CASE REPORT

Early intracardiac thrombosis in preterm infants and thrombolysis with recombinant tissue type plasminogen activator

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Abstract

***Objectives*—To determine the incidence of catheter related thrombosis and to test the efficacy of recombinant tissue type plasminogen activator (rt-PA) in preterm infants.**

***Study design*—From January 1995 to December 1998, echocardiography was performed in the first few days of life in 76 very low birthweight (≤ 1500 g) infants out of a total of 147 having an umbilical catheter placed. When intracardiac thrombosis was diagnosed, rt-PA infusion was performed.**

***Results*—Four infants (5%) developed an intracardiac thrombosis during the first few days of life. In three of them, rt-PA at a dose of 0.4–0.5 mg/kg in a 20–30 minute bolus led to dissolution of the clot. One patient received a three hour infusion after the bolus, at a dose of 0.1 mg/kg/h, with resolution of the thrombus. No systemic effects were observed after rt-PA infusion.**

***Conclusions*—Early thrombosis may occur as a complication of umbilical catheterisation in preterm infants; early echocardiographic detection of this disorder allows complete, safe, and rapid lysis with rt-PA.**

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Keywords: recombinant tissue type plasminogen activator; thrombosis; very low birthweight infants; echocardiography

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Central venous catheters are commonly used for drug administration and parenteral nutrition. Their use in low birthweight and critically ill infants has led to an increased incidence of thrombotic events.[1] It has been calculated[2] that up to 48% of central venous catheters can become obstructed by a thrombus in extremely low birthweight infants (< 1000 g).

The development of intracardiac thrombosis is a rare but severe complication of indwelling central lines.[3 4] It is usually observed several days after the line placement and, in small preterm infants, can lead to life threatening events such as valvular obstruction with heart failure, pulmonary and/or systemic thromboembolism, and superior or inferior vena cava syndrome[4 5]; occlusion of the right pulmonary artery has also been reported.[6]

Cardiotomy with surgical removal of the thrombus can be performed even in preterm infants,[7] but it has a high rate of mortality and, being a hazardous procedure, is considered too risky.[6]

Thrombolytic agents such as heparin and streptokinase are no longer considered to be the ideal treatment in the neonatal period, as they lead to a systemic coagulopathic state.[8]

Newer plasminogen activators, including recombinant tissue type plasminogen activator (rt-PA), are more clot selective and may represent a good alternative for thrombolytic treatment in neonatal practice.[9–12]

The incidence of atrial thrombosis in preterm infants is as yet unknown. Since the early 1990s, echocardiography has been routinely performed in low birthweight infants in our neonatal intensive care unit, and cardiac thrombi in all preterm infants with an umbilical catheter have been systematically screened since 1994. This report investigates the incidence of right atrial catheter related thrombosis in preterm infants and describes the efficacy and safeness of rt-PA treatment.

Methods

Over a four year period (from January 1995 to December 1998), a total of 147 newborn infants weighing 1500 g or less were admitted to our neonatal intensive care unit; 96 (65.3%) of these had a central venous umbilical catheter placed (poly(vinyl chloride) umbilical vessel catheter; Sherwood Medical, Argyle infusion, Tullamore, Ireland) during the first day of life. The position of the catheter tip was confirmed by chest radiograph. In 76 of the 96 preterm infants, the tip of the catheter, according to current practice,[13] was located at the outlet of the inferior vena cava or in the right atrium. In another 20 infants, the catheter impinged on the portal system and was withdrawn 1–2 cm. These 20 infants were excluded from the study.

No heparin was added to the fluids. The catheter was used for the infusion of 8–12% dextrose solution and drugs; the umbilical line was not used for infusion of packed red blood cells.

Table 1 Clinical characteristics of the patients and recombinant tissue type plasminogen activator (rt-PA) therapy

Case	*Sex*	*GA (weeks)*	*Birth weight (g) percentile*	*Prenatal and postnatal clinical data*	*Cardiac symptoms*	*Dose and duration of rt-PA therapy for complete dissolution of the clot*
1	M	28	640 <5th	PROM; Apgar at 1 min: 2; at 5 min: 5; IPPV for 2 days; streptococcal group B sepsis; death on the 2nd day	No	0.5 mg/kg in 20 min
2	M	30	1220 25th	PROM; Apgar at 1 min: 3; at 5 min: 7; IPPV for 6 days; PDA	Yes	0.5 mg/kg in 30 min
3	F	33	1440 5th–10th	Caesarean section for maternal hypertension; Apgar at 1 min: 6; at 5 min: 9; IPPV for 3 days	No	0.4 mg/kg in 30 min
4	M	26	1155 >95th	Abruptio placentae; Apgar at 1 min: 6; at 5 min: 8; right pneumothorax; left atelectasia; HFOV for 4 days; CPAP for 6 days	Yes	0.4 mg/kg in 30 min followed by 0.1/mg/kg/h for 3 hours

GA, Gestational age; PROM, premature rupture of membranes; IPPV, intermittent positive pressure ventilation; HFOV, high frequency oscillatory ventilation; CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus.

Echo-Doppler cardiography (Acuson 128XP/10 with 7.5 Hz transducer; examination recorded on videotapes and printouts) was routinely performed as part of an initial evaluation of respiratory distress in all preterm infants with an umbilical venous catheter, and it was repeated within one to four days.

As described by Dillon *et al*,[14] after the diagnosis of thrombosis, a bolus of 0.4–0.5 mg/kg rt-PA (Actilyse; Boehringer, Ingelheim, Germany) was administered through the catheter over 20–30 minutes; local infusion was maintained at a dose of 0.1 mg/kg/h, if necessary. The treatment was considered successful when Doppler echocardiography showed that the thrombus had been completely dissolved. In the four infants affected by thrombosis, blood samples were taken for measurement of prothrombin time, partial thromboplastin time, fibrinogen levels, and platelet count before and soon after rt-PA administration. Serial cerebral ultrasound scans showed no cerebral haemorrhages in the treated infants.

At the time the thrombus was detected, none of the patients was polycythaemic—that is, the venous packed cell volume was more than 60%. No congenital malformation, including congenital heart defect, was present in the series of patients.

Case reports

Echocardiography performed after line insertion showed catheter related thrombus formation in four of the 76 preterm infants (5.3%; 95% confidence interval 0.3% to 10.3%) with an umbilical venous catheter near or in the right atrium.

Tables 1 and 2 list the clinical characteristics and coagulation assessment respectively of the four patients.

Patient 1, an infant of extremely low birthweight and small for dates, 28 weeks gestational age, 640 g body weight (lower than the 5th centile), had the umbilical line positioned at 3 hours of life. The echocardiography performed at 14 hours of life showed the tip of the catheter protruding beyond the foramen ovalis, with a tip related elongated fibrin aggregation (2 mm × 8 mm) in the left atrium. No cardiac symptomatology was present at the time of diagnosis. Removal of the thrombotic formation was achieved with a 20 minute bolus of rt-PA.

This small patient died on the 3rd day of life after progressive deterioration of cardiac, respiratory, and renal functions. Streptococcal group B sepsis was diagnosed on the basis of positive blood and pharyngeal swab cultures. A post mortem study of the lungs showed bilateral pneumonia; no signs of pulmonary emboli or cerebral haemorrhage were observed.

In patient 2, echocardiography performed on the 4th day of life showed a tip related thrombus (3 mm × 8 mm) floating in the right atrium. An inconstant tachycardia was present. Dissolution of the clot was achieved with a 30 minute bolus of rt-PA.

In patient 3, echocardiography on the 2nd day of life showed an intra-atrial line tip roundish clot (5 mm × 2.5 mm) (fig 1). No cardiac signs were present, and a 30 minute bolus of rt-PA led to the disappearance of the echogenic formation.

Patient 4 had the echocardiograph scan on the 2nd day of life, when a cardiac systolic murmur and transient sinus bradycardia were present at clinical examination. A dishomogeneous thrombotic (8 mm × 2 mm) formation was hanging in the right atrium, intermittently reaching the tricuspid valve; a fibrin thread was stretched through the foramen ovalis, across the left section of the heart and aortic isthmus (fig 2a,b).

Doppler colour imaging did not show any tricuspid valve regurgitation or impairment of

Table 2 Laboratory data for the patients before and after treatment with recombinant tissue type plasminogen activator

	Before treatment				*After treatment*			
Case	*Fibrinogen (RR: 1.50–4.18) (g/l)*	*PT (RR: 10–16.2) (seconds)*	*PTT (RR: 26.9–79.4) (seonds.)*	*Platelets (RR: 80–502) (× 10^3/mm^3)*	*Fibrinogen (RR: 1.50–4.18) (g/l)*	*PT (RR: 10–16.2) (seconds)*	*PTT (RR: 26.9–79.4) (seconds)*	*Platelets (RR: 80–502) (× 10^3/mm^3)*
1	2.35	14	23.2	115	2.51	11	23.2	170
2	5.24	12.8	28.1	171	4.50	12.3	23.3	195
3	2.18	15.8	31	384	2.11	15.2	46.2	280
4	1.75	13.7	33	80	2.03	14	38	66

PT, Prothrombin time; PTT, partial thromboplastin time; RR, reference range.

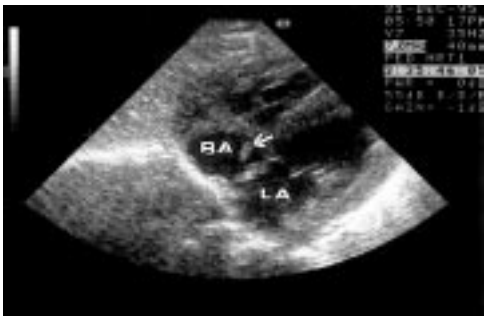

Figure 1 Subcostal image on two dimensional echocardiography in patient 3 showing an intra-atrial line tip roundish clot. RA, Right atrium; LA, left atrium.

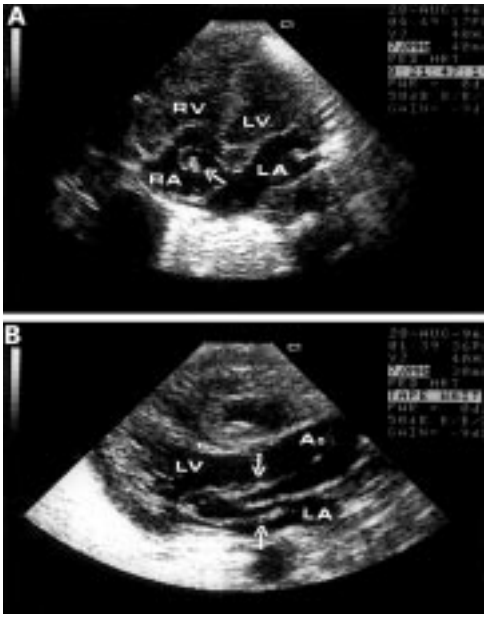

Figure 2 (A) Apical four chamber view on two dimensional echocardiography in patient 4 showing a dishomogeneous thrombotic formation in the right atrium (RA): a fibrin thread is stretched through the foramen ovalis into the left atrium (LA) of the heart. RV, Right ventricle; LV, left ventricle. (B) Long axis view on two dimensional echocardiography in patient 4. A long clot in the left atrium (A_1) reaches the left ventricular outflow passing through the mitral valve.

aortic blood flow. Dissolution of the thrombus was achieved after the bolus and a three hour infusion of rt-PA.

During rt-PA infusion, the patients did not exhibit any major changes in respiration, arterial blood gas values, or haemodynamic pressure. No haemorrhagic complications were discovered.

As shown in table 2, no alteration in coagulative patterns were observed after the treatment. Subsequent recurrent thrombosis was excluded at the follow up.

Discussion

Central catheter related thrombosis is a harmful and relatively common complication in very low birthweight infants; its incidence varies from 2 to 10% of patients with central venous catheters. The actual incidence of intracardiac thrombosis in this category of patients is still not known.

Data on atrial thrombosis in newborn infants are limited to case reports: most of these are represented by infected[6] or non-infected[3] atrial thrombi that did not develop until a few weeks after venous catheterisation.

Since 1994, in our neonatal intensive care unit, all low birthweight infants receiving a venous umbilical catheter have undergone early echocardiographic screening. During the last four years, four of the 76 preterm infants (5.3%; 95% confidence interval 0.3% to 10.3%) with an umbilical venous catheter located in the inferior vena cava or in the right atrium have been affected by early intracardiac thrombosis. The time to diagnosis ranged from a few hours to three days after catheter placement. Intracardiac thrombosis is probably not as rare as was thought in the past, and it can affect small preterm infants even during the first days of life.

Lack of evident cardiac symptomatology was an unexpected feature. We believe that the size and age of the thrombus are of crucial importance for functional disturbances and cardiac signs. Clots in our series varied in size, being associated in two cases with a fibrin thread across the left section of the heart, up to the aortic isthmus. Only two of the four preterm infants presented subtle cardiac symptomatology and none developed haemodynamic implications or heart failure.

It is likely that the early evaluation of cardiac morphology and functional indices resulted in the earlier detection and treatment of intracardiac thrombosis, preventing further enlargement of the clot, onset of valvular obstruction, functional disturbances, and deterioration of the patients' condition.

Should these "silent" thrombi be treated? Spontaneous regression of an intracardiac thrombus has been reported,[14] but most authors agree about the danger inherent in intracardiac thrombosis and hence the advisability of early treatment. The right atrial thrombi may enlarge, causing obstruction of the tricuspid orifice (potentially leading to heart failure) or inferior/superior vena cava syndrome; macro or micro embolisation in systemic or pulmonary circulation may also occur. A sudden deterioration in respiratory function can be caused by occlusion of the pulmonary artery by a life threatening embolisation. We believe that pulmonary embolism caused by intracardiac thrombosis or deep venous thrombosis must account for a certain number of sudden and apparently unexplained deaths of small preterm infants. Infected atrial thrombosis, on the other hand, may cause multiple septic embolisation and lead to a prolonged septic state or recurrent sepsis. Therefore intracardiac thrombi should be lysed even in the absence of definite symptoms.

Specific treatment is still a matter of debate. It has been suggested that infected atrial thrombi can be safely removed by cardiotomy even in very small preterm infants,[15] whereas other authors[6] claim that surgical removal of intracardiac thrombi in preterm infants is a hazardous operation. In fact, with the development of fibrinolytic agents, this procedure is being used less often.

Experience with classic thrombolytic agents in intracardiac thrombolysis of preterm infants is very limited. The use of heparin, streptokinase, or urokinase may be complicated in newborn infants by intracranial and/or systemic bleeding and may produce fibrin fragmentation, precipitating pulmonary embolisation.

rt-PA has produced encouraging results in adults and children.[16–19] In our four case studies, rt-PA was successfully used in small preterm infants affected by intracardiac thrombi. It was effective in dissolving the clots in all four patients and it was sufficiently safe, as no patient showed clinical or haematological signs of coagulopathy. This is of particular interest in the treatment of very low birthweight infants, who are at major risk of intracranial and other bleeding. Moreover, rt-PA acted surprisingly rapidly in achieving complete thrombolytic activity: 20–30 minutes of rt-PA bolus infusion led to the dissolution of the clot in three cases, and a three hour maintenance infusion after the bolus was effective in the fourth case. To our knowledge, previous reports on rt-PA infusion in newborn infants referred to complete clot dissolution being achieved only after some hours or days of continuous infusion. It can be reasonably argued that the rapidity of rt-PA action depends on timely diagnosis and thus early intervention: early detection of the intracardiac thrombosis allows treatment of "fresh" unformed clots and ensures a better and quicker response.

In conclusion, right atrial thrombosis may affect small preterm infants with a central umbilical catheter from the first days of life. Early echocardiographic detection, before the clot grows large and organised, allows complete, safe, and rapid thrombolysis with rt-PA.

1 Mactier H, Alroomi LG, Young DG, *et al*. Central venous catheterization in very low birthweight infants. *Arch Dis Child* 1986;**61**:449–53.

2 Girsoni ER, Mehata SK, Connors AF. Thrombosis and infection complicating central venous catheterization in neonates. *J Pediatr Surg* 1986;**9**:772–6.

3 Pongiglione G, Marasini M, Ribaldone D, *et al*. Right atrial thrombosis in two preterm infants: successful treatment with urokinase and heparin. *Eur Heart J* 1986:**12**:1086–9.

4 Van Overmeire B, Van Reempts PJ, Van Acker KJ. Intracardiac thrombus formation with rapidly progressive heart failure in the neonate: treatment with tissue type plasminogen activator. *Arch Dis Child* 1992; **67**:443–5.

5 Schmidt B, Zipursky A. Thrombotic disease in newborn infants. *Clin Perinatol* 1984;**11**:461–88.

6 Alkalay AL, Mazkereth R, Santulli T Jr, *et al*. Central venous line thrombosis in preterm infants: a case management and literature review. *Am J Perinatol* 1993;**10**:323–6.

7 Gamillscheg A, Nurnberg JH, Alexi-Meskishvili V, *et al*. Surgical emergency embolectomy for the treatment of fulminant pulmonary embolism in a preterm infant. *J Pediatr Surg* 1997;**32**:1516–18.

8 Holden RW. Plasminogen activators: pharmacology and therapy. *Radiology* 1990;**174**:993–1001.

9 Anderson BJ, Keeley SR, Johnson ND. Caval thrombolysis in neonates using low doses of recombinant human tissue-type plasminogen activator. *Anaesth Intensive Care* 1991;**19**:22–7.

10 Kennedy LA, Drummond WH, Knight ME. Successful treatment of neonatal aortic thrombosis with tissue plasminogen activator. *J Pediatr* 1990;**116**:798–801.

11 Kandler C, Ries M, Rupprecht T, *et al*. Successful systemic low-dose lysis of a caval thrombus by rt-PA in a neonate with congenital nephrotic syndrome. *J Pediatr Hematol Oncol* 1997;**19**:348–50.

12 Daoud P, Quetin P, Saillant A, *et al*. Spontaneous neonatal arterial thrombosis treated with tissue plasminogen activator. *Arch Pediatr* 1997;**4**:343–6.

13 Roberton NCR. *Textbook of neonatology*. 2nd ed. Edinburgh: Churchill Livingstone, 1992.

14 Dillon PW, Fox PS, Berg CJ, *et al*. Recombinant tissue plasminogen activator for neonatal and pediatric vascular thrombolytic therapy. *J Pediatr Surg* 1993;**28**:1264–8.

15 Mendoza GJB, Soto A, Brown EG. Intracardiac thrombi complicating central total parenteral nutrition: resolution without surgery or thrombolysis. *J Pediatr* 1986;108:610–13.

16 De Schepper J, Hachimi-Idrissi S, Cham B, *et al*. Diagnosis and management of catheter-related infected intracardiac thrombosis in preterm infants. *Am J Perinatol* 1993;**10**:39–42.

17 Rao KA, Pratt C, Berke, *et al*. Thrombolysis in myocardial infarction (TIMI) trial-phase I: haemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;**11**:1–11.

18 Verhaege R, Besse P, Bounameaux H, *et al*. Multicenterpilot study of the efficacy and safety of systemic rt-PA administration in the treatment of deep vein thrombosis of the lower extremities and/or pelvis. *Thromb Res* 1989;**55**:5–11.

19 Levy M, Benson LN, Burrows P. Tissue plasminogen activator for the treatment of thromboembolism in infants and children. *J Pediatr* 1991;**118**:467–72.