Thromboembolic Complications in Thai Pediatric Patients

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Abstract

Sixty patients with thromboembolic complications from 1987 to 1997 at the Department of Pediatrics, Ramathibodi Hospital were retrospectively studied. Twenty patients were infants and 40 patients were children and adolescents with a mean age of 18 days and 8 years, respectively. The sites of thromboembolic complications were in the central nervous system, 27.5 per cent; skin as purpura fulminans or necrotic lesions, 24.5 per cent; gangrene of the toe, finger or colon, 19 per cent; deep vein thrombosis, 16 per cent; and other sites such as heart and lungs, 13 per cent. Most of them had triggering conditions (80%) and underlying diseases (76.7%) causing thromboembolism. The low levels of either antithrombin III, protein C or protein S were found in 42 per cent (15/36). The management included administration of standard or low molecular weight heparin if not contraindicated, replacement of fresh frozen plasma 10 ml/kg twice a day and treatment of underlying and triggering conditions. The fatality rate was 15 per cent (9/60). Subsequent episodes of thromboembolism occurred in 6 patients including : pulmonary emboli in one patient with protein C deficiency who refused warfarin administration, deep vein thrombosis in 2 patients with unidentified etiology, and necrotic skin lesions in 3 patients with vasculitis who did not respond to treatment.

In conclusion, a comprehensive investigation and specific treatment for patients with thromboembolic complications are emphasized in order to prevent recurring episodes.

Key word : Thromboembolism, DIC

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Thromboembolism is not commonly found among Thai populations compared to Caucasian populations. Postoperative or postpartum deep vein thrombosis which was accurately demonstrated by ^{125}I fibrinogen scan, ultrasonography and/or venography from 1975 to 1984 revealed a rather low prevalence ranging from 1.7 to 14.3 per cent[1-3]. However, the number of patients with deep vein thrombosis and pulmonary embolism reported by Visudhiphan S. markedly increased from 54 cases in the period of 1977-1986 to 338 cases in the period of 1987-1996[4]. Additionally, the first case of inherited thrombophilia from homozygous protein S deficiency was reported by Mahasandana C. from Thailand in 1989[5]. Early recognition combined with advanced technology allows the physician to determine the thromboembolic complications. Although the chance of complete recovery among the young patients is higher than the adults, they risk developing subsequent episodes of thromboembolism if the specific etiology is not identified and the appropriate treatment is not given.

We reported the thromboembolic complications in pediatric patients receiving medical treatment at the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Bangkok during the decade of 1987 to 1997.

PATIENTS AND METHOD

Sixty patients with thromboembolic complications were retrospectively studied. The diagnosis of thromboembolism was based on physical examination and/or demonstration of occlusive sites by doppler ultrasonography, angiography, computerized tomography or magnetic resonance imaging.

The conditions inducing thromboembolic complications were searched for and the underlying diseases were treated accordingly. Intravenous or arterial catheters causing thrombosis were removed as early as possible. Heparin was given to most of the patients except those with cerebrovascular occlusive diseases. In the period of 1987 to 1989, standard heparin was given by intravenous infusion as a bolus of 50 units/kg followed by continuous infusion of 15-25 units/kg per hour to keep the activated partial thromboplastin time (APTT) or venous clotting time 1.5 to 2 times of the control or patient's baseline. Since 1990, low molecular weight heparin (LMWH, Fraxiparine®) in a dose of 450 anti-FXa units/kg divided into two subcutaneous injections has been introduced. Warfarin was started in a few patients on day 3 to 7 of heparin administration. Granulocyte-colony stimulating factor was given to five patients with febrile neutropenia after receiving chemotherapy for acute leukemia. In addition, patients who were suspected to have low natural anticoagulant levels of either antithrombin III (AT III), protein C (PC) or protein S (PS) received 10 ml/kg of fresh frozen plasma (FFP) twice a day for 7 to 10 days.

Method

Blood samples were obtained by standard two-syringe technique with 9 volumes of blood mixed with 1 volume of buffered citrate anticoagulant. By centrifugation at 3,000 rpm for 15 minutes, plasma was separated and divided into aliquots and stored at $-70^{\circ}C$. AT III, PC and PS antigens were determined by electroimmunoassay[6] of the plasma samples in 1 per cent agarose gel containing 1 per cent rabbit polyclonal antihuman antibodies (Behring). The low limit of detection of this assay was 10 per cent, and was based on normal plasma drawn from 10 healthy adults with normal coagulograms. The normal ranges of natural anticoagulants in preterm, term infants, and children described by Andrew M. et al were referred for normal and abnormal levels[7-9]. Other hematological determinations were performed by standard methods.

Statistics

The association between the variables was calculated by using Fisher Exact Test. A p value of less than 0.05 was considered significant.

RESULT

A total of 60 patients (males 38 and females 22) were included. Twenty patients were infants and 40 patients were children and adolescents with a mean age of 18 days (range 1-45 days) and 8 years (range 1 6/12–14 years), respectively.

The sites of thromboembolic complications are shown in Table 1. The common site was in the central nervous system, occuring in either arterial or venous sites. Necrotic skin lesions or purpura fulminans were commonly associated with sepsis or septicemia with disseminated intravascular coagulation (DIC). Deep vein thrombosis was frequently found in the lower extremities. Gangrene at the distal phalanges of fingers, tips of toes or colon was the result of complete occlusion of the small blood vessels caused by DIC or vasculitis. Lastly, throm-

Table 1. Sites of thromboembolic complications.

	Number of patients
Central nervous system (27.5%)	
- venous sinus thrombosis	8
- arterial occlusion	7
- emboli	4
Skin (24.5%)	
- necrotic lesion	9
- echythma gangrenosum	5
- purpura fulminans	3
Gangrene (19%)	
- finger	8
- toe	3
- colon	2
Deep vein thrombosis (16%)	
- upper extremities	1
- lower extremities	10
Thrombosis at various sites (13%)	
- atrium or ventricle	5
- pulmonary emboli	1
- arterial thrombosis*	3

* abdominal aorta, iliac artery, anastomosis site of resection of coarctation of aorta.

Table 2. Underlying diseases in patients with thromboembolic complications.

	Number of patients
Cardiovascular diseases (20%)	
- congenital anomalies	8
- acquired condition	7
Prematurity (16%)	
- < 1,000 grams	6
- 1,000-2,000 grams	6
Hematologic diseases (16%)	
- leukemia	6
- febrile neutropenia	5
- aplastic anemia	1
Postoperation (11%)	
- gastrointestine	4
- cardiovascular	4
Inflammatory process (11%)	
- vasculitis	4
- nephrotic syndrome	4
Gastrointestinal diseases (9%)	
- congenital anomalies	4
- acquired conditions	3
Other diseases* (13%)	17

* osteosarcoma, Down's syndrome, ricket, obesity, varicose vein, Klipple Trenaunay Weber syndrome, intraventricular hemorrhage, microcephaly, birth asphyxia, respiratory distress syndrome.

bosis was found at various sites such as the heart, lung and uncommon arteries. Arterial thrombosis was demonstrated in three patients; the first case was at the abdominal aorta which was associated with umbilical artery catheterization, the second case was at the iliac artery which was associated with prolapsed umbilical cord and the third case was at the anastomosis site of the resection of coarctation of the aorta.

Triggering conditions inducing thromboembolism could be identified in 48 of the 60 patients (80%). They could be divided into three groups : endothelial injury including catheter indwelling, 17 per cent; stasis of blood 19 per cent; and alteration of coagulation factors, 64 per cent. Fulminant systemic infection inducing DIC was the predominant cause of the alteration of coagulation factors. In addition, 46 of the 60 patients (76.7%) had underlying diseases as shown in Table 2. Twenty-five patients had one underlying disease while 21 patients had more than one.

The complete blood counts revealed platelet counts ranging from 5,000 to 880,000/μl. The low platelet counts of < 100,000/μl were found in 27 patients with infection while the high platelet counts (200,000-880,000/μl) were found in 8 patients with inflammatory process. Coagulograms were performed in 48 patients revealing normal (n= 20), prolonged (n=21) and shortened (n=7) results. The low levels of either AT III, PC or PS were found in 15 out of 36 tested patients (42%) as shown in Table 3. These low levels became normalized during the follow-up period except in four patients; two had no follow-up (patient No. 12 & 13), one was diagnosed with hereditary protein C deficiency (patient No. 14) and the last was diagnosed with physiologic protein C deficiency who achieved the normal level at the age of 4 years (patient No. 15).

Iliac artery thrombosis in patient No. 7 could have developed either *in utero* or during labour. She was the second twin of an uneventful pregnancy. Cesarean section was performed because of the prolapsed umbilical cord. Her birth weight was 2,060 grams and Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. She was found to have poor right femoral pulse and pallor of the right lower extremity at birth. Angiography revealed partial occlusion of the right iliac artery. Standard

Table 3. Natural anticoagulant levels in 15 patients with thromboembolic complications.

No.	Age	Underlying diseases	Sites of thrombosis	Natural anticoagulant levels (%) AT III	PPC	PS
1	6 d	Postop. duodenojejunostomy, *Acinetobacter* septicemia, DIC	Purpura fulminans	34*	***23****	64*
2	5 d	Sepsis, DIC	Necrotic skin lesion	***25***	28	33
3	3 d	Premature 830 g, *Enterobacter cloacae* septicemia, DIC	Tip of fingers & toes	37	***18***	29
4	28 d	Sepsis, DIC	Necrotic skin lesion	***24***	32	53
5	45 d	*E. coli* septicemia, DIC	Tip of fingers & toes	57	***23***	70
6	3 y	ALL, febrile neutropenia *Pseudomonas aeruginosa* septicemia, DIC	Purpura fulminans	***56***	***38***	nd
7	At birth	Second twin, birth weight 2,060 g	Iliac artery	***15***	***13***	***12***
8	8 y	Nephrotic syndrome**	Deep veins of leg	***35***	***< 10***	100
9	7 y	Nephrotic syndrome**	Deep veins of leg	***44***	170	220
10	4 y	Polyarteritis nodosa	Distal phalanges of fingers, necrotic skin lesion	170	***23***	78
11	3 y	Dermatomyositis	Necrotic skin lesion	***68***	180	170
12	9 y	Tetralogy of Fallot, postop corrective surgery	Left ventricle	***48***	***45***	110
13	14 y	Mitral valve prolapse	Left middle cerebral a. occlusion	nd	***42***	***42.5***
14	13 y	-	Cerebral venous sinus thrombosis	104	***52***	140
15	1y,7 m	Osteopetrosis	Cerebral venous sinus thrombosis	88	***34***	56

* after exchange transfusion,
** focal segmental glomerulosclerosis,
nd = not done, ALL = acute lymphoblastic leukemia, ATIII = antithrombin III, PC = protein C, PS = protein S.
The figures in bold and italic type indicate low levels for age.

heparin was given with dramatic response within 24 hours. Her AT III level was 15 per cent, PC 13 per cent and PS 12 per cent. They were lower than those of her monozygotic twin (AT III 22%, PC 18%, PS 23%). The infant at the age of 3 years, as well as her parents, had normal levels of AT III, PC and PS.

Even though comprehensive treatment was provided, the fatality rate was 15 per cent (9/60). All were patients with fulminant septicemia complicated with DIC occuring in the first month of life (n=6), at 45 days, 6 years and 14 years. Three patients had very low birth weights of less than 1,000 grams (850, 990 and 990 grams) and two patients had low birth weights of 1,960 and 1,750 grams. Patients with more than one underlying disease and alteration of coagulation factor possessed a higher fatality rate with p values of 0.005 and 0.043, respectively. The sequelae were found in 9 patients, which included neurological deficits (n=5) from thromboembolic complications in the central nervous system and autoamputation of gangrenous distal phalanges of the fingers (n=4).

The duration of follow-up ranged from 6 months to 7 years with a mean of 2 years. Subsequent episodes of thromboembolism occurred in 6 patients including : pulmonary emboli and deep vein thrombosis in one patient with hereditary protein C deficiency who refused warfarin administration; deep vein thrombosis in 2 patients with unidentified etiology of thromboembolism; and necrotic skin lesions in 3 patients with vasculitis which did not respond to treatment.

DISCUSSION

The common factors, which induce thromboembolism, include endothelial injury, stasis of blood and alteration of coagulation factors. Low levels of either AT III, PC or PS in patients with alteration of the coagulation factors are secondary

to the underlying diseases rather than the hereditary deficiency. The most common underlying disease, which is the cause of low natural anticoagulants, is infection. The severity of thrombosis varies from local to systemic involvement, which may be as mild as necrotic skin lesions or as serious as purpura fulminans[10]. The severity depends on the hemostasis defense mechanisms of each individual. Newborn and infants are at higher risk to thrombosis because of the physiologic hypercoagulable state [11]. In this study, one-third of the reported patients were newborn babies. Most of the natural anticoagulant levels in an infant are about half of an adults and will reach adult levels (70-130%) at the age of 6 months, except protein C level which will reach adult level as late as 4 to 6 years[12]. In addition, markedly low levels of natural anticoagulants, especially AT III and PC, were found in sick newborn infants and children with DIC as described in other studies[13-17].

Intrauterine thrombosis has seldomly been reported[18-20]. In patient No. 7, iliac artery thrombosis, which was detected at birth, might have developed *in utero* or during labour. The prolapsed umbilical cord might be one of the contributing factors of the thrombosis. In patients with nephrotic syndrome, the levels of AT III, PC and PS are usually markedly decreased in the active phase of heavy proteinuria[21]. Vasculitis which is directly caused by or closely associated with immunopathogenic mechanisms, produces necrosis, thrombotic occlusion or hemorrhage in the vessel wall and leads to necrotic skin lesions as well as peripheral gangrene[22].

In this study, 8.3 per cent (1/12) of the thrombotic patients without any triggering conditions, was caused by hereditary protein C deficiency. The other gene mutations inducing thrombosis in Caucasian populations such as resistance to activated protein C[23], prothrombin G 20210 A allele[24] and methylenetetrahydrofolate reductase mutation[25] should be included in further investigations.

APTT is a sensitive test for the hypercoagulable state and is helpful when it is shortened. However, hypercoagulable state can not be ruled out in patients with normal APTT. In addition, the measurement of natural anticoagulants is emphasized in patients with thrombosis. It is useful to explain the pathogenesis and monitor treatment. Patients in the active phase of underlying diseases have low natural anticoagulant levels which will become normal after the diseases are controlled.

Intravenous dose-adjusted heparin has proved to be effective, as it limits further thrombus formation. In cerebrovascular occlusive diseases, heparin is seldom used because the patients may develop hemorrhagic infarction. However, effective treatment of cerebral venous sinus thrombosis with heparin has been reported[26]. Recently, LMWH has been shown to be an effective anticoagulant in the prophylaxis and treatment of venous thromboembolism in adults[27,28]. The bleeding complication is less than that of the standard heparin. The main advantage is that there is no need to monitor the heparin levels. Therefore, it is beneficial especially in infants where the blood samples are obtained with difficulty[29]. Replacement of natural anticoagulants with FFP is an alternative to AT III or PC concentrates, which are not available in Thailand. Although the normal levels of 70-130 per cent of AT III or PC could not be achieved by FFP infusion, the hemostatic levels of 25-40 per cent could be reached[29].

As a result, the treatment of triggering conditions and underlying diseases in combination with heparin and FFP will effectively reduce the mortality and morbidity in patients with thromboembolism. Extensive investigations and prompt medical treatment will yield favorable outcomes. Associated disorders that may be complicated with thrombosis should be searched for and treated accordingly. For patients with hereditary natural anticoagulant deficiencies, lifelong warfarin is recommended.

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ภาวะลิ่มเลือดอุดตันในหลอดเลือดทั่วไปของผู้ป่วยเด็กไทย

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รายงานภาวะลิ่มเลือดอุดตันในหลอดเลือดของผู้ป่วยเด็กจำนวน 60 รายที่ได้รับการรักษาที่ภาควิชากุมาร-เวชศาสตร์ คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี ระหว่างพ.ศ. 2530 ถึง 2540 20 รายเป็นทารกที่มีอายุเฉลี่ย 18 วัน และ 40 รายเป็นเด็กและวัยรุ่นที่มีอายุเฉลี่ย 8 ปี ตำแหน่งที่มีการอุดตันได้แก่ ระบบประสาทร้อยละ 27.5, ผิวหนังร้อยละ 24.5, gangrene ปลายนิ้วมือนิ้วเท้าและลำไส้ร้อยละ 19, deep vein thrombosis ร้อยละ 16 และตำแหน่งอื่นๆอีกร้อยละ 13 ผู้ป่วยส่วนใหญ่มีตัวไกกระตุ้นการแข็งตัวของเลือดร้อยละ 80 และร้อยละ 76 มีสาเหตุของโรคอื่นๆร่วมด้วย ได้วัดระดับสารต้านการแข็งตัวของเลือดได้แก่ antithrombin III, protein C และ protein S ในผู้ป่วย 36 รายพบว่ามีระดับต่ำ 15 ราย คิดเป็นร้อยละ 42 ได้ให้การรักษาด้วย standard หรือ low molecular weight heparin ถ้าไม่มีข้อห้ามเฉพาะ fresh frozen plasma 10 มล./กก. วันละ 2 ครั้ง ร่วมกับการรักษาโรคที่เป็นอยู่และขจัดตัวไกกระตุ้น อัตราตายร้อยละ 15 (9/60) และผู้ป่วย 6 รายเกิดภาวะลิ่มเลือดอุดตันซ้ำ ได้แก่ pulmonary embolism ในผู้ป่วยหนึ่งรายที่มีภาวะพร่อง protein C และปฏิเสธการรักษาด้วยยา warfarin, deep vein thrombosis ในผู้ป่วย 2 รายที่ไม่ทราบสาเหตุของภาวะลิ่มเลือดอุดตัน และ necrotic skin lesion ในผู้ป่วย 3 รายที่เป็นโรค vasculitis ที่ไม่ตอบสนองต่อการรักษา

ดังนั้น การสืบค้นหาสาเหตุของภาวะลิ่มเลือดอุดตัน และการรักษาที่จำเพาะจะช่วยลดโอกาสเกิดภาวะลิ่มเลือด-อุดตันซ้ำ

คำสำคัญ : ภาวะลิ่มเลือดอุดตันในหลอดเลือดทั่วไป, ผู้ป่วยเด็กไทย

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