CASE REPORT

Successful Treatment of Arterial Thrombus in an Extremely Low-Birth-Weight Preterm Neonate

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Arterial thromboembolism in the pediatric population frequently occurs secondary to arterial catheterization. Catheterization-related complications are more common in smaller and sicker infants, due to high prothrombotic activity, low levels of natural anticoagulants, and various fibrinolytic imbalances. Arterial thrombus management in neonates remains controversial. Recombinant tissue plasminogen activator is the most commonly used thrombolytic agent in children, however there is very little experience with recombinant tissue plasminogen activator therapy in small prematures, especially in the first week of life. This case study reports catheter-related femoral artery occlusion in an extremely low-birth-weight preterm infant. Despite continuous heparin infusion for 6 hours, no resolution of the thrombus was seen by clinicians. Heparin was stopped, and recombinant tissue plasminogen activator therapy enabled complete recovery from the thrombus. The risk of bleeding (including intracranial hemorrhage) with recombinant tissue plasminogen activator treatment, especially in small preterm neonates is unknown. However, in this extremely low-birth-weight preterm infant, recombinant tissue plasminogen activator therapy was effective, and limiting the infusion rate to ≤0.4 mg/kg/hour was safe.

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1. Introduction

Arterial thromboembolism in the pediatric population frequently occurs secondary to arterial catheterization. Estimates of the frequency of arterial thrombus from umbilical artery catheterization (UAC) vary widely, from 9% to 32%. Perinatal asphyxia, hypovolemia, septicemia, dehydration, polycythemia, congenital heart disease, and other conditions are associated with disturbances in the hemostatic balance and may lead to a prothrombotic
are commonly associated with thrombotic episodes. Difficult catheterizations are more likely to produce intimal damage and are commonly associated with thrombotic episodes. Occurrence of UAC-related thrombus may be minimized by high umbilical positioning, end-hole, single-lumen construction and low-dose heparin infusion.

Arterial thrombus management in neonates remains controversial. Catheter removal is recommended when the thrombus is catheter related. Systemic anticoagulation using unfractionated or low-molecular-weight heparin constitutes standard therapy for children. Thrombolysis and surgical thrombectomy are other therapeutic options. Systemic thrombolytic therapy is indicated for arterial occlusion, massive pulmonary embolism, pulmonary embolism not responsive to heparin therapy, and threat to organ or limb viability. Streptokinase, urokinase, and recombinant tissue plasminogen activator (r-TPA) are the most commonly used thrombolytic agents in adults. Streptokinase is not advised for pediatric use due to a high prevalence of neutralizing anti-streptococcal antibodies, and urokinase is not considered safe by the Food and Drug Administration. Therefore, r-TPA is the thrombolytic agent of choice for children, however there is very little experience with r-TPA therapy in small preterms, especially in the first week of life.

This case study reports UAC-complicated femoral artery occlusion with thrombus that was dissolved completely after r-TPA infusion in an extremely low-birth-weight preterm neonate.

2. Case Report

A preterm female neonate (birth weight 920 g at 27 gestational weeks) was delivered via cesarean-section due to premature rupture of the membranes and fetal distress. Apgar scores were 7 (1 minute) and 9 (5 minutes). Umbilical venous and artery catheters were placed successfully. The neonate was intubated on day 5 because of sepsis. Planned replacement of umbilical catheters due to a leakage was performed on day 6. After the procedure, the left leg became cool and pale, and there was a clear demarcation line along the mid-femur. Doppler ultrasound revealed 70% occlusion, with a thrombus between the external iliac and femoral arteries. Tissue perfusion did not improve after the removal of both catheters. The patient was treated with an initial bolus dose of 75 IU/kg of unfractionated heparin, then continuous infusion at 25 IU/kg/hour. Since no improvement was observed after 6 hours of heparin infusion, therapy was stopped. Recombinant tissue plasminogen activator at 0.1 mg/kg/hour was started via the peripheral vein. The infusion rate was increased to 0.3 mg/kg/hour at the 3rd hour of r-TPA. After infusion of 10 mL/kg of prophyllactic fresh frozen plasma (FFP), r-TPA infusion was increased to 0.4 mg/kg/hour at the 7th hour. Tissue perfusion improved and distal pulses to the thrombus were palpable at the 8th hour. Infusion of r-TPA was stopped, and 10 IU/kg/hour of heparin infusion was continued for a further 4 hours. Doppler ultrasound demonstrated complete resolution. Cranial ultrasound was normal. The patient displayed no symptoms of bleeding. Long-term follow-up revealed normally perfused extremities, with no evidence of functional compromise or growth delay.

3. Discussion

When r-TPA binds to clot-bound fibrin, plasmin is produced at the clot site, resulting in clot dissolution. If thrombolytic therapy is utilized, r-TPA is generally favored due to its high fibrin specificity with poor activation of free plasmin, lack of antigenicity, and a short half-life. The optimal use, dosage, efficacy, and side effects of r-TPA thrombolysis in children are not well known.

Major surgery during the last 10 days and a history of bleeding are absolute contraindications to r-TPA therapy. Thrombocytopenia (platelets < 100,000), fibrinogen concentration < 100 mg/dL, and severe coagulation factor deficiencies must be corrected before thrombolytic therapy.

Administration of FFP prior to the utilization of thrombolytics may increase success rates by providing sufficient plasminogen. Frequent monitoring of fibrinogen levels during therapy is required, although blood sampling for monitoring can be difficult. Arterial punctures, urinary catheterizations, and subcutaneous or intramuscular injections should be avoided during thrombolytic therapy. It is recommended to image the thrombus every 12–24 hours and to cease r-TPA infusion when clot lysis is achieved or bleeding complications occur. Daily cranial sonograms are also recommended during r-TPA therapy.

Reocclusion is a potential problem after fibrinolytic therapy. Whether and for how long heparin therapy should be given during or after r-TPA infusion is currently unclear. Dosing for r-TPA infusion commonly ranges from 0.01 mg/kg/hour to 0.50 mg/kg/hour. Farnoux et al. reported 16 neonates (34–40 gestation weeks) treated with 0.3 mg/kg/hour of r-TPA therapy after an initial bolus of 0.1 mg/kg over 10 minutes. One neonate who was treated despite severe thrombocytopenia had massive intracranial bleeding and died. Weiner et al. used an initial dose of 0.1 mg/kg/hour of r-TPA for 6 hours that was increased by 0.1 mg/kg/hour at 6-hour intervals to a maximum of 0.5 mg/kg/hour. Two out of seven patients (1 term and 1 small preterm neonate) died at the highest infusion rate of 0.5 mg/kg/hour with severe bleeding complications. Hartman et al. reported r-TPA therapy in 14 neonates, three of whom were small preterm neonates and two of whom were in their first week of life. Administration of r-TPA was discontinued because of local bleeding from various venipuncture sites in one patient. In this study, no severe bleeding symptoms were reported with an initial bolus of 0.7 mg/kg of r-TPA over 30 minutes to 60 minutes followed by a maintenance dose of 0.2 mg/kg/hour. Wang et al. reported thrombolysis with a low-dose regimen (0.01–0.06 mg/kg/hour). Eight patients in this study were neonates at day 1 to 2 weeks of age. Three term neonates were treated with conventional doses (0.1–0.5 mg/kg/hour) for 3–16 hours with complete lysis and no bleeding complications. Five patients (4 preterm and 1 term neonate) were treated initially with low-dose r-TPA. The
infusion rate of 0.03 mg/kg/hour of r-TPA was effective in one preterm baby, the infusion was increased to 0.06 mg/kg/hour in two patients, and 0.1 mg/kg/hour in one patient. An 8-day-old preterm neonate at 28 gestational weeks with a catheter-related right atrial thrombus had severe subdural hematoma after r-TPA infusion was increased to 0.24 mg/kg/hour. Ferrari et al11 described the dissolution of intracardiac thrombi with r-TPA in four very low-birth-weight premature neonates. Three patients were treated successfully with a 0.4 mg/kg to 0.5 mg/kg bolus dose of r-TPA for 20–30 minutes. The bolus dose was followed by a 3-hour maintenance infusion (0.1 mg/kg/hour) in the fourth case, and there were no severe bleeding complications.

In the present case study, initial dose of r-TPA infusion was 0.1 mg/kg/hour and it was increased to 0.4 mg/kg/hour at 7 hours to protect limb viability. Additional FFP administration may be effective in the resolution of the clot. Effective and safe thrombolytic treatment is essential in the management of neonates with life-or limb-threatening vessel obstructions. Data on bleeding risks, especially for small premature infants during r-TPA treatment, are limited to case reports,6,11 however, limiting the infusion rate of r-TPA to ≤0.4 mg/kg/hour was safe and effective in this extremely low-birth-weight premature infant.

References


