ORIGINAL ARTICLE

Observation of short-term catheter induced thrombosis in children treated with blood purification

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Abstract

Background: No studies have assessed the safety of short-term catheter-induced thrombosis in children treated with blood purification. The aim of this study was to determine the incidence and evolution of thrombosis in the children.

Methods: One hundred nineteen **(**119) children treated with blood purification were enrolled. The data of baseline characteristics, coagulation status and type of catheters were recorded. Thrombosis- related symptoms and signs, ultrasound examinations of the right femoral veins were followed for 2 months. The relationship between associated risk factors (age, sex and type of catheters) and thrombosis was analyzed.

Results: Of the 119 patients, 95 (79.8%) developed deep venous thrombosis (DVT) in the right external iliac veins. In only one patient it was clinically obvious. The incidence of thrombosis had no significant difference between the following subgroups: 1. Children under 6 years (14/15, 93.3%), 6-12 years (63/78, 80.7%) and above 12 years (18/26, 69.2%) (p=0.436); 2. Male (57/66, 86.3%) and female patients (38/53, 71.6%) (p=0.448); 3. Children catheterized with 8F (52/63, 82.5%) and 11F catheters (43/56, 76.7%) (p=0.435). Thrombolysis was achieved in 77 cases (77/80, 96.3%) with treatment of oral dipyridamole at one month and 80 cases (100%) at two months.

Conclusion: Children treated with blood purification through short-term femoral venous catheters have an increased risk of developing DVT, which is usually asymptomatic and good in prognosis. Hippokratia 2014; 18 (3): 245-250.

Keywords: Deep venous thrombosis, femoral venous catheters, blood purification, hemoperfusion, children

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Introduction

Blood purification is used to remove waste, excess water, toxicants and inflammatory factors from the blood of the patients through an external artificial circuit. It includes hemodialysis (HD), hemofiltration (HF), hemoperfusion (HP), plasma exchange (PE), continuous renal replace- ment therapy (CRRT) and some combined types[1]. HP has been used for the treatment of drug/toxicants poisoning and uremia for decades. With the advances in technology, it is gradually used in hepatic encephalopathy, schizophrenia and some immune diseases[1]. In HP, liposoluble or protein- combining molecules are absorbed by the resin cartridge.

Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis of childhood presenting with a tetrad of purpura, arthritis or arthralgia, abdominal pain and renal disease. It is characterized by the deposition of immunoglobulin A (IgA)-containing immune complexes in the walls of small vessels[2]. In children with HSP who developed rapid progressive glomerulonephritis (RPGN) or other severe complications, plasma exchange (PE) is recommended[3]. However, PE requires a large amount of fresh frozen plasma and brings the risks associated with infusion of donor plasma. Thus, PE is replaced by HP in some cases of severe HSP in our hospital and satisfactory effects are achieved[4]. In severe cases, a high level of inflammatory mediators is active in the blood and usually the kidney is damaged even before Henoch-Schönlein purpura nephritis (HSPN) manifests. HP can decrease the serum level of immune mediators, reduce the disease severity, shorten the duration of acute abdominal and/or joint pain, and protect the kidney in the early stages[4].

However, there are some complications from blood purification, such as infection and thrombosis that may be caused by the catheter insertion and retention[5]. Little is known about the thrombosis in children treated with blood purification. Therefore, this study was conducted to show the incidence and evolution of short-term catheter induced deep venous thrombosis (DVT) in children treated with blood purification. In this study, 119 children were followed at one-month intervals by clinical observations, laboratory tests and ultrasound examinations.

Patients and Methods

Patients

Between September 2011 and March 2012, 656 children with HSP were admitted in our hospital. In the 656 children, 119 cases (18.14%) were severe and treated

with hemoperfusions at the Children Blood Purification Center. The diagnosis of HSP was in accordance with the guideline of the American College of Rheumatology (ACR)[6]. The definition of severe HSP were those who fulfilled ≥1 items of the following criteria: 1. Severe abdominal pain and/or gastrointestinal hemorrhage (occult blood test positive or hematochezia); 2. severe joint pain and swelling (or limitation of motion); 3. HSPN defined as hematuria on microscopic urinalysis ≥ 3 red blood cells per high power field, or proteinuria ≥ 1+ with a dipstick test); 4. waving and lingering disease condition, or frequent relapses, or poor response to the conventional drug therapy (corticosteroids and supportive treatment). Exclusion criteria included: existence of other disorders; previous thrombosis; tendency of bleeding or clotting; infection at the site of catheter insertion; and abnormal blood platelet count or blood coagulation test.

Approval for the study was obtained from the Clinical Research Ethics Committee of West China Second University Hospital of Sichuan University. Informed consents were obtained from parents or guardians of the children.

Methods

Each child had 3 daily sessions of HP (2 hours per session) by B.Braun machine (B.Braun Melsungen AG, Germany) with a blood flow rate at 50-150 ml/min.

Catheter types included Pediatric 8F (diameter 2.7mm, length 12.5cm) and 11F (diameter 3.6 mm, length 12.5cm) double-lumen catheters (Gambro Corp., Lund, Sweden). The type was chosen according to the patient's body weight: 8F in children less than 25kg and 11F in those over 25kg. All 119 catheters were inserted through the right femoral vein using the Seldinger technique and were in place for 3 days. Ultrasound examination of the deep venous systems of the lower limbs was performed before catheter removal and at every month after the procedure to observe the evolution of the thrombi. Diagnosis of DVT was made by ultrasound examination of the deep venous systems using the Acuson X300 machine (Siemens AG Corp., Munich, Germany). DVT was diagnosed when the thrombus was visible; the vein cannot be compressed; no spontaneous Doppler flow; no phasicity and augmentation; and Doppler and color spectral flow void[7]. Dipyridamole (2mg/kg/d) was given to the patients with thrombosis orally until the thrombolysis was confirmed by ultrasound examination.

Demographic data, baseline coagulation status, and type of catheters used during the hemoperfusion were recorded. After blood purification, thrombosis-related symptoms and signs were observed. Incidence of thrombosis and sizes of the thrombi were determined by ultrasonagraphy at one-month intervals. The relationship between associated risk factors (age, sex and the type of catheters) and thrombosis was analyzed. Data analysis was performed using SPSS 17.0 software (IBM Corporation, New York, USA). Between-group comparisons of continuous variables and rates were conducted using the Students't-test, One-way ANOVA and Chi-square test when appropriate. A p value of <0.05 was considered significant.

Results

Demographics

In total 119 children with severe HSP were included in the study (Table 1). The 119 children (69 males, 50 females) were at a mean age of 9.0 years (range 3.4-17.0 years). Forty five (45) children were presented with severe abdominal pain and/or gastrointestinal hemorrhage; 37 had HSPN; 22 both severe abdominal pain and HSPN; 7 frequent relapses; 8 both HSPN and frequent relapses. No patient developed acute renal failure. Before blood

Table 1: Clinical and laboratory features at baseline of the 119 children enrolled in this study.

	Thrombosis positive (n=95)	Thrombosis negative (n=24)
Age, years		
Median	8.9	10.0
Range	3.4-16.2	4.3-17.0
Male (%)	58 (61.1)	11 (45.9)
Weight (kg)	30.0 (11.1)	31.4 (13.4)
Coagulation status		
PLT ($x10^9$/L)	312 (103)	269(92)
PT (sec)	11.3 (0.9)	11.1(0.9)
APTT (sec)	26.7 (4.0)	27.6(5.3)
Fg (mg/dl)	297 (77)	284(89)
TT (sec)	16.9 (1.0)	16.7(0.8)
Catheter size, No. (%)		
8 F	52 (54.7)	11 (45.8)
11 F	43 (45.3)	13 (54.2)

Data were expressed as mean (standard deviation) unless otherwise indicated. PLT: platelet count, PT: prothrombin time, APTT: activated partial thromboplastin time, Fg: fibrinogen, TT: thrombin time.

purification all patients were normal on blood platelet counts and coagulation tests.

Incidence and characteristics of the thrombi

Before catheter removal, ultrasound examination of the lower limbs of the children was performed. Of the 119 patients, 95 (79.8%) had mural thrombosis in the right external iliac vein, yet only one patient had acute thrombosis-related symptoms or signs (swelling of the right lower limb and right greater lip of pudendum, without pain or redness).

The sizes of the thrombi of the 95 patients are analyzed in Table 2. The largest thrombus (1.84cm^3, 4.60cm×0.70cm×0.57cm) occurred in a 7-year-old boy. The smallest thrombus (0.01cm^3, 0.30cm×0.20cm× 0.20cm) occurred in an 8-year-old boy. The longest thrombus (4.90cm), seen in a 10-year-old girl, was not the thickest with a cross sectional area of 0.10 cm^2 (0.40 cm × 0.25 cm). The thickest thrombus (0.42 cm^2, 0.70 cm × 0.60 cm) was observed in a 5-year-old boy. The average size of the thrombi in 95 patients was 0.37 ± 0.35 cm^3 (Table 3).

Table 2: Sizes of thrombi in the right external iliac veins detected by ultrasound examination in 95 children with short-term catheterization for hemoperfusion.

	Mean (SD)	Maximum	Minimum
Length (cm)	2.33 (1.22)	4.90	0.30
Width (cm)	0.43 (0.16)	0.88	0.18
Height (cm)	0.34 (0.15)	0.96	0.16

SD: standard deviation.

The only symptomatic patient, a 14-year-old girl with HSPN, had swelling of the right lower limb and right greater lip of pudendum. A mural thrombus of 0.06 cm^3 (1.50 cm × 0.20 cm × 0.20 cm) in the right external iliac vein was detected. A single dose of urokinase (100,000 IU) was injected and heparin sodium (1,875 IU) was given intravenously twice a day for 8 days. The swelling disappeared and thrombolysis was confirmed by the ultrasound examination.

Risk factors of thrombosis

The relationship between age, sex, type of catheters and thrombosis is summarized in Table 4. The incidence of thrombosis had no significant difference between the following subgroups: 1. children under 6 years (14/15, 93.3%), 6-12 years (63/78, 80.7%) and above 12 years (18/26, 69.2%) (χ^2=1.660, p= 0.436); 2. male (57/66, 86.3%) and female patients (38/53, 71.6%) (χ^2 =3.927, p=0.448); 3. children inserted with 8F catheters (52/63, 82.5%) and those with 11F catheters (43/56, 76.7%) (χ^2=0.610, p=0.435).

There was no significant difference in the size of thrombi between: 1. children under 6 years, 6-12 years and above 12 years (F=0.633, P= 0.533); 2. males and female patients (t=0.172, p=0.864); 3. children who received 8F and those who received 11F catheters (t=0.989, p= 0.325).

Table 3: Characteristics of children with the largest and smallest five thrombi in the right external iliac veins after short-term catheterization for hemoperfusion.

	Size of thrombi, cm^3 (cm×cm×cm)	Age (years)	Sex (M/F)	Weight (Kg)	Catheter size
Largest DVT					
1st	1.84 (4.60×0.70×0.57)	7.8	M	23.0	8F
2nd	1.36 (4.20×0.66×0.49)	13.3	F	29.0	8F
3rd	1.28 (3.76×0.85×0.40)	5.7	M	18.0	8F
4th	1.22 (2.90×0.70×0.60)	7.6	F	19.0	8F
5th	0.93 (4.84×0.55×0.35)	16.1	M	50.0	11F
Smallest DVT					
1st	0.01 (0.30×0.20×0.20)	8.1	M	24.0	8F
2nd	0.06 (2.10×0.18×0.16)	9.0	F	30.0	11F
3rd	0.06 (1.50×0.20×0.20)	14.0	F	45.0	11F
4th	0.07 (1.20×0.30×0.20)	7.7	M	21.0	8F
5th	0.09 (1.50×0.30×0.19)	6.2	M	31.5	11F

DVT: deep venous thrombosis, M: male, F: female.

Table 4: Characteristics of thrombosis after short-term catheterization for hemoperfusion in different subgroups of children stratified by age, sex and catheter size.

	Incidence of DVT n(%)	Length (cm)	Width (cm)	Height (cm)	Size (cm^3)
Age,years					
<6	14(93.3)	2.82(1.19)	0.36(0.108)	0.27(0.241)	0.31(0.28)
6-12	63(80.7)	2.19(1.22)	0.41(0.158)	0.24(0.206)	0.21(0.28)
>12	18(69.2)	2.47(1.21)	0.45(0.176)	0.20(0.184)	0.28(0.47)
Sex					
Male	57(86.3)	2.37(1.29)	0.43(0.163)	0.23(0.210)	0.23(0.33)
Female	38(71.6)	2.15(1.10)	0.39(0.148)	0.23(0.195)	0.22(0.30)
Catheter size					
8F	52(82.5)	2.15(1.17)	0.41(0.15)	0.23(0.17)	0.26(0.37)
11F	43(76.7)	2.43(1.27)	0.42(0.16)	0.23(0.23)	0.20(0.25)

Data were expressed as mean(standard deviation) unless otherwise indicated,n: number of children, DVT: deep venous thrombosis.

Table 5: Evolution of the thrombi and coagulation status in two months after catheter removal in 95 children who received short-term catheterization for hemoperfusion.

	Before catheter removal	1 month later	2 months later	p value
No of cases	119	95	3	
Loss of cases	0	15	0	
Cases examined	119	80	3	
Coagulation status				
PLT ($x10^9$/L)	282 (99)	258 (92)	260 (85)	0.12
PT (sec)	11.0 (0.7)	10.3 (0.8)	10.8 (0.9)	0.08
APTT (sec)	26.4 (4.1)	26.2 (3.8)	26.0 (4.3)	0.22
Fg (mg/dL)	295 (69)	241 (62)	260 (72)	0.57
TT (sec)	16.7 (1.0)	17.1 (1.3)	16.8 (0.8)	0.14
Cases of thrombosis, n (%)	95 (79.8)	3 (3.7)	0	
Cases of thrombolysis, n(%)	-	77 (96.3)	3 (100%)	

Data were expressed as mean (standard deviation) unless otherwise indicated. PLT: platelet count, PT: prothrombin time, APTT: activated partial thromboplastin time, Fg: fibrinogen, TT: thrombin time.

Evolution of the thrombi

After catheter removal, no clinically detectable embolus detachment or organ embolism was observed in the 95 patients with thrombosis. The 95 patients were given oral dipyridamole (2 mg/kg/d) and followed up at one-month intervals to monitor the evolution of the thrombi. Of the 95 cases, 15 were lost at the first month of follow-up because they did not come back to the outpatient department after discharge. Among the 80 patients available, 77 (96.3%) achieved thrombolysis at the first month. The remaining 3 cases had thrombi organization and were continuing in the treatment of dipyridamole. Thrombolysis of them was achieved at the second month under ultrasound examination. The typical process of thrombus evolution in an 8-year-old boy is displayed in Figure 1.

Patients' coagulation tests right before catheter re-

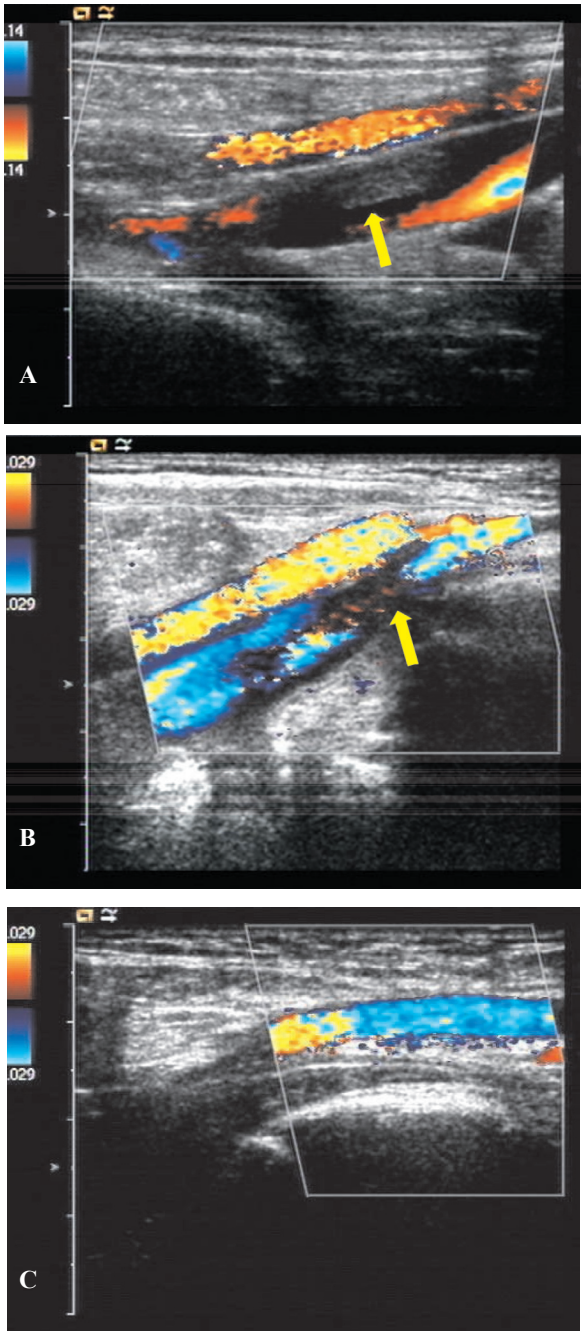

Figure 1: Series of ultrasound scans of catheter-related thrombus in the right external iliac vein in an 8-year-old boy with Henoch-Schönlein purpura who received three daily sessions of hemoperfusion. **(A)** before catheter removal: thombus size 2.5 cm × 0.47 cm × 0.4 cm; **(B)** after one month of oral dipyridamole (2 mg/kg/d): thombus size 1.5 cm × 0.5 cm × 0.5 cm; **(C)** after two months of oral dipyridamole (2 mg/kg/d): no thombus was visible. The yellow arrows show the sites of thrombi.

moval, at the first month and second month of follow-up were all normal and had no significant difference with those detected before HP (Table 5). No thrombosis-associated adverse events were observed at follow-up.

Discussion

To our knowledge, no published studies exist with regard to the safety of short-term catheter induced thrombosis in children treated with blood purification. This study prospectively examined the incidence and evolution of thrombosis in 119 children who were followed up at one-month intervals after blood purification with ultrasound examinations. Of the 119 patients, 95 (79.8%) had mural thrombosis, which was more than our expectation and some previous reports.

Previous research in adults[7] documented an incidence rate of 11.2% (14/124) of DVT developed among the intensive care unit (ICU) patients undergoing femoral vein catheterization, which is lower than the incidence of DVT in children treated with blood purification in our study. We speculate that the incidence of DVT may be different between adult and pediatric patients.

In a study involving 287 children with cancer who needed central venous catheters (CVC) for fluid administration, 21 (7%) had catheter- related DVT[8]. In their report, imaging study of the deep venous system was only performed in children with arm swelling or catheter occlusion. Thus we speculate that many thrombotic events in the patients may have gone unrecognized for the lack of symptoms.

Male et al, reported the incidence and risk factors of CVL (central venous line) -related venous thrombosis in 158 children with catheters of different location, duration and types[9]. They reported that the incidence of DVT was 32% in children with femoral catheters, and catheter type or duration was not associated with the incidence of DVT. In our study, the incidence of DVT in children with femoral catheters was 79.8%. One of the possible explanations for the difference may be the usage of catheters: the CVLs were used for fluids infusion in their work while in our study the femoral catheters were used for blood purification.

Some risk factors of developing DVT were analyzed including age, sex, and the type of catheters. Surprisingly, it was found that none of the risk factors above affected the incidence of thrombosis or the sizes of the thrombi. It partially agrees with what Male et al[9], reported earlier that catheter location, not catheter type or duration, was related to the incidence of DVT.

In our study, DVT was detected in 79.8% of the patients, yet only one patient was clinically obvious. Similar asymptomatic characteristic of the DVT was also found in adult patients[10]. The asymptomatic feature may lead to a false sense of security so physicians need to be very cautious and continuous follow-up for the evolution of the thrombi is necessary.

Of the 95 children with thrombosis, 80 were traceable at follow-up. 77 (96.3%) of the 80 patients achieved thrombolysis at the first month of follow-up with treatment of oral dipyridamole. No symptoms or signs of embolus detachment and organ embolism occurred during observation. The results suggest that short-term femoral venous catheter-related DVT in children treated with

blood purification had good prognosis. However, further outcomes still need to be monitored in our future studies, like post-thrombotic syndrome (PTS), a syndrome of chronic venous insufficiency which often develops following DVT and presents with limitation in physical activities. Up to 70% of children with DVT are reported to be affected by PTS[11].

In conclusion, children treated with blood purification through short-term femoral venous catheters have an increased risk of developing DVT, which is usually asymptomatic and has good prognosis.

Conflict of Interest

The authors declare that they have no conflict of interests.

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