35 – 55	2 – 3	20
Sin[10]	1	Argatroban	0	0.8	Popliteal venous sheath	40 – 50	1	18
Sharifi[11]	33	Argatroban	0	0.3 – 1.0	Popliteal venous sheath	50 – 90	0.75 – 1	20 – 24
Maldonado[12]	1	Argatroban	0	0.75	Peripheral IV	50 – 75	0.5	48
Turba[13]	1	Argatroban	350 over 3 – 5 min	25	Femoral artery	2 – 3 x baseline	1	14
Jang[14]	125	Argatroban	100 over 1 min	1 or 3	Peripheral IV	50 – 70	15mg bolus followed by: - 0.75 mg/kg for 30 minutes (max 50mg) - 0.5 mg/kg for additional 60	1.5 – 72

							minutes (max 35mg)	
Barreto[15]	65	Argatroban	100 over 3 – 5 min	1	Peripheral IV	N/A	0.9	48