Ultrasound Assisted Endovascular Thrombolysis in Adolescents: 2 Case Reports

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Thromboembolic events in childhood are rare, with an approximate annual incidence of 0.07 to 0.14 per 10,000 children and 5.3 per 10,000 hospital admissions of children, with peaks during the neonatal period and adolescence. In the general population, the incidence of thrombosis increases, reaching nearly 1 to 2 per 1000 persons for deep venous thrombosis (DVT) per year in adults.1,2 Raffini et al3 reported an annual increase in the incidence of venous thromboembolism in pediatric hospitals of 70%. Central venous catheters are a main cause of thrombosis in children (incidence up to 70%),4 as are underlying sepsis, cancer, heart disease, immobilization, and medications (eg, antithrombin mutation in 1 girl (ie, the 15-year-old). May-Thurner syndrome was identified in both girls, necessitating stenting of the left common iliac veins and continuation of anticoagulation therapy with enoxaparin and acetylsalicylic acid. No rethrombosis or complications occurred during the follow-up period. Ultrasound-assisted catheter-directed local thrombolysis with the EkoSonic Mach 4e system was effective in achieving immediate recanalization of the occluded veins and should be considered in children experiencing descending iliofemoral thrombosis. The fast recanalization might reduce the incidence of postthrombotic syndrome. May-Thurner syndrome is regularly found in these patients, and if present, requires stenting of the common iliac vein to avoid early reocclusion. However, long-term patency of iliac vein stenting in children remains to be examined.
oral contraceptives, asparaginase). In addition, several hereditary risk factors for thromboembolism have been discussed. May-Thurner syndrome (MTS), a compression of the common iliac vein by the crossing common iliac artery, is observed in up to 50% of adult patients with descending iliofemoral DVT and is associated with a recurrence rate of up to 73% for thrombosis. 

There are no data on the incidence of MTS in childhood. Despite a lack of evidence-based therapy guidelines, anticoagulation therapy with low-molecular-weight heparin (LMWH) or vitamin K antagonists is the current standard of care. In concomitance with severe hereditary risk factors or recurrent thrombosis, anticoagulation therapy for several years (long-term) is necessary. However, complete patency can only be achieved in up to 50% of cases, increasing the risk for rethrombosis (4%–21.3%) and postthrombotic syndrome (PTS). Data from a meta-analysis reported PTS in up to 26% of patients, varying in different studies from 10% to 70%. In the latter study, PTS was strongly associated with the extent of thrombosis, extent of recanalization, and preserved residual venous valve function. In rare cases, local or systemic lysis or thrombectomy is necessary to prevent loss of extremities.

Due to the bleeding risk of systemic lysis and the high risk of rethrombosis after surgical procedures, different methods for local lysis with reduced recombinant tissue plasminogen activator (rtPA) dosing have been established over the last few decades. Catheter-directed thrombolysis in adults experiencing descending iliofemoral DVT is an accepted therapeutic tool to restore patency as quickly as possible. Percutaneous endovascular thrombolysis includes: (1) mechanical aspiration of thrombi; and (2) catheter-directed thrombolysis and, as a recent development, an additional high-frequency, low-power ultrasound. Ultrasound causes a disaggregation of fibrin fibers, and pressure waves increase thrombus penetration of thrombolytic agents. A multicenter, randomized study in adults reported a decreased incidence of PTS (from 55% to 37%) compared with standard anticoagulation therapy. In MTS, stenting of the common iliac vein is necessary to prevent recurrent thromboembolism. For children, the published experience using endovascular thrombolysis is limited to 2 single-center reports with 16 and 41 patients, respectively. In both studies, a device without ultrasound was used.

The present article reports on 2 adolescents in whom ultrasound-assisted catheter-directed thrombolysis (USAD) was used.

**CASE 1**

A 15-year-old girl presented with pain, swelling, and dysesthesia of the left leg for 4 days. D-dimer levels were within normal range. Ultrasound examination and MRI angiography detected a thrombotic occlusion of the common iliac, internal, and external iliac veins, and the superficial femoral, popliteal, and saphenous veins. Screening for thrombophilic risk factors revealed no hereditary thrombophilia, a negative family history for thrombosis, no immobilization in the last weeks, no smoking, and a normal weight. The patient had started contraception with ethinylestradiol/chlormadinone acetate (0.03 mg/10 mg) 10 months earlier. After a diagnosis of descending iliofemoral thrombosis was made, anticoagulation therapy with enoxaparin (2 × 1 mg/kg body weight/d) was initiated. Informed consent of parents was obtained, and a catheter (EkoSonic Mach 4e; EKOS Corporation, Bothell, WA) for ultrasound-assisted local thrombolysis with rtPA and administration of unfractionated heparin (target activated partial thromboplastin time [aPTT]: 60 seconds) was inserted fluoroscopically through a 6-F sheath placed in the left popliteal vein after ultrasound-guided puncture; the procedure was performed on day 5 after symptom onset. Local lysis was started with rtPA 4 mg/h and reduced after 3 hours to 2 mg/h according to institutional protocol. Success was monitored by increases in D-dimer levels and ultrasound results. Twenty-four hours after the start of USAD, control phlebography demonstrated a residual occluded common iliac vein, and local lysis was continued for another 24 hours. After complete resolution of thrombus, the USAD was stopped. Results of a final phlebography revealed a stenosis of the common iliac vein consistent with MTS as the underlying cause of thrombosis. After balloon dilation, a self-expanding Nitinol stent (sinus-Repo-Visual 12 mm × 6 mm; OptiMed GmbH, Ettlingen, Germany) was inserted. Except for minimal local bleeding at the insertion site, no complications occurred. After the intervention, anticoagulation therapy was continued with LMWH and acetylsalicylic acid for 6 months. The patient wore compression stockings for 1 year. According to ultrasound examinations at follow-up over a 3-year period, no rethrombosis was detected. Thus far, no PTS has occurred (Villalta scale score: 0).

**CASE 2**

A 15-year-old girl presented with pain, swelling, and discoloration of the left leg. D-dimer levels were elevated. Ultrasound and MRI angiography revealed a thrombosis of the common femoral vein, superficial femoral vein, common iliac vein, and external iliac vein (Fig 1). Screening for thrombophilic
risk factors revealed a heterozygous mutation in the SERPINC1 gene (c.1157T>C, p.Ile386Thr). Her family history was positive for DVT and pulmonary embolism. The patient did not smoke and did not take hormonal contraceptives. Her BMI was within normal range. Anticoagulation therapy was initiated with enoxaparin (2 × 1 mg/kg body weight/d) until fluoroscopically guided insertion of the EkoSonic Mach 4e catheter. On day 4 after symptom onset and receipt of informed consent from the girl’s parents, lysis was performed according to weight-adapted protocols with rtPA 1 mg/h for 24 hours; anticoagulation therapy was continued for 24 hours with unfractionated heparin (aPTT target: 60 seconds). After 24 hours, complete recanalization was observed phlebographically. In the presence of MTS as an additional cause of thrombosis, the common iliac vein was also stented by using a self-expanding Nitinol stent (sinus-Repo-Visual; 12 mm × 6 mm), and anticoagulation therapy was continued with enoxaparin and acetylsalicylic acid. After 3 months, anticoagulation therapy with acetylsalicylic acid was stopped and, due to the hereditary antithrombin deficiency, continued with oral vitamin K antagonists (goal international normalized ratio: 2–2.5). Thus far, the girl has worn compression stockings on a regular basis. No rethrombosis or PTS has occurred after 3 years of follow-up (Villalta scale score: 0).25

**DISCUSSION**

Thrombosis in childhood is rare, with 2 peaks of incidence (the perinatal period and puberty) and is provoked by acquired prothrombotic risk factors and/or underlying hereditary thrombophilia. The goal of acute management is recanalization of occluded vessels as quickly as possible, prevention of rethrombosis, and reduction of the risk of PTS. Standard therapy consists of anticoagulation with LMWH. Due to the higher risk of bleeding with systemic rtPA, this therapy is reserved for life-compromising conditions. Since several years different gadgets for interventional mechanical thrombectomy and catheter-directed local thrombolysis are in use in adulthood. Despite lower rtPA doses, combined with mechanical removal of the thrombus and minimization of the bleeding risk, serious bleeding remains the most common complication.26 Only a few case reports depict the use in children. The present article describes 2 case reports in which a device with additional local ultrasound promoting fibrin degradation of the thrombus was used; the goal was to further reduce the rtPA doses and minimize bleeding complications. Except for minor bleeding from the insertion site, no severe bleeding occurred in the study patients. Laboratory monitoring revealed high D-dimer levels (a parameter of effectiveness of lysis) and prolonged aPTT and prothrombin time, probably due to the systemic activity of rtPA. A systemic bleeding risk must be assumed, and standard contraindications for systemic lysis should be applied.

Two case series published by Dandoy et al23 and Goldenberg et al24 showed the feasibility of available devices for use in children aged 3 months to 21 years. However, the size of available devices and lack of long-term data still limit widespread use in children. In adults, the use of additional ultrasound

**FIGURE 1**

Interventional treatment of acute descending iliofemoral DVT in a 15-year-old girl (case 2). A, Phlebographic depiction of the thrombotic occlusion of the left common, external, and internal iliac veins (white arrows). B, Control phlebography after 24 hours of catheter-directed thrombolysis. Partial recanalization of the distal iliac veins with residual thrombus in the common iliac vein (black arrow). C, MTS before stent implantation. The black arrowheads mark an elucidation in the contrast-filled lumen of the common iliac vein/inferior caval vein that corresponds to the impression of the vessel by the right common iliac artery. D, Final phlebogram after 48 hours of thrombolysis and stenting of the underlying MTS with extension of the stent into the external iliac vein.
yielded no benefits regarding time of recanalization and occurrence of PTS.\textsuperscript{16} No comparison data are yet available in childhood. After 3 years, neither of the present study patients exhibited PTS. Data regarding PTS after endovascular treatment in childhood are limited to the 2 aforementioned case series. In these studies by Dandoy et al and Goldenberg et al, the incidence of PTS was 13\% to 14\%. Delays to recanalization >10 days were associated with a higher risk of PTS.\textsuperscript{23,24}

In both of our study patients, MTS as an additional risk factor for lower limb thrombosis was identified, and according to adult guidelines for preventing recurrence of thrombosis, stents were placed. For children, no data on the incidence of MTS and the occurrence of thrombosis and their recurrence exist, and the indication of stenting must be deduced from adult data. Anticoagulation therapy with acetylsalicylic acid and/or LMWH to prevent stent thrombosis should be prescribed for 3 to 6 months depending on additional underlying risk factors. Long-term follow-up, especially in smaller children, is necessary to detect stent problems.

**CONCLUSIONS**

Percutaneous endovascular thrombolysis may be effective in achieving immediate recanalization of occluded veins in cases of descending iliofemoral DVT and should be considered a feasible method for supplementing anticoagulation therapy in children. Fast recanalization might reduce the incidence of PTS in children similar to adults. The presence of MTS requires stenting of the common iliac vein, and long-term patency remains to be examined. Currently, no data regarding the superiority of USAD compared with mechanical endovascular thrombolysis without ultrasound in children exist. Adolescents may be treated according to adult guidelines and treatment standards; for younger children, weight-adapted protocols and devices are necessary. Further studies to evaluate possible benefits in childhood are needed.

**ABBREVIATIONS**

- aPTT: activated partial thromboplastin time
- DVT: deep venous thrombosis
- LMWH: low-molecular-weight-heparin
- MTS: May-Thurner syndrome
- PTS: postthrombotic syndrome
- rtPA: recombinant tissue plasminogen activator
- USAD: ultrasound-assisted catheter-directed thrombolysis

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