Successful Secondary Endovascular Intervention in Pediatric Patients with Venous Thromboembolic Events

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Abstract

Background In the past, pediatric patients with venous thromboembolic events (VTE) were treated with low-molecular-weight heparin (LMWH) which was successful in around 70% of the cases. However, anticoagulation alone might not restore patency in all patients, and advanced therapeutic options to prevent postthrombotic syndrome are needed. During recent years, endovascular interventions have become a treatment option for pediatric patients with persistent thrombotic occlusion, not only in life- or limb-threatening VTE.

Methods We evaluated 12 consecutive patients (11–17 years) with newly diagnosed VTE being treated at our department during the last 4 years (2017–2020). In case follow-up examination showed persistent venoocclusion under anticoagulation, patients received secondary interventional therapy like recanalization, percutaneous transluminal angioplasty with or without catheter-directed thrombolysis, and stenting. Patients with no clinical signs of venoocclusion or regredient thrombosis in imaging examination received anticoagulation alone.

Results Six of 12 (50%) patients underwent catheter intervention. Median time from diagnosis to intervention was 4 months (0–12 months). Reintervention was necessary in one (8%) case and complete recanalization failed in one (8%) case. There were no major bleeding events or other major postinterventional complications, no acute or late local recurrence, and all patients reported clinical improvement after the procedure.

Keywords
- endovascular intervention
- children
- venous thromboembolic event

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Conclusion If endovascular intervention is used in teenage patients with persistent symptomatic VTE, reduction of postthrombotic symptoms is possible, even if intervention is performed secondary to failure of anticoagulation. Multidisciplinary treatment decisions can be based on the clinical course and follow-up imaging.

Introduction

Venous thromboembolism (VTE) affects 0.07 to 0.14/10.000 of all children.[1,2] However, there seems to be a substantial increase in cases since the 1990s, mainly due to a higher rate of malignant diseases being treatable and a higher rate of pediatric patients having central venous lines.[3–5]

VTE is a multivariate condition. In children, Peter and coworkers reported that around 90% of cases are associated with prothrombotic risk factors.[2] Risk factors comprise hereditary deficiencies or mutations in coagulation factors, autoimmune diseases, malignant conditions, and anatomic risk factors, as well as transient risk factors like immobilization, infection, or intake of certain medications.[6,7]

Differences in underlying risk factors, associated chronic diseases, and natural course of thrombotic closure impose a specific pediatric approach to therapeutic strategies. For example, central venous lines are a common risk factor for thrombosis in children, whereas VTE recurrence is less common in children compared with adults.[8] Additionally, the occurrence of concurrent problems like postthrombotic syndrome and chronic thrombotic closure demand further examination of alternative treatment options besides therapeutic anticoagulation, like it has been already established in adult patients. Specific interest should be given to the optimal treatment in children, as the possibility to enhance quality-adjusted life-years increases significantly.

Current initial treatment of choice in pediatric patients is the use of anticoagulants. Dosing of heparin in children was established by Massicotte et al.[9] Treatment time is recommended for 6 weeks to 3 months in children with identified risk factors and 6 to 12 months in children with idiopathic VTE (CHEST guidelines).[10] In case of specific hereditary predisposition, long-term or even life-long anticoagulation may be necessary.[11]

Thrombolysis has been used as a treatment option for children with life- or limb-threatening VTE.[11] Since postthrombotic syndrome occurs in up to 70% of children with total venous occlusion, interventional treatment options should be considered even in non–life- or limb-threatening deep vein thrombosis (DVT).[12,13] Thus, during recent years different strategies of thrombolysis have been successfully used in pediatric patients.[14] Current CHEST recommendations suggest use of thrombolysis in acute DVT for young patients with a prospected long lifespan and low risk of bleeding but only in cases where intervention can be safely performed. All other cases should receive anticoagulant therapy.[10,15] Regarding time point of endovascular intervention, thrombolysis has been recommended within 60 days post diagnosis. However, recent findings in adults suggest that successful restoration of venous flow can be achieved even later than 60 days.[16,17]

Different strategies of endovascular intervention can be applied to restore venous flow. First, recanalization must be performed using various devices. Percutaneous transluminal angioplasty (PTA) uses a catheter that is placed through the vessel and once the catheter is in place, a balloon is inflated to further reopen the vessel. Catheter-directed thrombolysis is a pharmacological strategy administering mostly recombinant-tissue plasminogen activator (r-tPA) continuously into the affected vein distal of the thrombus. Also systemic lysis can be applied; however, bleeding risk increases relevantly up to 15% of cases.[18] Concurrent anticoagulation is necessary in both cases. Other techniques include percutaneous mechanical thrombolysis where the thrombus is removed mechanically and pharmacomechanical catheter-directed thrombolysis where after mechanical removal thrombolysis is administered locally. Percutaneous mechanical thrombolysis and pharmacomechanical catheter-directed thrombolysis seem to be the most commonly used technique in children,[19] but they also increase the risk of vessel injury.

As data on interventional strategies in children with VTE are still scarce, we aimed to investigate all cases treated with interventional strategies for VTE in our center regarding safety and efficacy. In addition, we hypothesized that even late intervention (>60 days post diagnosis) may be successful and safe. Furthermore, we also describe patients of our cohort who did not receive endovascular intervention and investigated their outcome.

Methods

Patients

Retrospective data collection of 12 consecutive pediatric cases with VTE was performed by a clinician regularly examining outpatients at our department of hemostaseology.

Study inclusion criteria were as follows[1]: diagnosis of VTE; objectively confirmed by compression duplex ultrasound, magnet resonance angiography (MRA), or computed tomography (CT) angiography[2]; time of diagnosis from February 2017 to October 2020[3]; age less than 18 years at diagnosis[4]; follow-up examination via compression duplex ultrasound or MRA.

Indication for Intervention

Initial treatment of all patients was unfractionated heparin (for ~24 hours) followed by therapeutic dosage of low-molecular-weight heparin (LMWH). Regular follow-up examinations were performed on the ward (daily) and in

the outpatient department (at least every 4 weeks). Indication for a secondary intervention included (a) continued clinical signs of veno-occlusion (swelling, pain, discoloration, massive collateralization) and (b) MRA and compression duplex ultrasound with persistent complete occlusion. If residual flow was seen in imaging, a short follow-up examination was performed to evaluate reperfusion progress. A consensus statement was achieved involving the section of pediatric hemostaseology, the center for vascular diseases, and the pediatric cardiac interventionalists.

The intervention was performed by the pediatric cardiac interventionalists or members of the center for vascular diseases using PTA and/or catheter-directed thrombolysis. Stents were placed in case of residual thrombus or stenosis.

Data Collection

The retrospective systematic collection of clinically derived data included patient demographics, time of symptoms onset, thrombus location, clinical findings at presentation, risk factors for VTE, the presence of May–Thurner anomaly, interventions performed, postinterventional outcome, and follow-up results.

Risk Factors for Thrombophilia

- Presence of factor V-Leiden mutation (homo-/heterozygous).
- Presence of factor II mutation (homo-/heterozygous).
- Protein C, protein S, antithrombin deficiency. Genetic testing was performed to differentiate between hereditary and acquired reduction.
- Hypodysfibrinogenemia.
- Antiphospholipid antibodies and antinuclear antibodies, respectively, which persisted more than 3 months from onset of symptoms.

Radiologic Imaging

Most patients received MRA and duplex ultrasound as initial investigation and as follow-up, whereas some patients received only duplex ultrasound as follow-up due to optimal visualization.

In case of persistent clinical symptoms after intervention, a reintervention was scheduled that included fluoroscopy to establish the extent of chronic thrombus burden or residual stenosis.

Statistical Methods

Descriptive statistics were used to characterize continuous data and frequencies of categorical data.

Results

A total of 12 patients met the inclusion criteria. Six of 12 (50%) patients underwent endovascular intervention, whereas 6 of 12 (50%) patients were treated with anticoagulation alone.

Study population demographics, baseline patient characteristics, thrombus characteristics, and VTE risk factors are shown in ►Table 1.

Median age was 14 years (11–17.1 years). Ten of 12 (83%) patients suffered from pelvic vein thrombosis, and 2 of 12 (7%) patients had thrombotic closure of the inferior vena cava (IVC). May–Thurner anomaly was diagnosed in 2 of 12 (17%) of cases.

Interventional therapy was performed in 6 patients because of (a) clinical signs of claudication (3/12; 25%), (b) continuous extensive thrombosis (2/12; 17%), or (c) impaired prehepatic flow (1/12; 8%). If the patient did not show any clinical signs of claudication and patent collateralization was already shown or if thrombus resolved under therapeutic anticoagulation, intervention was not performed.

No IVC filters were used in this cohort.

Time from diagnosis to intervention was 4 (1–12 months) months. Five of 12 (42%) patients received stenting during intervention. Applied techniques included PTA only in 5 of 12 (42%) cases and PTA plus catheter-directed thrombolysis in 2 of 12 (17%) cases. Techniques, outcomes, and anticoagulant regime are shown in ►Table 2. ►Fig. 1 shows patient number 10 with an IVC thrombosis and successful recanalization.

Safety and Efficacy

There were no periprocedural major bleeding complications during or after intervention. One patient suffered from minor puncture site bleeding post intervention. No pulmonary embolism occurred.

Full technical success was achieved in five if six (83%) cases within the first procedure. In one case, recanalization was only partially possible (until lumbosacral transition zone) and in one case recanalization failed at the first intervention and needed to be repeated in a second procedure (►Fig. 2). In one case, redilatation was necessary after 7 months due to in-stent stenosis. Otherwise, there was no acute local recurrence and no late recurrence.

Outcome

All patients reported clinical improvement after the procedure and MRA or ultrasound follow-up exams showed sustained flow at intervention site. Four of six (67%) patients did not show any signs of postinterventional residual thrombosis or in-stent thrombosis, and three (50%) demonstrated a smaller caliber of the affected vessel or minimal residual thrombosis.

In patients not receiving intervention, follow-up showed either partial or complete reperfusion or patent (sufficient) collateralization and no signs of postthrombotic syndrome.

Clinical follow-up showed mild differences in lower limb circumference in 2 of 12 (17%) patients (one in intervention and one in nonintervention group) and one patient had mild abdominal caput medusa in nonintervention group. Nine of the 12 (75%) patients do not have any clinical symptoms of DVT or postthrombotic syndrome. Mean follow-up time was 26 months.

Risk Factors

With regard to the question whether patients with thrombophilic risk factors are more likely to suffer from symptomatic closure and therefore undergo intervention after initial

Table 1 Demographic and clinical characteristics of patients

Case no.	Age (y)	Gender	VTE site(s)	PE	Time from symptom to diagnosis	Intervention	Time from diagnosis to intervention	Clinical triggers	Thrombophilia findings	Vascular findings	Other diagnosis
1	16	F	L, iliac, femoral		3 d	Yes	9 mo	Estrogen, nicotine, obesity, bruise of toe	FV het	May–Thurner	
2	13	F	L, iliac, femoral		3 d	Yes	4 mo	Flue	FV het, APLAs, (temporary)		
3	16	F	R, iliac		3 d	Yes	12 mo	Estrogen, flight 6 wk before	FV het, hypodysfibrinogenemia		
6	14	F	R, iliac, femoral, popliteal		1 d	Yes	1 mo	None	FII het, ANA		
8	17	M	L, iliac, femoral		7 d	Yes	2 mo	Nicotine, flue	Protein S het (23%)		
10	12	M	IVC, left iliac		Unclear, no acute onset	Yes	4 mo	CVL in the past	None performed		
4	13	F	R, iliac	Yes	Weeks–1 mo	None		None	APLAs (temporary)		
5	17	F	L, iliac	Yes	Several days	None		Estrogen	FV het, ANA (temporary)	May–Thurner	
7	14	F	R, iliac, femoral		Several days	None		Estrogen, flue	FV het, protein C het		
9	11	M	IVC, left fem		1 d	None		Obesity	AT III deficiency		VKA resistance
11	16	M	L, iliac, femoral	Yes	2 wk	None		None	APLAs		APS
12	14	F	L, iliac, femoral, popliteal		1 wk	None		Estrogen, obesity	FV het		Trisomy 21

Abbreviations: ANA, antinuclear antibodies; APLA, antiphospholipid antibodies; APS, Antiphospholipid-Antibody-syndrome; CVL, central venous line; F, female; IVC, inferior vena cava; M, male; PE, pulmonary embolism; VKA, vitamin K antagonist.

Table 2 Endovascular intervention, strategies applied, outcome

Case no.	Procedure	Stent	Anticoagulant post intervention	Anticoagulant regimen	Duration	Imaging outcome	Clinical outcome	Follow-up time
1	PTA, conventional catheter	None	LMWH	LMWH	3 mo	V. iliaca comm. weak caliber, but continuous contrasting	No PTS	26 mo
2	1: PTA, radiofrequency catheter 2. PTA (cutting balloon)	Yes	LMWH 1 y	VKA	3 y in total	Good reperfusion, no stent thrombosis	Clear improvement after stenting	46 mo
3	1: PTA, conventional catheter 2: PTA, redilatation	Yes	LMWH 16 mo	DOAC	Continued	Thrombi receding, patent flow	No PTS	41 mo
6	PTA, conventional catheter (cutting balloon), CDT	Yes	LMWH	VKA	Continued	No postthrombosis residuals	No PTS	18 mo
8	PTA, conventional catheter	Yes	LMWH 4 mo	DOAC/ASS	Continued	Nearly complete recanalization	Minimal difference in circumference	10 mo
10	PTA, conventional catheter (cutting balloon)	Yes	UFH 48 h	ASS/Clopidogrel	12 mo	No stenosis	No PTS	24 mo
4	n/a	None	LMWH	LMWH	14 mo	Partial recanalization, collaterals	No PTS	27 mo
5	n/a	None	LMWH bis 06/20	DOAC	Continued	Patent reperfusion	No PTS	16 mo
7	n/a	None	LMWH	LMWH, DOAC	Continued	Chronic closure	No PTS	24 mo
9	n/a	None	LMWH short	VKA	Continued	Weak caliber, but continuous contrasting	Abdominal veins	21 mo
11	n/a	None	LMWH	LMWH	Continued	Chronic closure of L iliac	No PTS	2 mo
12	n/a	None	LMWH	LMWH	Continued	Residual thrombosis	Minimal difference in circumference	8 mo

Abbreviations: CDT, catheter-directed thrombolysis; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PTA, percutaneous transluminal angioplasty; PTS, post-thrombotic syndrome; UFH, unfractionated heparin; VKA, vitamin K antagonist.

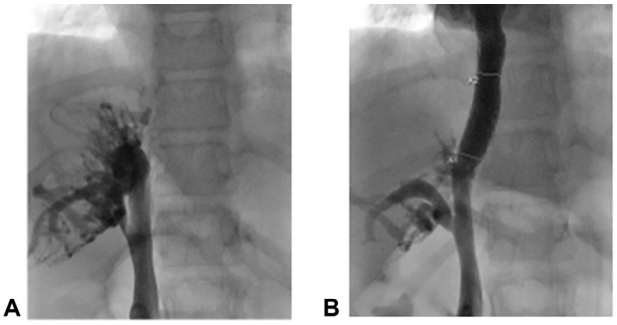

Fig. 1 Patient 10; inferior vena cava thrombosis before (**A**) and after percutaneous transluminal angioplasty (**B**).

anticoagulation, we analyzed the amount of thrombophilic risk factors (antiphospholipid antibodies, antinuclear antibodies, protein C deficiency, protein S deficiency, hetero/homozygous factor V-Leiden mutation, and factor II mutation) as well as positive family history and other risk factors for thrombosis (hormonal contraceptives, nicotine abuse, obesity, infection, immobilization). The average thrombophilic risk factors of patients receiving intervention was 1.16 versus 1 within the group not receiving intervention (►**Table 3**). Due to its mild thrombophilic effect, we also calculated the differences without heterozygous factor V-Leiden mutation (average: 0.71 vs. 0.5). The other risk factors like hormonal contraceptives, etc., did not differ substantially as well (average: 1.66 vs. 1). Due to low patient number, significance levels cannot be given, but the difference between predisposing risk factors in our cohort did not seem to influence the need for intervention.

Discussion

As the number of children with chronic diseases increases and because the rate of postthrombotic syndrome in adults can reach as high as 60%, treatment options beyond anticoagulation in case of persistent VTE may need to be applied also in children.[12,20] Postthrombotic syndrome is not only a

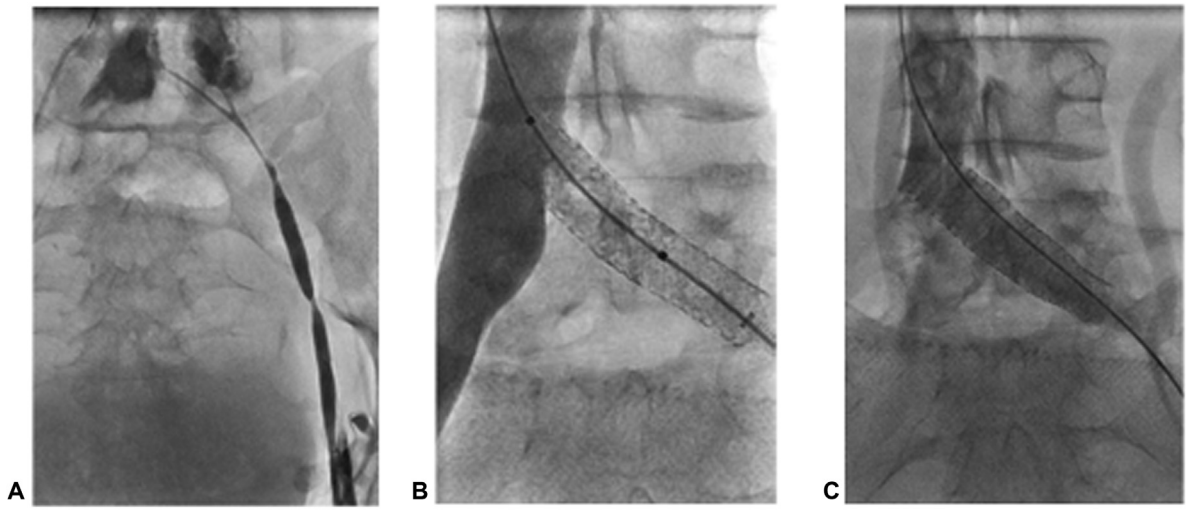

Fig. 2 Patient 2; thrombosis of left iliac and femoral vein before (**A**); while recanalization, percutaneous transluminal angioplasty, and stenting (**B**); and after stenting (**C**).

Table 3 Thrombophilia in patients with intervention and without intervention

Intervention	Pat. no.	Thrombophilia	Risk factors[a]	Family history	Intervention	Pat. no.	Thrombophilia	Risk factors[a]	Family history
Yes	1	FV het	4	/	No	4	–	/	/
	2	FV het	1	+		5	FV het	1	+
	3	FV het, hypodys-fibrinogenemia	2	+		7	FV het, protein C het	2	+
	6	FII het, ANA	/	/		9	AT III	1	/
	8	prot-S het	2	–		11	APLAs	/	/
	10	–	1	/		12	FV het	2	–
		Average: 1,16	Average: 1,66				Average: 1	Average: 1	

Abbreviations: ANA, antinuclear antibodies; APLAs, antiphospholipid antibodies.
[a]Hormonal contraceptives, nicotine abuse, obesity, infection, immobilization.
/: No data available.

cosmetic or comfort problem, but it imposes a high risk of reduced quality of life.[21]

In recent years, few publications showed that thrombolysis can be safely administered in children with total venoocclusive thrombosis to lower rates of postthrombotic syndrome.[12,13,22–25] If residual thrombus mass exists, angioplasty and stenting can be used to reopen stenosis of veins.

Additionally, some studies used placement of an IVC filter (retrievable and nonretrievable). However, there are reports of accumulation of organized thrombus at the site of the IVC filter in nonretrievable IVC filters.[13] Therefore, in 2020 a review by Kelkar et al emphasized on the importance of an evidence-based approach to IVC filters in adults, focusing its use mainly on patients with contraindication for anticoagulation.[26]

In 2018, the American Society of Hematology (ASH) published a guideline for the management of pediatric thrombosis. The authors emphasized that there is a wide variety of approaches on pediatric thrombosis and use of endovascular procedures, depending on local expertise. Therefore, the ASH recommendations 3 and 6 generally suggest against thrombolysis and thrombectomy followed by anticoagulation and support anticoagulation alone; however, they add the remark that in some patients thrombolysis or thrombectomy might be appropriate.[27] Other guidelines suggest endovascular procedures in children with DVT only in life- or limb-threatening cases, or recommend thrombolytic options in cases in which "the benefits may outweigh the risks."[10,28] Altogether, those recommendations stress the point that in certain cases, treatment options beyond anticoagulation are needed.

Bleeding is the most serious risk in patients undergoing endovascular thrombolysis. Major bleeding occurs in around 5.7% of children.[27] In our case series, peri- or postprocedural complications were rare (one case of bleeding from puncture site). No major bleeding occurred.

A small meta-analysis of endovascular intervention in pediatric DVT reported similar safety rates in children, with two pulmonary embolisms among a total of 215 patients and two major hemorrhages.[14]

Locally recurrent DVT did not appear in our cohort, and redilatation was necessary in only two cases. All patients reported markedly improved clinical phenotype postprocedure.

The low rate of recurrence might be explained by the fact that the patients did not show any signs of a hypercoagulability state during the time of the procedure. Other studies reported recurrence rates of 27 and 12%.[13,23] It can be hypothesized that late intervention leads to lower rates of recurrence as endothelial activation has reduced during the time from onset of thrombosis to intervention under anticoagulation therapy.

The low rate of postthrombotic syndrome in our intervention cohort (i.e., one patient with minimal difference in circumference) might be explained by the small cohort number, but it is in line with other findings of postthrombotic syndrome in 13% of patients at 1 and 2 years of follow-up[13] and 14% in the cohort described by Dandoy et al.[22]

There have been adult trials trying to improve outcome of percutaneous mechanical thrombolysis by adding systemic thrombolysis. These data showed that the rate of complete patency is significantly increased, and risk of postthrombotic syndrome is decreased. However, the rate of major bleeding also increased (nonsignificant).[29] Thus, Enden et al suggested that additional catheter-directed thrombolysis should be applied in patients with proximal DVT and low risk of bleeding.[30] So far, studies questioning systemic thrombolysis in combination with percutaneous mechanical thrombolysis have not been published in children, as risk of bleeding might be significantly increased.

This case series adds to the current knowledge, as it shows that even if not immediately applied, percutaneous mechanical thrombolysis can improve outcome regarding postthrombotic syndrome. Our small case series shows that even in chronic VTE, interventional procedures can improve outcome.

The patients of this cohort, not receiving intervention, showed either partial or complete reperfusion or had developed patent collateralization and none of the patients developed postthrombotic syndrome. Therefore, anticoagulation alone is still a treatment option if clinical symptoms do clearly improve within the first months of anticoagulant treatment.

Limitations to this study are its retrospective design and small sample size. This might cause underreporting of postthrombotic syndrome. However, the mean follow-up time of 26 months is comparably high and all patients are still regularly visiting our department and are screened for clinical symptoms.

In summary, our data show that in case of secondary endovascular intervention, applied in pediatric patients with persistent clinical signs of venous occlusion, improvement can be achieved, even if intervention is performed months after diagnosis and initial anticoagulation treatment.

Conflict of Interest

B.Z. reports grants from Takeda, CSL Behring, Biotest to the University Medical Center Freiburg.

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B.S. reports participation on a Data Safety Monitoring Board or Advisory Board from Studie CV185–362, Apixaban for Bristol-Myers Squibb GmbH & Co. KGaA Arnulfstraße 29, and D-80636 München.

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