Successful thrombolytic treatment of neonatal arterial thromboses

J. Stächele1; J. Dinger2; S. Brenner2; S. R. Hofmann2; S. Ifflaender2; R. Knöfler1

1Fachbereich Hämostaseologie, Klinik und Poliklinik für Kinder- und Jugendmedizin, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden; 2Fachbereich Neonatologie und Pädiatrische Intensivmedizin, Klinik und Poliklinik für Kinder- und Jugendmedizin, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden

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Summary
Compared to children of other age groups neonates show an increased thrombotic risk. The acute therapy depends on thrombus age, the localisation of vascular occlusion and the severity of the underlying disease. The treatment of choice is represented by the administration of unfractionated (UFH) or low molecular weight heparin (LMWH). If loss of limbs or organs is imminent, the application of thrombolytic treatment with recombinant tissue-type plasminogen activator (rt-PA) should be considered whilst taking into account the associated bleeding risk. We report on two patients in which thrombolytic therapy has been conducted successfully.

Correspondence to:
Julia Stächele
Klinik und Poliklinik für Kinder- und Jugendmedizin, Fachbereich Hämostaseologie, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden
Fetscherstraße 74, 01307 Dresden, Germany
E-Mail: Julia.Staechele@uniklinikum-dresden.de

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In children neonates bear the highest risk of developing thromboses. The incidence of symptomatic neonatal thrombosis is reported with 5.1 per 100 000 births (13). Correspondent to Canadian Registry data, deep vein thrombosis or pulmonary embolism affect 5.3 of 10 000 admitted children (3). Since thrombotic events are often associated with acquired risk factors such as central vessel catheters, sepsis or immobilisation they play a major role in neonatal and paediatric intensive care units. We report on two neonates with limb-threatening arterial thromboses who were treated successfully by thrombolytic therapy.

Two cases
Patient 1
A female preterm neonate born at 29 weeks of gestational age presented with an initial haematocrit of almost 80% due to feto-fetal transfusion syndrome. In order to prevent circulatory problems blood was replaced by fresh frozen plasma and human serum albumin. Further, the patient received a platelet transfusion based on a platelet count of $85 \times 10^9$. However, an impaired microcirculation and subtle livid discolouration of the right foot were found on the first day of life. In the course of the day the discolouration became darker and affected almost the entire right leg (Fig. 1a). By Doppler ultrasound an extended thrombosis of the aortic bifurcation with almost complete occlusion of the right iliac artery was diagnosed which led to the immediate removal of the umbilical artery catheter.

Due to extreme prematurity and the presence of a grade 1 intracerebral haemorrhage the patient was initially treated with an aPTT and anti-Xa level adjusted therapeutic dosage of intravenous UFH (~ 400 U/kg/d, target range anti-Xa level 0.35 to 0.7 U/ml). During the next day the clinical findings of the impaired circulation worsened by showing necroses of the right toes and affecting the left leg as well. Subsequently, treatment was switched to thrombolytic therapy with concomitant low-dose heparinisation (100 U/kg/d UFH). The patient initially received an intravenous bolus injection of 0.3 mg/kg rt-PA. Since the clinical situation did not improve and the intracerebral haemorrhage was stable the bolus application was repeated on the next day, followed by a continuous intravenous infusion of 2.5 mg/kg/d rt-PA over a period of three days. During thrombolytic therapy the D-dimers were determined several times showing a fibrinolytic effect by a distinct increase.

Clinically, the circulatory situation in the leg advanced significantly during continuous administration of rt-PA. Doppler ultrasound showed a complete recanalisation of the aortic bifurcation.

After stopping rt-PA infusion the patient again received a therapeutic dosage of...
intravenous UFH for three more weeks, followed by the subcutaneous application of LMWH (~ 1.5 mg/kg enoxaparin once daily) for another month.

During thrombolytic therapy, cranial ultrasound was performed daily and detected a small subarachnoidal haemorrhage on day 3 of the treatment with rt-PA. Fortunately, this bleeding did not show any progress and disappeared in the long term. Concerning the outcome, the patient lost three of the already mummified toes (▶ Fig. 1b).

Thrombophilia diagnostics have not been performed yet; however, plethora and umbilical artery catheter have to be mentioned as potential risk factors.

Patient 2
A male term neonate was born in an external hospital by Caesarean section due to breech presentation. The child was found in an abnormal position with the left leg located in the birth canal. After birth this leg presented with a pale to livid colour. Doppler ultrasound showed a complete occlusion of the left femoral artery which was the reason for the immediate transfer of the patient to our neonatal intensive care unit. Here, this sonographic finding was confirmed and in addition a total occlusion of both renal veins with a partial occlusion of the inferior caval vein and a middle cerebral artery infarction due to paradoxical embolism were found. Despite bilateral increase of renal volume and echogenicity the renal function was not affected. Thrombolytic therapy with rt-PA was started immediately with an initial bolus of 0.1 mg/kg, followed by 1.0 mg/kg/d as continuous infusion for five days. Also in this patient the D-dimers showed a significant increase. Concomitantly, a low-dose heparinisation with UFH at 200 U/kg/d was administered. After stopping rt-PA infusion the patient received an anti-Xa level adjusted therapeutic dosage of intravenous UFH (target range of anti-Xa level 0.35 to 0.7 U/ml) for two weeks and enoxaparin at prophylactic dosage (~ 1 mg/kg once daily s.c.) for 3.5 months.

The clinical situation of the left leg improved markedly under rt-PA infusion showing a complete clot lysis of the femoral artery by Doppler ultrasound on day 5 of thrombolytic treatment. Initially, the occlusions of both renal veins and the inferior caval vein remained steady. However, after three months a partial recanalisation of the renal veins could be detected.

The patient did not suffer from any bleeding complications and showed an age corresponding development including a so far regular growth and normal function of the kidneys; the latter has to be monitored regularly due to the increased risk of hypertension or chronic renal failure on long-term follow-up. Thrombophilia diagnostics revealed the presence of a heterozygous factor V Leiden mutation as an inherited, mild thrombophilic risk factor.

Discussion
According to the recently published guideline of the American College of Chest Physic (ACCP) the administration of unfractionated or low molecular weight heparin represents the treatment of choice concerning vessel occlusions in paediatric patients (11). However, the administration of thrombolytic agents should be considered when limbs, organs or even life are at risk (6, 11). Recombinant tissue-type plasminogen activator (rt-PA) represents the agent of choice due to its low immunogenicity and better in vitro clot lysis compared to streptokinase and urokinase (1, 4, 7, 16). rt-PA can be given systemically or locally which allows the application of a lower dosage. Before initiating thrombolytic therapy in neonates the administration of fresh frozen plasma is suggested since neonates have physiologically low levels of plasminogen which is required for the efficacy of a thrombolytic agent (2, 11). Concomitantly to thrombolytic treatment a low-dose heparinisation is recommended in order to prevent the prothrombotic effect of fibrin degradation products (5, 8, 9). However, this suggestion is only based on single-centre studies. Apparently, this com-
Combination does not seem to increase the risk of bleeding (15).

Regarding the optimal dosage of rt-PA in neonates there is only few data available. A dosage of 0.5 mg/kg/h administered over a six hour period has been recommended (4, 12). Another study reported on a wide rt-PA dosage range from 0.015 to 0.06 mg/kg/h administered over 12 to 96 hours (15).

Compared to these recommendations the rt-PA dosage of 2.5 mg/kg/d as applied to the first reported patient is quite high. However, in vitro data suggests that neonates may require a higher concentration of rt-PA to successfully induce thrombolysis (17).

Since the latest ACCP guideline does not take up position concerning the duration of anticoagulation after umbilical artery catheter-related thrombosis (patient 1) or bilateral renal vein and limb-threatening femoral artery thrombosis (patient 2) our decisions were based on individual radiological findings (11).

In contrast to conventional anticoagulant therapy with UFH and LMWH the application of thrombolytic agents is associated with an increased risk of bleeding complications. Therefore, the potential benefit and risk of thrombolytic therapy must be considered very carefully in every affected patient. Schmidt and Andrew described a mortality rate of 21 % of neonates suffering from an arterial thrombosis treated with thrombolytic therapy (14).

In a total number of 413 paediatric patients treatment with rt-PA resulted in 17 % in major bleedings affecting the central nervous system or requiring a red cell transfusion and in 22 % in minor bleedings (1).

Prematurity of less than 32 weeks of gestational age has been described as a relative contraindication for thrombolytic therapy since preterm neonates are particularly susceptible to intracerebral haemorrhages (10). Accordingly, the first reported patient developed a small – clinically irrelevant – subarachnoidal haemorrhage on day 3 of rt-PA treatment.

Considering the remarkable complication rate of thrombolytic therapy especially in neonates these patients should obligatorily be treated interdisciplinarily in experienced paediatric centres.

**Conclusion**

Systemic thrombolytic treatment with rt-PA represents an important therapeutic option for the treatment of critical vascular occlusions in neonates. The potential benefit of thrombolytic therapy must be balanced very carefully against the risk of threatening bleedings.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

**References**