

VASCULAR THROMBOSIS IN NEWBORN INFANTS

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The incidence of neonatal thrombosis can reach 2.4 per 1000 admissions to the neonatal intensive care unit (NICU).¹ This may be due to the widespread and prolonged use of intravascular catheters in the NICUs, and increased survival rate of very ill and extremely low birthweight infants.² The accessibility of modern imaging techniques enables early recognition and diagnosis of vascular thrombosis in newborn infants. Contrast angiography, with the use of non-ionic contrast media, is recommended as a gold-standard imaging technique for the confirmation of thrombotic vessel occlusion before starting the therapy.³ Other less invasive tests, such as Doppler flow studies, color Doppler, real-time ultrasonography, or radioisotope scans, may be helpful adjunctive diagnostic tests.³

The use of thrombolytic agents for the treatment of vascular thrombosis in newborn infants has increased. Organ or limb dysfunction as a result of thrombosis is the most important indication for active therapy.³ However, there is insufficient data regarding the choice of drugs, indications, dosage, duration of treatment and safety of these agents in newborn infants.⁴

The objective of this retrospective study was to review our experience with this problem in the NICU at King Faisal Specialist Hospital and Research Centre, and to identify contributory factors, methods of diagnosis, dosage, side effects and efficacy of therapy, in the management of neonatal vascular thrombosis.

Patients and Methods

The medical records of all newborn infants admitted to the NICU between 1986 and 1995 who developed vascular thrombosis were reviewed. No routine ultrasonography was performed, and only infants who were suspected of having thrombosis were scanned. The symptoms and signs indicating ultrasonographic examination were tissue ischemia, and unexplained hepatomegaly, hypertension and hematuria.

Only infants with vascular thrombosis confirmed by at least one imaging technique were included in the study. Data obtained included gestational age, birthweight, primary diagnosis, age of presentation, clinical manifestations, method of diagnosis, location of the thrombus risk factors, possible etiology, treatment (including the thrombolytic agent, dosage and duration), complications, and efficacy of the treatment in resolution of the thrombus.

Results

Thirteen infants were diagnosed with vascular thrombosis during the study period. Three infants were excluded because the thrombus was suspected but not confirmed by any imaging technique. The data of 10 infants were analyzed. All infants had ultrasonographic examination and only three had angiography.

Five infants had venous, and another five had arterial thrombosis. All infants who had venous thrombosis, and three of those who had arterial thrombosis, had a history of umbilical catheter insertion. Of the 10 infants studied, four had thrombosis in the abdominal aorta, one in the right renal artery, one in the portal vein, and four in the vena cava or the atria. None had simultaneous arterial and venous thrombosis. The age at presentation ranged between 1 to 30 days, and seven infants had umbilical catheters at the time of the diagnosis of thrombosis. Six infants were diagnosed to have sepsis. Two infants were diagnosed as infants of diabetic mothers (IDM), but their hematocrits did not indicate significant polycythemia. The clinical characteristics, methods of diagnosis and location of the thrombus of the infants with venous or arterial thrombosis are summarized in Table 1.

The dosages used on these infants were variable. Of the two infants, one had the thrombus in the inferior vena cava (IVC), and the other had it in the superior vena cava right atrial junction (SVC-RA), but none required treatment with a thrombolytic agent. Serial Doppler ultrasonography for these two infants showed a decrease of the thrombus size, and then a complete disappearance. Two infants with arterial thrombosis and one infant with venous thrombosis failed the thrombolytic therapy. One infant was initially diagnosed to have antithrombin III deficiency, but the repeat follow-up level was normal. One infant presented at 10 days of age, with bluish discoloration and absent pulses

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TABLE 1. Demographic data, clinical characteristics of patients and the thrombolytic agents used in this study.

Gestational age (wk)	Weight at birth (g)	Primary diagnosis	Thrombus location	Drug	Loading dose	Maintenance dose
40	3000	Birth asphyxia, sepsis	Portal vein	SK	3000 U/kg locally to thrombus (via UVC)	1500-3000 U/kg/hr
29	1320	Candida sepsis, endocarditis, DIC	Both atria	Heparin	50 U/kg	20 U/kg/hr
24	600	Candida sepsis, renal failure	Right atrium, SVC, IVC	Heparin, SK	25 U/kg 8000 U/kg	20 U/kg/hr 800 U/kg/hr
40	3470	Congenital diaphragmatic hernia	IVC	None	-	-
25	700	RDS, patent ductus arteriosus, NEC, endocarditis	SVC-RA	None	-	-
30	1500	RDS, IDM, Down syndrome, congenital heart disease (AV canal)	Right renal artery	Heparin, SK	25 U/kg 750 U/kg	10 U/kg/hr 100-1000 U/kg/hr
31	950	RDS	Abdominal aorta	Heparin, SK, rTPA	50 U/kg 500 U/kg 1 mg/kg/hr	20 U/kg/hr 250 U/kg/hr 0.1 mg/kg/hr
40	2000	Small for gestational age, birth asphyxia, NEC, renal failure	Abdominal aorta	Heparin, SK	50 U/kg 1250 U/kg	20 U/kg/hr 1000 U/kg/hr
38	3250	IDM, sepsis, protein C deficiency	Abdominal aorta	SK, rTPA	1000 U/kg -	1000 U/kg/hr 3 mg/kg q6h
40	3400	Persistent fetal circulation	Abdominal aorta	SK, UK	- 1500 U/kg (single dose)	50 U/kg/hr -

AV=atrioventricular; DIC=disseminated intravascular coagulation; IDM=infant of diabetic mother; IVC=inferior vena cava; NEC=necrotizing enterocolitis; RDS=respiratory distress syndrome; rTPA=recombinant tissue plasminogen; SK=streptokinase; SVC=superior vena cava; SVC-RA=superior vena cava at right atrial junction; UK=urokinase; UVC=umbilical vein catheter.

of the lower limbs, which subsequently developed gangrene, and was diagnosed to have protein C deficiency, but no follow-up level was obtained. Angiogram for this infant showed complete occlusion of the abdominal aorta, with distal reconstruction via collaterals (Figure 1). Only two infants had complications to the treatment, intraventricular hemorrhage and hydrocephalus, and bleeding from punctured sites (Table 1).

Discussion

The coagulation and the fibrinolytic systems of infants are different from those of adults. Normally, the plasminogen, when activated, is converted to plasmin, which lyses the fibrin clot. Newborn infants have dysfunctional and decreased concentration of plasma plasminogen and tissue plasminogen activators. They also have increased concentration of tissue plasminogen activator inhibitors.⁵ In addition, severe transient deficiencies of antithrombin III, protein C and protein S in sick newborn infants increase the risk of vascular thrombosis.^{6,7} Neonatal thrombosis is a serious event that can cause mortality or result in severe morbidity and disability.⁸

Umbilical catheterization is identified as a risk factor of vascular thrombosis in neonates. Clinically, non-apparent thrombotic lesions have been detected by angiography in 20% to 95% of newborn infants with umbilical arterial catheters, whereas severe clinically evident thromboembolic complications requiring aggressive therapeutic

intervention occurred in 41 out of 4000 newborn infants with umbilical arterial catheters.⁸ Between 20% and 61% of newborn infants who had umbilical vein catheters (UVC) showed evidence of thrombosis on postmortem examinations.⁵ Thrombosis was also seen in the absence of vascular catheterization.⁶ In this study, there was a history of UVC insertion in all infants with venous thrombosis and three with an arterial one. Thrombosis can occur without history of umbilical catheter insertions, as in two of our patients.

Preterm infants are more prone to catheter-related thrombosis because of the slow flow rate of infusion, the larger size of the catheter in comparison to the size of the vessel, which may occlude the vessel, and the longer period these catheters are kept in these sick preterm infants. In our study, six infants were premature and all had umbilical catheterization.

Other contributing factors that precipitate newborn infants to thrombosis include sepsis, polycythemia, dehydration, asphyxia, cyanotic congenital heart disease (CHD), birth trauma, small for gestational age (SGA), raised antiphospholipid antibody titers, and maternal diabetes or hypertension.^{2,9} In this study, sepsis was diagnosed in the majority of patients (6/10), while other risk factors such as CHD, SGA, asphyxia, and IDM were seen in a few infants.

Doppler ultrasonography is the most useful and most popular method of diagnosis of neonatal thrombosis, however, its diagnostic accuracy remains uncertain.¹⁰ Angiography is the best method for confirming the

diagnosis.^{3,10} In this study, angiography was used in only three infants, and the remaining were diagnosed by ultrasonography.

In general, thrombolytic therapy in children has been extrapolated from the adult literature. There are no clear guidelines for the management of neonatal thrombosis. This lack of guidelines may be because thrombosis in neonates is not prevalent enough to prompt controlled clinical trials. This study and other published studies indicate that the treatment of neonatal thrombosis varies among neonatologists and even individual centers.⁸ However, there have been attempts to publish recommendations for the management of neonatal thrombosis which might assist clinicians in managing this problem.³

In conclusion, the population in this study was small, however, prematurity, the use of umbilical catheters, and sepsis were identified as contributing factors in neonatal vascular thrombosis. Early diagnosis and prompt thrombolysis of significant lesions may contribute to their successful management.

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