Treatment of neonatal thrombus formation with recombinant tissue plasminogen activator: six years experience and review of the literature

Abstract

Background—Thrombosis is a relatively rare event in children. However, many conditions in the neonatal period result in an increased risk of thrombus formation. The major risk factor is the indwelling intravascular catheter. Numerous small studies have reported experience of thrombolytic treatment for neonatal thrombotic disease with a wide range of different thrombolytic agents in various forms of administration, dosage, and duration, but no conclusions on the most effective treatment for neonates has been reached.

Objective—To assess the efficacy and safety of thrombolytic treatment of neonatal catheter related thrombus (CRT) formation with recombinant tissue plasminogen activator (rt-PA).

Method—Over a six year period, 14 neonates with CRT were treated with the same rt-PA protocol (an initial bolus of 0.7 mg/kg over 30–60 minutes followed by infusion of 0.2 mg/kg/h).

Results—Complete clot dissolution was documented in 11 patients, and partial clot lysis in two patients, leading to a patency rate of 94%. In two cases, local bleeding occurred, resulting in treatment failure in one case. Finally, antithrombin III substitution was required in one case. No other complications such as severe bleeding were recognised.

Conclusion—With the use of close clinical and haematological monitoring on a neonatal intensive care unit combined with serial two dimensional colour echocardiography, the present rt-PA protocol was shown to be a safe and effective method of clot dissolution in neonates.

Keywords: thrombus; thrombolyis; blood clot; tissue plasminogen activator

Thrombosis is a relatively rare event in children. In adults the incidence of thrombotic complications increases with increasing age.1 However, in childhood, newborns are at the greatest risk of thromboembolic complications.2 The incidence of clinically apparent neonatal thrombosis in recent reports varies from 5.1 per 100 000 births3 to 2.4 per 1000 admissions.4

There are numerous clinical and environmental conditions during infancy and childhood, such as peripartum asphyxia, infant of diabetic mother, renal disease, dehydration, septicaemia, malignant or autoimmune diseases, trauma or surgery, that result in increased thrombin generation with subsequent fibrin or thrombus formation.5 One of the major risk factors is undoubtedly the widespread use of indwelling intravascular catheters. The reported incidence is 13–14% in term infants,7 8 but rises to 64–85% in low and very low birthweight infants,9 although thrombosis prophylaxis with low dose heparin is used in probably all neonatal units when central lines are in use. Clinical outcome is often serious.10

Although small catheter related thrombi (CRTs) do not usually cause a problem if the line is simply removed, there is general agreement that treatment is needed in cases of large and fragile CRTs, because of the risk of embolism. This is particularly high in persistent ductus arteriosus and persistent foramen ovale. Treatment varies from centre to centre, with a wide range of administration, dosage, and duration of treatment, and different thrombolytic agents—for example, streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA).

rt-PA offers several theoretical advantages to the newborn infant, including short half time, minimal antigenicity, direct activation of plasminogen, lack of inhibition by α2 antiplasmin, and localisation of fibrinolytic activity.11 12 The literature on thrombolytic treatment with rt-PA for neonatal thrombotic disease contains numerous reports of single cases and small series,13 14 15 16 17 18 but no conclusions about the efficacy and safety of thrombolytic treatment in neonates can be drawn.

The aim of this study was to assess the efficacy and safety of a thrombolytic treatment for neonatal CRT, using a standardised rt-PA protocol.

Materials and methods

STUDY DESIGN

Over six years, all neonates in a critical condition—for example, severe neonatal sepsis, prolonged asphyxia, severe respiratory distress syndrome, see also table 2—who developed CRT were matched for possible fibrinolytic treatment. The diagnosis of formation of an intracardiac or great vessel thrombus was established by two dimensional echocardiography (see example in fig 1) and clinical examination in 14 neonates. All patients were monitored in the neonatal intensive care unit and were treated with rt-PA. All data were collected prospectively, including birth weight, gestational age, underlying disease, treatment regimen, clot patency, and complications or side effects.

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Thrombolysis with tissue plasminogen activator

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were used.ected catheter or peripheral venous lines V mostly by using a new central line. Sometimes echocardiography. Treatment was stopped in controlled at least daily by two dimensional ection studies, including prothrombin time, acti-

TREATMENT MONITORING

The effect of the thrombolytic treatment was controlled at least daily by two dimensional echocardiography. Treatment was stopped in the case of total clot lysis, partial clot lysis with only minor clot residue after five days of treatment, or complications, such as general or signif-

LITERATURE REVIEW

All reports of rt-PA use in neonates found in Medline by the keywords neonates-infan-

Results

The diagnosis of CRT was established by two dimensional echocardiography (except for pa-

Evaluation before treatment and contraindications

Before initiation of rt-PA treatment, coagula-

RT-PA protocol

By analysing rt-PA studies in adults, we created the rt-PA protocol given in fig 2. Babies were treated with rt-PA (Actilyse; Boehringer, Ingel-

Treatment monitoring

The effect of the thrombolytic treatment was controlled at least daily by two dimensional echocardiography. Treatment was stopped in the case of total clot lysis, partial clot lysis with only minor clot residue after five days of treatment, or complications, such as general or sig-

Figure 1 Thrombus formation in the right atrium (four chamber view). RV, Right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.

Figure 2 Schedule for thrombolytic treatment with rt-PA in neonatal period. Dose modification depended on the success of the thrombolytic treatment, complications, and coagulation status (see also table 2). Heparin prophylaxis was continued as long as central venous lines were required.

Over 30–60 minutes:

i.v. bolus of rt-PA 0.7 mg/kg

Continuous infusion with:

rt-PA 0.2 mg/kg/h + heparin 4–10 IU/kg/h

Dose modification:

rt-PA 0.1–0.3 mg/kg/h + heparin 4–10 IU/kg/h

After end of thrombolytic treatment: low dose heparin (2–6 IU/kg/h)

neumosthrombus formation-thrombolysis-rt-PAurokinase-streptokinase were reviewed. Basic data, thrombus location, rt-PA and heparin dosage regimens, treatment duration, compli-

After end of thrombolytic treatment:

low dose heparin (2–6 IU/kg/h)

Addi-

Gender was determined as far as possible.

cations, labour findings, and clot outcome were reviewed. Basic data, thrombus location, rt-PA and heparin dosage regimens, treatment duration, complications, labour findings, and clot outcome were determined as far as possible.

Results

The diagnosis of CRT was established by two dimensional echocardiography (except for pa-

The latter was included because of extreme immaturity with prolonged growth failure and because he remained in the neonatal intensive care unit.

Neonates with sepsis (71%), preterm delivery (64%), or respiratory distress syndrome (57%), and infants of diabetic mothers (43%) were most affected (table 2), whereas persistent pulmonary hypertension (29%), peripartum asphyxia, small size for gestational age (each 21%), meconium aspiration (14%), extreme immaturity (birth weight ≤1000 g or gestational age ≤28 weeks; 14%), patent ductus arteriosus, transient tachypnoea, and hypoglycaemia (each 7%) were rarer events.

In 10 cases, the precipitating cause was an umbilical venous catheter, in three cases (21%) an umbilical artery catheter, and in one case a central venous line.

Complete clot dissolution was documented in 11 patients, and partial clot lysis in two patients; in the first of these, the thrombus had disappeared at the time of discharge, and in the second the thrombus was completely dissolved by 9 months of age. Duration of lysis was on average three days (range one to five). The patency rate was 94%. In one patient (number 4), rt-PA administration was discontinued because of local bleeding from various venepuncture sites. In another patient (number 10), treatment had to be interrupted for three hours because of the same minor complications; after the infusion was stopped, the symptoms subsided and reinstitution of rt-PA treatment was successful. Severe complications such as intracranial bleeding were not seen. In patient number 2, we were able to reduce the rt-PA
Table 1  Selected values (taken from Weiner et al.) for components of the coagulation, coagulation inhibitor, and fibrinolytic system in neonates

<table>
<thead>
<tr>
<th>Coagulation tests</th>
<th>Reference values</th>
<th>Preferred values under treatment with rt-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preterm infants</td>
<td>Full term infants</td>
</tr>
<tr>
<td>PT (seconds)</td>
<td>14.6–16.9</td>
<td>11.8–13.0</td>
</tr>
<tr>
<td>PT (%)</td>
<td>31–48</td>
<td>46–68</td>
</tr>
<tr>
<td>aPTT (seconds)</td>
<td>80–168</td>
<td>40–42.9</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>160–550</td>
<td>270–312</td>
</tr>
<tr>
<td>ATIII (%)</td>
<td>0.38–0.59</td>
<td>0.62–0.78</td>
</tr>
<tr>
<td>ATIII (%)</td>
<td>28–38</td>
<td>63–78</td>
</tr>
<tr>
<td>Plasminogen (U/ml)</td>
<td>1.70–1.91</td>
<td>1.95–2.17</td>
</tr>
</tbody>
</table>

The reference values for the preterm infants are values at birth, and those for the full term infants are mean values during the first month of life. rt-PA treatment was monitored only by PT (in seconds and %), aPTT, ATIII (%), fibrinogen, and fibrin split products.

Table 2  Clinical data

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Gestational age (weeks)</th>
<th>Birth weight (g)</th>
<th>Underlying disease</th>
<th>Thrombus (focus and day of life)</th>
<th>rt-PA bolus (mg/kg)/ day</th>
<th>Heparin dose (IU/kg/day)</th>
<th>Clot outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>2200</td>
<td>IDM neonatal sepsis</td>
<td>In right atrium at day 9 UVC</td>
<td>0.7/0.2/4</td>
<td>100/10</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>5360</td>
<td>IDM hypoglycaemia</td>
<td>In right atrium at day 8 UVC</td>
<td>0.7/0.2–0.1/2</td>
<td>150</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>1980</td>
<td>IDM, RDS</td>
<td>In right atrium at day 21 UVC</td>
<td>0.7/0.2/1</td>
<td>250</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>4300</td>
<td>IDM transient tachypnoea</td>
<td>In right atrium at day 10 UVC</td>
<td>0.7/0.2/2</td>
<td>150+</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>3040</td>
<td>RDS, PPHN neonatal sepsis</td>
<td>In aorta at day 15 UCV and UAC</td>
<td>0.7/0.2/1</td>
<td>150</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>3450</td>
<td>Peripartal asphyxia PPHN, neonatal sepsis</td>
<td>In aorta at day 22 UCV and UAC</td>
<td>0.7/0.2–0.3/3</td>
<td>150</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>1190</td>
<td>RDS, PDA neonatal sepsis</td>
<td>In left atrium at day 12 UCV and UAC</td>
<td>0.7/0.2/1</td>
<td>150</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>1450</td>
<td>SGA, RDS neonatal sepsis</td>
<td>In right atrium at day 19 UCV</td>
<td>0.7/0.2–0.3/2</td>
<td>250</td>
<td>(+)</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>1315</td>
<td>IDM, RDS neonatal sepsis</td>
<td>In right atrium at day 6 UVC</td>
<td>0.7 (2 times)/0.2–0.3/2</td>
<td>150</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>4550</td>
<td>Peripartal asphyxia IDM, MAS, PPHN neonatal sepsis</td>
<td>In right atrium at day 16 UVC</td>
<td>0.7/0.2/4</td>
<td>100</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>1900</td>
<td>RDS, SGA neonatal sepsis</td>
<td>In right atrium at day 14 UCV</td>
<td>0.7/0.2/3</td>
<td>200/100–150/300</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>585</td>
<td>RDS, IVH neonatal sepsis</td>
<td>In right atrium (6th month) CVL and VAS</td>
<td>0.7/0.2/4 (2 times)</td>
<td>100</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>41</td>
<td>4200</td>
<td>Peripartal asphyxia IDS, PPHN</td>
<td>In right atrium at day 21 UVC</td>
<td>0.7/0.2/4</td>
<td>150</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>27</td>
<td>750</td>
<td>RDS, SGA neonatal sepsis</td>
<td>In aorta at day 3 UCV and UAC</td>
<td>0.7 (interrupted)</td>
<td>200 (interrupted)</td>
<td>+</td>
</tr>
</tbody>
</table>

rt-PA, Recombinant tissue plasminogen activator; IDM, infants of diabetic mothers; RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension; PDA, patent ductus arteriosus; SGS, small for gestational age; MAS, meconium aspiration; IVH, intraventricular haemorrhage; UVC, umbilical venous catheter; UAC, umbilical artery catheter; CVL, central venous line; VAS, ventricular-atrial shunt.

Discussion

The thrombotic risk of central lines used in neonates7–9 and the pathophysiology of thrombogenesis2 11 20–23 have been extensively reported. Since the use of central catheters in neonates, CRT is an increasingly observed complication,7 20 and, although overall it is still rare, in major neonatal units it is increasing.

Effective and safe thrombolytic treatment is essential in the management of neonates and infants with life threatening thrombosis. Efficient thrombolytic agents available are streptokinase, urokinase, and rt-PA. Administration of streptokinase has been abandoned because of its antigenic qualities, relatively long half time (20–30 minutes), and systemic side effects.24 Nowadays, rt-PA is commonly recommended, because of its short half time (about five minutes), non-antigenic qualities, and local specific action on plasminogen bound fibrin.25

![Image](http://fn.bmj.com/)

www.archdischild.com
Table 3  Literature review (Medline) on recombinant tissue plasminogen activator (rt-PA) treatment in neonatal period

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>rt-PA dose</th>
<th>Clot outcome</th>
<th>Complications/side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bopus (mg/kg)</td>
<td>Infusion (mg/kg/h)</td>
<td>Duration (h)</td>
</tr>
<tr>
<td>Anderson†††</td>
<td>4</td>
<td>None</td>
<td>0.05</td>
<td>96–240</td>
</tr>
<tr>
<td>Diligio††††††</td>
<td>3</td>
<td>0.5</td>
<td>0.04–0.08</td>
<td>58</td>
</tr>
<tr>
<td>Nowak-Göttli†††</td>
<td>19</td>
<td>0.1–0.75</td>
<td>0.03–0.375</td>
<td>0.5–240</td>
</tr>
<tr>
<td>Farnoux††††††</td>
<td>16</td>
<td>0.1</td>
<td>0.3</td>
<td>3</td>
</tr>
<tr>
<td>Weiner††††††</td>
<td>7</td>
<td>None</td>
<td>0.1–0.5</td>
<td>6–39</td>
</tr>
</tbody>
</table>

Single cases

- Zenz: 2 patients, Bopus 0.1–0.5 mg/kg, Infusion 0.25 mg/kg/h, Duration 4–9 h, Clot outcome Complete 1, Complications: None
- Trowitzsch: 1 patient, Bopus 0.3 mg/kg, Infusion 0.2 mg/kg/h, Duration 7 h, Clot outcome Complete, Complications: None
- Kennedy: 1 patient, Bopus 0.47 mg/kg, Infusion 0.3 mg/kg/h, Duration 3 h, Clot outcome Complete, Complications: Amputation of toes
- Levy: 2 patients, Bopus 0.47 mg/kg, Infusion 0.47 mg/kg/h, Duration 2–72 h, Clot outcome Complete, Complications: Local bleeding
- Deeg: 1 patient, Bopus 0.5 mg/kg, Infusion 0.2 mg/kg/h, Duration 48 h, Clot outcome Complete, Complications: IVH extension
- Van Overmeire: 1 patient, Bopus 0.5 mg/kg, Infusion 0.2 mg/kg/h, Duration 3 h, Clot outcome Complete, Complications: None
- Schneider: 1 patient, Bopus 0.1 mg/kg, Infusion 0.2 mg/kg/h, Duration 6 h, Clot outcome Complete, Complications: None
- Guerin: 2 patients, Bopus 0.05–0.2 mg/kg, Infusion 0.03 mg/kg/h, Duration 12–24 h, Clot outcome Complete, Complications: None
- Berger: 2 patients, Bopus 0.1 mg/kg, Infusion 0.3 mg/kg/h, Duration 3 h, Clot outcome Complete, Complications: None
- Rieß: 1 patient, Bopus 0.1–0.2 mg/kg, Infusion 0.03–0.06 mg/kg/h, Duration 34 h, Clot outcome Complete, Complications: None
- Thui⊥: 1 patient, Bopus 0.2 mg/kg, Infusion 0.4 mg/kg/h, Duration 2 h, Clot outcome Complete, Complications: Bleeding
- Ahiwaya: 1 patient, Bopus 0.5 mg/kg, Infusion 0.5 mg/kg/h, Duration 10 h, Clot outcome Complete, Complications: None
- Smet: 2 patients, Bopus None, Infusion 0.1–0.4 mg/kg/h, Duration 48–264 h, Clot outcome Partial, Complications: Significant bleeding
- Seibold-Weiger: 1 patient, Bopus 0.08 mg/kg, Infusion 0.12 mg/kg/h, Duration 12 h, Clot outcome Complete, Complications: Local bleeding
- Kandler: 1 patient, Bopus 0.02 mg/kg, Infusion 0.36 mg/kg/h, Duration 36 h, Clot outcome Complete, Complications: None
- Daoud: 1 patient, Bopus 0.3 mg/kg, Infusion 0.3 mg/kg/h, Duration 3 h, Clot outcome Complete, Complications: None
- Torkington**: 1 patient, Bopus 0.15 mg/kg, Infusion 0.3–0.75 mg/kg/h, Duration 3 h, Clot outcome Complete, Complications: NEC
- Giuffre: 2 patients, Bopus None / 0.5 mg/kg, Infusion 0.5 mg/kg/h, Duration 4–6 h, Clot outcome Complete, Complications: None
- Grieß: 1 patient, Bopus 0.1 mg/kg, Infusion 1 mg/kg/h, Duration 15 h, Clot outcome Complete, Complications: None
- Di Bernardo: 1 patient, Bopus 0.3 mg/kg, Infusion 0.3 mg/kg/h, Duration 16 h, Clot outcome Partial, Complications: IVH, bleeding
- Krienke: 2 patients, Bopus 0.3–0.5 mg/kg, Infusion 0.02–0.04 mg/kg/h, Duration 8–64 h, Clot outcome Complete 1, Complications: None
- Glover: 1 patient, Bopus 0.48 mg/kg, Infusion 0.27 mg/kg/h, Duration 6 h, Clot outcome Complete, Complications: IVH
- Klünger††††††: 1 patient, Bopus 0.01 mg/kg, Infusion None, Duration —, Clot outcome Partial, Complications: Vascular spasm
- Malm: 1 patient, Bopus 0.05 mg/kg, Infusion None, Duration —, Clot outcome Complete, Complications: IVH

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>rt-PA dose</th>
<th>Clot outcome</th>
<th>Complications/side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bopus (mg/kg)</td>
<td>Infusion (mg/kg/h)</td>
<td>Duration (h)</td>
</tr>
<tr>
<td>Sum: 80</td>
<td>0.0–0.75</td>
<td>0.02–1</td>
<td>½–264</td>
<td>Complete 55</td>
</tr>
<tr>
<td>Own collection</td>
<td>14</td>
<td>0.7</td>
<td>(0.1–0.2)</td>
<td>24–120</td>
</tr>
</tbody>
</table>

Only data of reports with complete information were included. Requests for entire literature list of single cases to jhartmann@hdz-nrw.de. The bolus was a short infusion (10–60 minutes).

*Data collection was performed as a meta-analysis of all reports; †up to four additional rt-PA infusions were given at intervals of 12–24 hours; ‡only data of reports with complete information were included. Requests for entire literature list of single cases to jhartmann@hdz-nrw.de. The bolus was a short infusion (10–60 minutes).

There are established protocols for fibrinolytic treatment with rt-PA in adults. However, there is still very little experience with fibrinolytic treatment in the neonatal period. Treatment for neonatal thrombosis remains controversial, guidelines are available but rare, and randomised double blinded trials are still lacking. Therefore many doctors follow adult guidelines. Table 3 gives an overview of studies focusing on thrombolytic treatment with rt-PA in neonatal arterial and venous diseases, including CRT and spontaneous thrombotic disease. The overall patency rate of 94% (68% for complete clot dissolution and 26% for partial clot dissolution) is comparable with our experience (94% patency rate: 79% complete clot dissolution and 14% partial clot dissolution). Comparison of the reports of a low dose rt-PA regimen (0.02–0.08 mg/kg/h) with those of a high dose regimen (0.1–1 mg/kg/h) shows an apparently significant difference in patency rate (81% vs. 95%), although in the first group an initial bolus was given. In both groups, complications ranged from none to severe, but, for both patency rate and complications, data collection was too random to draw any conclusions.

Another comparison between bolus or no bolus shows interesting results. Whereas in the bolus group 95% of the patients were detected with positive clot outcome (39 of 56 patients (70%) with complete, and 25 of 56 patients (25%) with partial, clot dissolution), in the no bolus group only 88% (16 of 23 (67%) with complete, and 5 of 24 (21%) with partial, clot dissolution) showed an effect. Again, the groups are very small and bolus dose varies widely, so that conclusions should be made carefully. However, these results seem to justify an rt-PA bolus before continuous infusion.

In addition, thrombosis prophylaxis with low dose heparin is widely recommended, but the administration of heparin is controversial and the different regimens ranged from no heparin to low dose treatment during thrombolytic treatment. In most reports, administration of low dose heparin (an average of 5 IU/kg/h) was recommended. Statistical analysis of this data collection gives no further information about suitable thrombolytic treatment in the neonatal period because of
inhomogeneous and incomplete data collection in several reports. Nevertheless, thrombolytic treatment with rt-PA combined with low dose heparin administration seems to be very efficient and safe.

There are still some reports of the successful use of urokinase and even streptokinase for thrombosis in the neonatal period. Randomised double blind trials, based on results from adult patients, have led to the recommendation that rt-PA should be used on the one hand and equal benefits for rt-PA and urokinase on the other. rt-PA seems to act faster and to have more side effects. Interest-

ingly, several authors reported successful rt-PA treatment after insufficient trials with urokinase.

Reports differ with regard to the incidence of complications. In our experience, severe complications were rare and intracerebral haemorrhage did not occur. This is in agreement with other reports.

To summarise, the literature does not provide enough information to enable recommendations to be made about rt-PA use in the newborn. The present rt-PA protocol with high dose infusion after an initial bolus seems to be an efficient and safe conservative procedure for neonatal clot dissolution. Although a homogeneous collection of cases has been presented, the study has several limitations. However, we feel that these promising results can be used as a starting point for further investigation.

3 Nowak-Göttl U, Kreuz W, Göbel U. Neonatal sympto-
4 Manco-Johnson MJ. Disorders of hemostasis in childhood:
5 Berman W, Fripp RR, Yabek SM. Great vein and right atrial
6 Manco-Johnson MJ. Diagnosis and management of throm-
79.
82
84.
85.
11. Schmidt B, Andrew M. Report of scientific and standardiza-
14. Zenna LA, Dougherty VH, Knight ML, et al. Successful treat-
Treatment of neonatal thrombus formation with recombinant tissue plasminogen activator: six years experience and review of the literature
J Hartmann, A Hussein, E Trowitzsch, J Becker and K-H Hennecke

Arch Dis Child Fetal Neonatal Ed 2001 85: F18-F22
doi: 10.1136/fn.85.1.F18

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