Anticoagulation Therapy and Imaging in Neonates With a Unilateral Thalamic Hemorrhage Due to Cerebral Sinovenous Thrombosis

Karina J. Kersbergen, BM; Linda S. de Vries, MD, PhD; H.L.M. (Irma) van Straaten, MD, PhD; Manon J.N.L. Benders, MD, PhD; Rutger A.J. Nievelstein, MD, PhD; Floris Groenendaal, MD, PhD

Background and Purpose—Cerebral sinovenous thrombosis is a rare disorder with a high risk of an adverse neurodevelopmental outcome. Until now, anticoagulation therapy has been restricted to neonates without an associated parenchymal hemorrhage. In this study, we describe sequential neuroimaging findings and use of anticoagulation therapy in newborn infants with a unilateral thalamic hemorrhage due to cerebral sinovenous thrombosis.

Methods—Ten neonates with a unilateral thalamic hemorrhage and cerebral sinovenous thrombosis were studied. Diagnosis was suspected using cranial ultrasound and confirmed with MRI/MR venography. Eight infants had a repeat MRI at 3 to 7 months. Neurodevelopmental outcome was assessed from 3 months until 5 years.

Results—One infant died. Seven infants were treated with low-molecular-weight heparin. No side effects were noted. MRI showed involvement of multiple sinuses, additional intraventricular hemorrhage, and white matter lesions in all infants. Recanalization was present on the repeat MRI at 3 months in all infants. Treatment was delayed in one infant and anticoagulation was started only after extension of the thalamic hemorrhage. He required a ventriculoperitoneal drain for posthemorrhagic ventricular dilatation and developed cerebral visual impairment and global delay. Two other infants showed global delay and one of them also developed postneonatal epilepsy. Mild asymmetry in tone was present in 4 children.

Conclusions—Cerebral sinovenous thrombosis was found in 10 neonates with unilateral thalamic hemorrhage. Diagnosis was suspected on cranial ultrasound and confirmed with MRI/MR venography. Treatment with low-molecular-weight heparin in newborn infants with a thalamic hemorrhage due to cerebral sinovenous thrombosis appears to be safe and should be considered. Long-term follow-up will be needed to assess cognitive outcome. (Stroke. 2009;40:2754-2760.)

Key Words: anticoagulation ■ neuroradiology ■ pediatric stroke ■ venous thrombosis

Cerebral sinovenous thrombosis (CSVT) is a rare disorder in neonates with an estimated incidence of approximately 0.41 per 1000 live births.1,2 Diagnosis of CSVT is difficult due to nonspecific presentation. Most infants present with seizures, lethargy, and apnea,2,3 but presentation can also be asymptomatic.3 Congestion in an occluded vessel may lead to a usually unilateral, thalamic hemorrhage. Although the disorder has been known since the early 1930s,6 it is today more often recognized due to the increasing sensitivity of modern neuroimaging techniques. There are several known risk factors for CSVT such as perinatal complications and asphyxia, which are different in neonates compared with older children.2,4 Treatment for CSVT is limited to symptomatic treatment. During the last few years, anticoagulation therapy has been suggested to avoid thrombus enlargement but is usually restricted to neonates without an associated parenchymal hemorrhage.2,4,7-9 Over 50% of earlier reported neonates with CSVT have an adverse outcome and mortality is high.2,9 In surviving children with CSVT, cognitive impairment, motor impairment, and/or epilepsy are found in 46% to 79%.2,3,9,10 The presence of associated cerebral infarct appears to be predictive of an adverse neurological outcome.1,2,4,9,10

In neonates with an intraventricular hemorrhage (IVH) and a unilateral thalamic hemorrhage diagnosed using cranial ultrasound, CSVT should be considered as the most likely diagnosis and further neuroimaging is indicated to confirm the diagnosis.5,11 In the present study, we describe neuroimaging findings as well as the effect of anticoagulation therapy on recanalization in neonates with a thalamic hemorrhage due to CSVT in 2 Level III Neonatal Intensive Care Units (NICUs) in The Netherlands.

Subjects and Methods

Patients

Patients with a diagnosis of CSVT and thalamic hemorrhage on neuroimaging who were admitted during the neonatal period (0 to 28 days) were included. At the time of inclusion, all patients were already on a cranial ultrasound follow-up.

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Subjects and Methods

Patients

Patients with a diagnosis of CSVT and thalamic hemorrhage on neuroimaging who were admitted during the neonatal period (0 to 28
days) to the NICU of the Wilhelmina Children’s Hospital between April 2003 and October 2008 and to the NICU of the Isala Clinics between January 2006 and October 2008 were studied. The diagnosis was based on clinical presentation and neuroimaging findings. Both term and preterm infants were included.

A total of 26 infants with CSVT were identified and 12 of them showed a thalamic hemorrhage on cranial ultrasound. One infant had a thalamic hemorrhage, CSVT, and multiple cerebral abnormalities, probably due to nonaccidental injury, and was excluded. We also excluded one infant with a thalamic hemorrhage but no obvious signs of CSVT on subsequent MR venography. The remaining 10 infants are the subjects of this study.

Cranial Ultrasound
Cranial ultrasound (cUS) was performed in all infants immediately after admission, as is the protocol in our NICUs. The examination was done using an Aplio XG scanner (Toshiba Medical Systems, Zoetermeer, The Netherlands) with a multifrequency transducer (5 to 8.5 MHz). The examination was performed 2 to 3 times during the first week of admission and one to 2 times per week until discharge to assess the development of associated posthemorrhagic ventricular dilatation.

Magnetic Resonance Imaging
All infants had at least one MRI during the first week after admission to the neonatal unit. The MR investigations were performed on a 1.5-T ACS-NT system or 3.0-T whole-body Achieva system (Philips Medical Systems, Best, The Netherlands). According to our protocol, a follow-up MRI was performed 3 to 5 months later and at the age of 5 to 7 years in those patients who survived the neonatal period. MRI included T1-weighted sagittal images, T2-weighted axial images, T1-weighted or inversion recovery axial images, and diffusion-weighted images in neonates. In older infants, sagittal T1, axial inversion recovery, axial T2, and fluid-attenuated inversion recovery images were made. During the last 4 years, phase contrast sagittal images were added to the protocol.

Table 1. Clinical Records

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<th>Child</th>
<th>Gestational Age at Birth, Weeks</th>
<th>Gender</th>
<th>Mode of Delivery</th>
<th>Birthweight (g)</th>
<th>Perinatal Asphyxia †</th>
<th>Birthweight Centile*</th>
<th>Presenting Symptoms</th>
<th>Age at Last Follow-Up Visit, Months</th>
<th>Outcome</th>
<th>Postneonatal Epilepsy</th>
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<td>M</td>
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<td>2, 5, 6§</td>
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<td>65</td>
<td>0</td>
<td>Prematurity, respiratory insufficiency, possible intrauterine infection</td>
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<td>Seizures</td>
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<td>7, 9, 10</td>
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<td>Seizures</td>
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<td>2</td>
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<td>F</td>
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<td>None</td>
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<td>1</td>
<td>Seizures</td>
<td>12</td>
<td>65</td>
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</table>

*Percentiles according to the new Dutch perinatal growth charts (www.perinatreg.nl/referentiecurven).
†Asphyxia as defined previously.12
‡Patients treated with anticoagulation.
§With resuscitation.
M indicates male; F, female; SVD, spontaneous vaginal delivery, PPROM, prolonged premature rupture of membranes; cs, cesarean section; NA, not available.

Figure 1. Left, Cranial ultrasound of Child B shows a left-sided thalamic hemorrhage and small ipsilateral IVH. Mild increase in echogenicity of the periventricular white matter is seen bilaterally. Right, Lack of flow in the superior sagittal sinus with Doppler assessment.
Diagnosis of CSVT
In all children, the initial cUS performed after admission, showing an IVH and an ipsilateral thalamic hemorrhage, was highly suggestive of a CSVT. A definite diagnosis was made when MR venography (MRV) was performed showing clear lack of flow in a sinus at flow velocities of 300 and 150 mm/s. We re-evaluated the MRIs of all infants to determine the site and extent of the thrombosis and the thalamic hemorrhage. We also looked for associated white matter injury and infarction.

Clinical Data
The following data were retrieved from the charts: gender, gestational age at birth, parity of the mother, birth weight and centile,
complications during pregnancy, mode of delivery, complications during delivery, Apgar scores, umbilical cord pH (if measured), age at onset of symptoms, initial presentation, need for mechanical ventilation, occurrence of sepsis or meningitis, blood transfusions, treatment of the convulsions, course during the NICU admission, and possible treatment with anticoagulation. Perinatal asphyxia was defined as described previously.12

Therapy
Since September 2005, infants with CSVT were treated with subcutaneous low-molecular-weight heparin (LMWH) 2 times daily for a period of 3 months. Seven of the 10 infants were treated. One infant died due to severe lung hypoplasia before therapy could be initiated and 2 surviving infants were born before LMWH therapy became standard therapy in our centers.

The aim of the therapy was to reduce growth of the thrombus. Therapy was started with 150 to 200 U/kg dalteparin (Fragmin) subcutaneously and the dose adjusted based on anti-Xa levels, aiming at values between 0.5 and 1.0 U/mL. Treatment was started on the day of diagnosis. At 3 months of age, follow-up MRIs and MRVs were made assessing flow over the occluded veins. In case of positive flow through the previously thrombosed vein, anticoagulation therapy was stopped.

Follow-Up
Neurodevelopmental outcome was measured at regular visits to the follow-up clinic. In the first year of life, standardized items from Amiel-Tison, Grenier,13 and Touwen14 and the Alberta Infant Motor Scale15 were used to assess development. The Griffiths’ developmental scale16 was used to assess the developmental quotient between 12 and 24 months. The development and time of onset of postneonatal epilepsy was also recorded.

Informed consent from the parents and permission from our medical ethical review board were obtained.

Results
Patients
Clinical characteristics of the infants are summarized in Table 1. Three infants were born prematurely (gestational ages 32, 36, and 36 weeks). Mean gestational age of the full-term neonates was 40.4 weeks (SD, 1.5 weeks). Eight of the 10 neonates were male (80%). Three mothers had pre-eclampsia. One mother had pregnancy-induced diabetes and also a fever during delivery. Four neonates had perinatal asphyxia (40%). One neonate had birth weight below the 2.3rd centile (10%). Age at presentation ranged from the day of birth to 19 days after birth with 7 neonates presenting during the first week of life (70%). Eight of 10 neonates presented with seizures (80%). One neonate needed resuscitation because of severe lung hypoplasia and one neonate was admitted because of feeding difficulties and was neurologically asymptomatic. Findings on her routine ultrasound (IVH and a unilateral thalamic hemorrhage) were reasons for further investigations.

Cranial Ultrasound
Nine infants had a bilateral intraventricular hemorrhage and a unilateral thalamic hemorrhage on ultrasound (Figure 1). One infant, who was asymptomatic, had a unilateral thalamic hemorrhage with a small ipsilateral IVH. Increased echogenicity of the periventricular white matter was seen in 8 infants. Posthem-
orrhagic ventricular dilatation developed in 4 infants, which required intervention (a ventriculoperitoneal shunt) in one. This last infant showed an extension from a unilateral thalamic hemorrhage, diagnosed on cUS and MRI on Day 3, to a bilateral thalamic hemorrhage on cUS and MRI on Day 7.

Magnetic Resonance Imaging
MRI and MRV findings of our patients are shown in Table 2. All patients had involvement of multiple sinuses seen on MRV. The straight sinus was involved in 9 of our patients (90%). MRI findings regarding a unilateral or a bilateral IVH were similar to diagnoses made with cUS. All patients had associated punctate lesions in the periventricular white matter. In 2 infants, a repeat MRI was performed during the first week to assess propagation of thrombosis. In the first infant, CSVT was suspected on the first MRI and confirmed with a second MRI 1 week later. He was treated with LMWH and is currently doing well. In the second infant, CSVT with a left-sided thalamic hemorrhage was seen on Day 3, but extension to a bilateral thalamic hemorrhage was seen on Day 7 (Figure 2). In this case, LMWH was started on the day of the second MRI. This infant developed severe posthemorrhagic ventricular dilatation and required a ventriculoperitoneal shunt.

Eight infants had a repeat MRI at 3 months of age and one at 7 months. The MRIs at 3 to 7 months showed total recanalization in 6 of the 8 patients and partial recanalization in 2 (Figure 3). Cavitation at the site of the thalamic hemorrhage was seen in 5 infants. Three patients showed early gliotic changes in the periventricular white matter. Two of them had moderate frontal atrophy and in one, delayed myelination of the internal capsule was present. Two other patients also had frontal atrophy and 2 other patients showed delayed myelination of the internal capsule. Since the introduction of anticoagulation treatment at our centers, all 7 surviving infants were treated with LMWH. There was no increase in the thalamic hemorrhage in any of the infants and no side effects were reported.

Follow-Up
One infant (A) died after withdrawal of intensive care treatment because of severe intracranial pathology. This infant also had severe lung hypoplasia after ruptured membranes at 16 weeks of gestational age. One child (G) had 2 episodes of clinical seizures at 4 years of age. Epileptic activity could not be confirmed with an electroencephalogram. At present, he is seizure-free without medication at the age of 5 years. One child (E) developed epilepsy at the age of 8 months, for which he received antiepileptic medication. Infant J who developed bilateral thalamic hemorrhages and posthemorrhagic ventricular dilatation required placement of a ventriculoperitoneal shunt and developed global developmental delay and cerebral visual impairment. Four of the surviving children have mild asymmetry in tone (40%). They are all currently >1 year of age (B,G, H, J), and do not show any signs of a developing hemiplegia. Only 3 of the survivors have been seen when they were >18 months of age. All 3 had a developmental quotient within the normal range using the Griffiths’ developmental scale.

Discussion
In this study, we have shown that treatment with LMWH appears to be safe in neonates with CSVT even in the presence
of a thalamic hemorrhage. Because our study was nonrandomized, contained small numbers, and had a relatively short neurodevelopmental follow-up, we were unable to assess whether treatment was associated with a faster recanalization of the occluded vessels and with a better long-term outcome.

Eight of 10 patients presented with seizures. A probable diagnosis of CSVT was made in all infants using routine cranial ultrasound examination performed as part of the admission procedure. Diagnosis was confirmed using MRI/MRV.

LMWH was given although a thalamic hemorrhage was present on MRI. In the literature, there is concern about the extension of a hemorrhage after LMWH. In our small study population, this was not observed. No extension of hemorrhage or other complications were noted and recanalization of the obstructed sinus was seen in all infants on the repeat MRI performed at 3 months. In one infant (J), in whom treatment was delayed to assess propagation of the thrombosis, progression from a unilateral to a bilateral thalamic hemorrhage was seen on the second MRI 4 days later. This is the only infant who needed a ventriculoperitoneal shunt and has severe adverse sequelae with cerebral visual impairment (Figure 2). LMWH was chosen as the anticoagulant drug of choice because of the therapeutic profile to prevent propagation of the clot with a small risk of bleeding in contrast with the choice of fibrinolytic agents.

According to previous studies, the presence of associated parenchymal infarction is a predictor of adverse neurological outcome in neonates with CSVT. Patients with an IVH as well as a thalamic hemorrhage are at risk to have an adverse outcome with neurological sequelae and especially cerebral palsy. Of our 4 children with mild asymmetry in tone, 2 were not treated with anticoagulation. From one of the nontreated children, Child G, a follow-up MRI at 5 years shows some asymmetry in myelination of the internal capsule along with gliotic changes in the periventricular white matter of the right frontal lobe (Figure 4). Because the 7 infants who did receive treatment are not yet 2 years old, we cannot yet give reliable results about their cognitive outcome. We do however know that 4 of these infants are currently doing well at 7 to 18 months of age, whereas 3 developed global developmental delay, in one associated with postneonatal epilepsy.

Cranial ultrasound performed immediately after admission in all neonates with neonatal seizures and/or apneas can help to make a diagnosis of CSVT. When IVH is seen and especially when this is associated with a unilateral thalamic hemorrhage, additional MRI and MRV studies should be performed within the next 24 to 48 hours to confirm the diagnosis and consider anticoagulation. It was previously shown by Wu and colleagues that IVH in full-term infants is often associated with CSVT. They showed a diagnosis of CSVT in 34% and suspected it in another 19% of term neonates with an IVH. Neonates with IVH and a thalamic hemorrhage were more likely to have CSVT than those with IVH without thalamic involvement.
Others have suggested that CT should be used for imaging because of the easier and earlier accessibility, although MRI is the imaging method of choice.\(^2,14\) In our experience, MRI and MRV are excellent techniques to diagnose cerebral abnormalities, including sinovenous thrombosis in patients admitted to a NICU. Associated punctate white matter lesions will be better seen with MRI than with CT. Furthermore, a major disadvantage of CT is the use of ionizing radiation, which theoretically may induce secondary cancers.\(^19\) In addition, CT venography requires the intravenous application of an iodinated contrast agent with a small but nonnegligible risk of induction of an allergic reaction, (transient) hypothyroidism, or contrast nephropathy.\(^20,21\)

All patients were noted to have involvement of several sinuses on the MRI. The straight sinus was most often affected. Because we focused on infants with an associated thalamic hemorrhage, it is not unexpected that thrombosis of the straight sinus was more often diagnosed than in previous studies about CSVT.\(^3,4,9,22,23\)

In our cohort, we found a male predominance, consistent with previous studies.\(^4,24\) In agreement with the 2 largest studies reported so far, those from deVeber and colleagues\(^2\) and Fitzgerald and colleagues,\(^4\) perinatal complications and perinatal asphyxia were frequent findings in our patients. All our symptomatic patients had seizures at some point during their stay in the NICU and 80% presented with seizures. All but 2 of the symptomatic patients needed at least 2 different antiepileptic drugs to control the seizures.

This study has several limitations. First, one of our patients was asymptomatic. Because cUS is not performed in all neonates admitted outside the NICU, we cannot exclude that the real incidence of CSVT with thalamic hemorrhage is higher than is reported in this study. Asymptomatic CSVT is a known entity previously described by Golomb and colleagues.\(^25\) Second, we excluded one patient with thalamic hemorrhage without CSVT on MRI/MRV. It is possible that small thromboses were not detected by MRI/MRV. This could also have led to a lower incidence. Finally, we cannot yet draw any conclusions about differences in cognitive outcome between treated and nontreated neonates because we only recently started treatment with LMWH. A multicenter randomized, controlled trial is needed to study this prospectively.

In conclusion, we demonstrated that treatment with LMWH, using our clinical dosage scheme, appears to be safe in neonates with CSVT even in the presence of a thalamic hemorrhage. We therefore suggest that in neonates with a thalamic hemorrhage and a proven CSVT, treatment with LMWH should be considered. Further studies are warranted to confirm our preliminary observations.

Acknowledgments
We thank C. Koopman-ESseboom, MD, PhD, and I. C. van Haastert, MA, for performing assessments in the follow-up clinic and the MRI technicians for their support and advice.

Disclosures
None.

References
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*Stroke*. 2009;40:2754-2760; originally published online June 18, 2009;
doi: 10.1161/STROKEAHA.109.554790

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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