CASE REPORT

Clinical Case Reports   WILEY

Recombinant tissue-type plasminogen activator treatment in an extremely low birth weight infant

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Abstract
Tissue plasminogen activator can effectively treat clinical thrombosis in premature infants 11 hours after birth.

KEYWORDS
24 weeks of gestation, catheter-related intracardiac thrombus, ELBW, tPA

1 | INTRODUCTION

A newborn infant born at 24 weeks of gestation and carrying a high risk of postnatal IVH caused by catheter-related thrombosis underwent treatment with tPA. No hemorrhage was observed after the administration of tPA. Despite the lack of optimal dose guidelines, tPA can effectively treat clinical thrombosis in neonates.

Clinical thrombosis occurs in 2.4 cases per 1000 admissions to a neonatal intensive care unit in Canada and 5.1 cases per 100 000 births in Germany.[1,2] Thrombolytic therapy can help prevent organ infarction by thrombolysis and rapidly restore the normal blood flow. High-risk thrombi appear large (>2 cm), pedunculated and mobile, or snake-shaped and mobile. The mortality rate in patients at a high risk of clinical thrombosis has been reported to be 16.7%, and tissue plasminogen activator (tPA) therapy is supposedly an effective management technique.[3] tPA is a specific thrombolytic agent manufactured using recombinant DNA technology. tPA has a few advantages. It has a thromboselective mechanism (through increased fibrin specificity) wherein it causes fibrinolysis of thrombi without activating systemic proteolysis, a low affinity for circulating plasminogen, and a short half-life.[4]

Nearly 90% of all intraventricular hemorrhage (IVH) cases occur within the first 72 h after birth.[5] It is unclear whether tPA can be effective in infants with extremely low birth weight (ELBW) (birth weight <1000 g) who develop thrombi with high-risk features of IVH within 72 hours of birth.

2 | CASE PRESENTATION

A female infant (544 g, 2nd twin) was delivered at 24 weeks by cesarean section due to the onset of labor. Apgar scores at 1 and 5 minutes were 4 and 5, respectively. Surfactants were administered through an endotracheal tube, and she was mechanically ventilated for respiratory distress syndrome. At birth, a central venous line was placed into the inferior vena cava through the right great saphenous vein, and an arterial line was placed via the radial artery. Similarly, prophylactic ampicillin and amikacin were administered. Nine hours after birth, desaturation and bradycardia occurred. Leukocytosis (6.8×10^9 L^{-1}) with no left shift and thrombocytosis (272×10^9 L^{-1}) were noted; hemoglobin, hematocrit, C-reactive protein, immunoglobulin G, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, antithrombin III activity, fibrin degradation products (FDP), and D-dimer levels were 151 g/L, 0.464 L^{-1}, 0.1 mg/L, 1.82 g/L, 17.9 s, 132.8 s, 0.97 g/L, 0.23, 13.4 mg/L, and 4700 ng/mL, respectively.

Tension pneumothorax and cardiac tamponade were excluded after radiography and echocardiography, respectively. Echocardiography showed a 21 × 3 mm high-intensity mass extending from the inferior vena cava region into the right atrium (Figure 1). The mass included high-risk features [large sized (>2 cm), snake-shaped, and mobile].

In the treatment of the thrombus using tPA, it was necessary to confirm the absence and risk of IVH development. Therefore, cerebral echocardiographic evaluation of the perfusion waveform of the internal cerebral vein (ICV) was performed using an approach via the anterior fontanel in the sagittal section by the pulsed wave Doppler method; simultaneously, IVH was evaluated. The ultrasound devices used consisted of a Philips CX50 system (Philips Ultrasound, Bothell, WA) with a S12-4 transducer. The grades of the ICV waveform were defined as follows: grade 0, steady flow waveform with a constant perfusion speed; grade 1, the waveform fluctuates, but the minimum speed is never less than half the maximum speed; grade 2, although the waveform fluctuates and the minimum speed is less than half the maximum speed, it never drops to 0 cm/s; and grade 3, the waveform fluctuates, with the speed sometimes dropping to 0 cm/s. Cerebral echocardiography classified the perfusion waveform of ICV as grade 0 in this case. In addition, IVH confined to the subependymal germinal matrix or within the lateral ventricles

FIGURE 1 Echocardiography of a 21 × 3 mm high-intensity mass extending from the inferior vena cava region into the right atrium

without dilatation or with distention resulting in ventricular dilatation, or in the cerebral parenchyma was not observed.[6]

Eleven hours after birth, we administered 0.05 mg/kg dose of recombinant tissue-type plasminogen activator (rt-PA) via a central venous line in 2 min, followed by a continuous infusion at 0.45 mg/kg/h for only 1 h. Further, heparin was additionally administered intravenously at 10 U/kg/h. Notably, combination therapy (tPA and heparin) was used in this case because it was safe and effective.[7]

Fresh frozen plasma (20 mL/kg/9 h) and antithrombin (AT) gamma (72 U/kg/h), which binds to and activates heparin as an inhibitor of coagulation proteases, were administered. Brangenberg, R. reported that AT-III substitution in preterm infants may reduce the incidence and progression of IVH.[8]

This premature infant had a low antithrombin activity; therefore, AT was administered to prevent IVH. Fibrinogen level and platelet count were maintained at >1 g / L and $>100 \times 10^9$/L, respectively. APTT was used to monitor heparin, aiming for two to three times the child's baseline APTT as long as this was within the normal range for neonates born at <27 weeks' gestation (APTT median (range): 67.4 s (34.9-191.6 s)).[9,10]

The therapeutic range of thrombolytic agents is yet to be scientifically established, and successful lysis was confirmed based on ultrasonographic changes. Echocardiography performed 6 hours after rt-PA administration did not show the thrombus, and heparin administration was suspended for 15 hours. During treatment with rt-PA and post-treatment, we ordered cranial and heart sonograms every 5 hours for 5 d and subsequently every day for 5 d thereafter. Complete blood count and fibrinogen levels were examined every 6 hours during treatment. Hemoglobin, thrombocytes, and fibrinogen levels were maintained at >100 g/L, $>10^{11}L^{-1}$, and >1.0 g L^{-1}, respectively. The infant did not have a deficiency of protein C, protein S, or antithrombin; she was discharged without any bleeding complications or other adverse events.
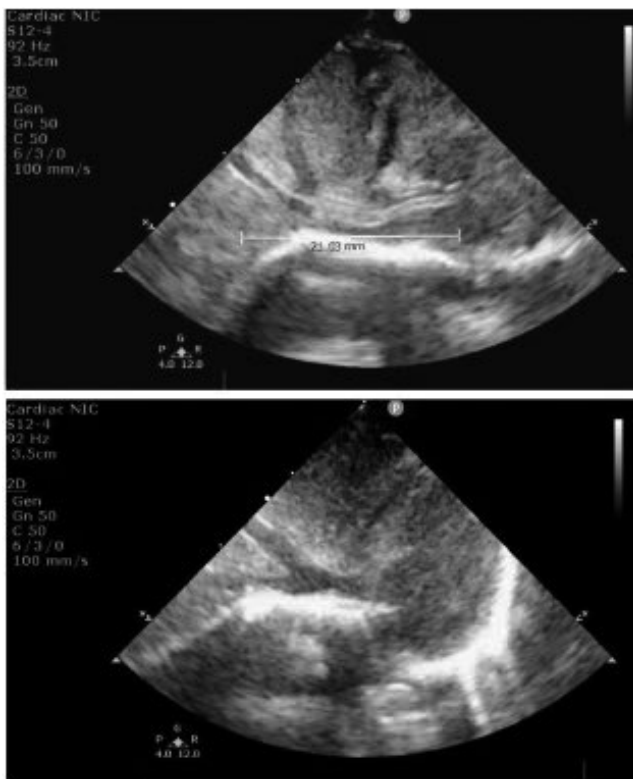
3 | DISCUSSION

This study is novel in that it is the first case report of a very preterm baby born at 24 weeks of gestation who was diagnosed with catheter-related right atrial thrombus 9 hours after birth and administered thrombolytic therapy during the high-risk period for IVH (within 72 hours after birth).

It has been reported that no relationship exists between the duration of catheter placement and the incidence of thrombosis. A previous study revealed that birth weight, gestational age, weight, and age contribute significantly to the development of thrombosis.[11]

The central venous catheter has been identified as an independent risk factor for venous thromboembolism in critically

ill neonates.[12] Catheters may lead to thrombosis through mechanisms, such as vessel wall damage, disruption of blood flow, infusion of hyperosmolar substances, and thrombogenic catheter materials.[13]

Infusates flow at a relatively low rate through the catheter in neonates compared to older infants; additionally, the size of the catheter relative to the vessel is such that it occupies a more significant portion of the cross-sectional area of the vessel in neonates than in older infants, resulting in the development of the classic elements of Virchow's triad: stasis, hypercoagulable state, and vascular injury.[14,15] Therefore, thrombus formation occurred 9 h after birth. Other risk factors for venous thromboembolism include low procoagulant factors (especially the contact activation factors and vitamin K-dependent factors), low anticoagulant factors (including antithrombin, protein C, and protein S levels in premature infants), and higher infection rates which premature infants have due to their impaired immunologic defense mechanisms.[16,17] The use of high-osmolar parenteral nutrition solutions became standard practice in our unit during the treatment period of our patient, which might similarly have contributed to the infiltrations.

In summary, all these factors may contribute to the frequent occurrence of catheter-related thrombosis in premature infants in neonatal intensive care units.

Capps et al reported the diameter of the pulmonic valve to be 10.0 ± 1.1 mm or less.[18] Therefore, the pulmonic valve or the pulmonary artery itself could have been sufficiently embolized when the thrombus (21×3 mm) in the right atrium was liberated. However, our patient was discharged from the hospital without pulmonary embolism or IVH due to the use of tPA.

In this study, tPA therapy was used to treat thrombosis in a high-risk patient with a high mortality rate after confirming the absence of IVH.

Contraindications include major surgery or significant bleeding within 10 d, severe asphyxia within 7 d, an invasive procedure within 3 d, a seizure within 2 d, gestational age of <32 weeks, severe septicemia, active bleeding at the time of therapy, and an inability to maintain a platelet count above 100×10^9/L or plasma fibrinogen at >1.0 g/L. It is clear from more recent studies that with increasing experience in the use of rTPA, these contraindications would no longer be considered absolute. Therefore, rTPA was used in this patient who was delivered at 24 weeks of gestation.[9]

The optimal dose of tPA remains undetermined. A 0.03-0.1 mg/kg/h (maximum 2 mg/h) dose of tPA was recommended by Raffini for a 6 h to 4 d regimen.[19] However, European guidelines recommend a tPA dose of 0.1-0.6 mg/kg/h for 6 h.[20] The use of thrombolytic therapy in children has been limited by tPA-related bleeding, and major bleeding complications have been reported at the standard dose in recent reports (mean dose of 0.5 mg/kg/h).[21]

The optimal treatment strategy for neonatal thrombosis remains unclear. In neonates with severe catheter-related thrombosis, rt-PA is an acceptable treatment, although the optimal dose has not been determined. Therefore, multicenter treatment trials are required to define the optimal duration and dosage of this therapy.

4 | CONCLUSION

An infant (a newborn at 24 weeks) with a high risk of postnatal IVH was administered tPA, and no hemorrhage was observed in the infant. Premature infants may have unbalanced hemostasis, predisposing them to bleeding or thrombotic complications. Catheter-related thrombosis is increasingly being reported in premature neonates. Therefore, it is important to evaluate the necessity of thrombolytic therapy. Evidence for optimal therapeutic doses of tPA in neonates determined by randomized clinical trials is lacking. Therefore, it is necessary to start tPA treatment with a small dose.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS
YS, AS, and TO conceptualized this study. TK conceptualized and designed the study, and wrote and edited the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ETHICAL STATEMENT
Parents or guardians provided informed consent. Additionally, this case study was conducted in accordance with the provisions of the Declaration of Helsinki, as revised in Tokyo in 2004, and was approved by the Ethics Committee of Okinawa Prefectural Nanbu Medical Center and Children's Medical Center.

INFORMED CONSENT
Informed consent was appropriately obtained.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this Article as no datasets were generated or analyzed during the current study.

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