Low-molecular-weight heparins, such as enoxaparin, are often used to treat thrombosis in infants. We present 4 infants with diffuse brain injury who developed cerebral venous sinus thrombosis or deep vein thrombosis and were treated with enoxaparin. These infants subsequently developed subdural hemorrhages, and enoxaparin was stopped. In 3 cases, the subdural hemorrhages were found on routine surveillance brain MRI, and in 1 case imaging was urgently obtained because of focal seizures. Two patients needed urgent neurosurgical intervention, and all subdural hemorrhages improved or resolved on follow-up imaging. Each infant developed severe neurologic deficits, probably from the coexisting diffuse brain injury rather than from the subdural hemorrhages themselves. The risk of intracranial hemorrhage from enoxaparin may be accentuated in patients with diffuse brain injury, and careful consideration should be given before treatment in this population. Pediatrics 2014;134:e889–e893
Neonates and infants receive antithrombotic therapy such as low-molecular-weight heparin (LMWH) for treatment of cerebral venous sinus thrombosis (CVST) or deep vein thrombosis (DVT). Antithrombotic therapy with LMWH is reported to be safe for infants, because resultant intracranial hemorrhage (ICH) is rare, and in cases with ICH, there is usually no significantly increased morbidity or mortality from the ICH. However, anticoagulation in the setting of co-existing diffuse brain injury, such as hypoxic–ischemic injury, has not been well studied.

**METHODS**

We studied clinical and radiographic features of 4 infants (ages 1–11 weeks) who each had CVST or DVT and comorbid diffuse brain injury and were treated with enoxaparin, with goal anti-Xa levels between 0.5 and 1 U/mL. The University of Michigan institutional review board approved this study, and a waiver of informed consent was granted.

**RESULTS**

The clinical attributes of the 4 cases are summarized in Table 1.

**Case 1**

A term infant girl, born with respiratory depression in the setting of maternal chorioamnionitis, was presumed to be septic. She developed seizures, evolving to status epilepticus on day of life (DOL) 2. A brain MRI with magnetic resonance venogram (MRV) on DOL 7 showed extensive cerebral injury and a probable right transverse sinus thrombosis. Enoxaparin was initiated, and 4 days later, a surveillance cranial ultrasound showed no apparent ICH. She was discharged from the hospital after 2.5 weeks, on phenobarbital and enoxaparin.

A surveillance MRI performed at 2.5 months of age showed large bilateral subdural hematomas (SDHs) at various stages of maturation, 8 × 3.5 cm on the right and 8 × 2.7 cm on the left, with mass effect (Fig 1A). There was extensive cystic encephalomalacia and evidence of laminar necrosis. The anti-Xa level was 0.29 U/mL, and enoxaparin was discontinued. Her anti-Xa levels never exceeded 1.06 U/mL. The patient was admitted to the ICU. She was found to have infrequent seizures on continuous video EEG monitoring, and she underwent bilateral parietal craniotomies for evacuation of the SDH. Whether the underlying brain injury was caused by ischemia, infection, a metabolic derangement, or another cause is unclear. Her SDH improved significantly on repeat MRI scans (Fig 1E). At 12 months of age, she continued to need anticonvulsant medications and displayed severe neurologic impairment, with microcephaly and a static head circumference equal to the 50th percentile for a 3-week-old.

**Case 2**

An 11-week-old full-term girl who was previously healthy presented with vomiting, fever, and lethargy and was found to have severe hypernatremia with a sodium of 189 mmol/L. On admission, a head CT scan showed a hyperdensity in the right transverse sinus, and a brain MRI with MRV done shortly thereafter confirmed that there was a CVST in the right transverse sinus and superior sagittal sinuses. She was started on enoxaparin, and soon thereafter, she developed seizures, evolving into status epilepticus.

A repeat head CT scan with venogram on hospital day 3 showed no hemorrhage, with a stable transverse sinus thrombus. On hospital day 9, a head CT scan revealed poor gray/white differentiation but no hemorrhage. A brain MRI with MRV on hospital day 15 demonstrated impeded diffusion in bilateral thalami, cerebral peduncles, and the corpus callosum, with improvement in the CVST. On hospital day 40, a surveillance brain MRI with MRV showed bilateral SDH of 13 mm thickness (Fig 1B) and extensive impeded diffusion in the cerebral hemispheres. Her anti-Xa level was 0.47 U/mL, and enoxaparin was withdrawn. Her maximum anti-Xa was 1.73 U/mL, occurring 3 days after initiation of enoxaparin. This patient underwent surgery for SDH drainage, and a cranial ultrasound on postoperative day 3 found no significant SDH. She was discharged from the hospital a few days later, after a 6-week hospitalization.

One month after discharge, a repeat brain MRI with MRV showed improvement in the size of her SDH, with no worsening of the CVST. Four months later a follow-up brain MRI showed marked decrease in size of the SDH and also demonstrated brain atrophy, thought to be from the metabolic injury due to hypernatremia and dehydration (Fig 1F).

At 9 months of age, she had severely impaired development and microcephaly with a static head circumference equal to the 50th percentile for a 2-month-old, and she was almost continuously irritable and crying. The cause of the severe hypernatremia has not been definitively identified.

**Case 3**

A 21-day-old infant boy who was born at 35 weeks’ gestational age with Pierson’s syndrome (congenital nephrotic syndrome withdependence on peritoneal dialysis and microcoria), with a history of methicillin-resistant *Staphylococcus aureus* sepsis, developed a catheter-associated thrombus in the right internal jugular vein. He was placed on enoxaparin, but a repeat ultrasound of the vessel 2 days later revealed propagation of the clot into the wall of the internal jugular
vein. He was given an unfractionated heparin infusion for 1 day and then converted back to enoxaparin. Routine cranial ultrasounds at DOL 4, 28, and 37 found no hemorrhage. A brain MRI at DOL 42 showed diffusely reduced brain volume with worsening brain atrophy and increased extraaxial space. On DOL 70, this infant developed seizures, which evolved into status epilepticus and necessitated treatment with phenobarbital, midazolam infusion, levetiracetam, fosphenytoin, and topiramate. A cranial ultrasound on the same day revealed no evidence of hemorrhage. On DOL 77, a brain MRI demonstrated a 4.5 × 2.7 × 5.3 cm left frontal/parietal SDH (Fig 1C), along with worsening brain atrophy. His anti-Xa level was 0.7 U/mL, and enoxaparin was discontinued.

**TABLE 1** Summary of Clinical Attributes of 4 Infants Who Developed SDH During Treatment With Enoxaparin

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age of Initiation of LMWH</th>
<th>Reason for Anticoagulation</th>
<th>Age at Finding of SDH</th>
<th>SDH Characteristics [Associated Symptoms]</th>
<th>Comorbid Brain Injury</th>
<th>Neurosurgical Intervention</th>
<th>Follow-up Imaging</th>
<th>Neurologic Follow-up</th>
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</table>
| 1           | 1 wk                     | Right transverse CVST     | 2.5 mo               | Bilateral SDH, 2.7–3.5 cm thick, with 8 cm cranio-caudal extension and 1 cm mass effect [incidental finding] | Severe cystic 
encephalomalacia and 
laminar necrosis from unknown cause | Yes | Repeat MRI at 2 and 6 mo after bleed, with improvement in size of SDH | Severely impaired, treatment-resistant epilepsy at 12 mo of age. |
| 2           | 11 wk                    | Right transverse and superior sagittal CVST | 4 mo | Extensive bilateral SDH, 1.3 cm thick [incidental finding] | Severe brain atrophy, probably from metabolic injury due to severe hypernatremia | Yes | Cranial ultrasound 3 d after bleed. MRIs at 4 and 8 mo after bleed with improvement in size of SDH. | Severely impaired, controlled epilepsy at 9 mo of age. |
| 3           | 3 wk                     | Catheter-associated right internal jugular venous thrombus | 2.5 mo | Focal left frontal/parietal SDH, 4.5 × 2.7 × 5.3 cm, with mild mass effect [caused focal status epilepticus] | Brain atrophy, probably from a genetic cause | No | Cranial ultrasounds at 4 and 11 d after bleed. Head CT scan 6 d after bleed and MRI 3 mo after bleed with mild improvement in size of SDH. | Severely impaired. Death at 7 mo of age from respiratory failure after transition to comfort care. |
| 4           | 1 wk                     | Right transverse and superior sagittal CVST | 3 mo | Small focal left parietal SDH, 0.3 cm thick, without mass effect [incidental finding] | Extensive cystic 
encephalomalacia from hypoxic ischemic injury | No | Head CT scan 1 mo after bleed and MRI 10 mo after bleed with evidence of SDH. | Severely impaired at 12 mo of age. |

**Case 4**

An infant girl born at 42 and 1/7 weeks' gestational age via emergent cesarean section secondary to nonreassuring fetal heart tones. A cranial ultrasound on DOL 2 raised suspicion for CVST. On DOL 7, a brain MRI with MRV confirmed CVST in the right transverse and entire sagittal sinuses. There was also extensive impeded diffusion in both cerebral hemispheres, consistent with a diagnosis of CVST. An infant girl born at 42 and 17 weeks' gestational age via emergent cesarean section secondary to nonreassuring fetal heart tones. A cranial ultrasound on DOL 2 raised suspicion for CVST. On DOL 7, a brain MRI with MRV confirmed CVST in the right transverse and entire sagittal sinuses. There was also extensive impeded diffusion in both cerebral hemispheres, consistent with a diagnosis of CVST. An infant girl born at 42 and 17 weeks' gestational age via emergent cesarean section secondary to nonreassuring fetal heart tones. A cranial ultrasound on DOL 2 raised suspicion for CVST. On DOL 7, a brain MRI with MRV confirmed CVST in the right transverse and entire sagittal sinuses. There was also extensive impeded diffusion in both cerebral hemispheres, consistent with a diagnosis of CVST.
hemispheres. Enoxaparin therapy was subsequently initiated.

At 3 months of life, a surveillance MRI revealed a 3-mm left parietal SDH (Fig 1D). The venous sinuses were mostly recanalized, with minimal residual thrombus, and there was diffuse encephalomalacia. Her anti-Xa level was 0.25 U/mL, and enoxaparin was discontinued. She was admitted to the hospital for evaluation, and no neurosurgical intervention was needed. A head CT scan at 4 months of age showed resolution of the SDH. At 7 months of age, she had slow head growth and significant microcephaly, equal to the 50th percentile for a 3-week-old. At 12 months of age, the patient had significant neurologic impairments but had been weaned off anticonvulsant medications, except gabapentin, which was initiated for agitation.

**DISCUSSION**

We present 4 infants, 3 with CVST and one 1 catheter-associated DVT. Each was treated with enoxaparin and subsequently developed an SDH within 6 to 12 weeks after initiation of anticoagulation. One infant had diffuse comorbid brain injury from a presumed perinatal hypoxic–ischemic insult and 1 from severe hypernatremia and dehydration. Two infants had brain atrophy of unknown origin. All 4 infants developed seizures before or coincident with the development of SDH, but only in 1 was the hemorrhage discovered through urgent imaging triggered by new-onset seizures. The other 3 patients had significant SDH revealed on routine surveillance imaging with brain MRI with MRV. Only 2 needed urgent neurosurgical intervention.

Developmental outcomes at 7 to 12 months of age have been unfavorable for these patients. This is more likely to be a result of the underlying brain abnormalities (ischemic, metabolic, or genetic etiologies) rather than a direct consequence of the SDH, because extensive encephalomalacia or brain atrophy was present on MRI at the time of discovery of the SDH (in cases 1, 2, and 4). We are unaware of data on unfractinated heparin or warfarin in this context but would expect similar safety concerns.

In patients with brain atrophy, the increased extraxial space may stretch the fragile bridging veins, predisposing the patients to hemorrhage. Our data suggest that the decision of whether to initiate anticoagulation for infants with venous thromboembolism should take into account this risk of intracerebral hemorrhage and the benefits of anticoagulation. This consideration is especially important in cases where there is comorbid cerebral hypoxic–ischemic injury, infection, or a metabolic–genetic abnormality that is likely to result in brain atrophy. Surveillance brain imaging of infants on anticoagulation not only should examine recanalization of the sinuses in CVST, but also should be considered to monitor for intracerebral hemorrhage in patients with concurrent brain atrophy. CT and MRI scans are likely to be more sensitive than cranial ultrasound in detecting hemorrhage, especially for SDHs that are not near the fontanel. However, this has to be balanced with the necessity of sedation or anesthesia for imaging in this age group. Our data suggest the need for additional studies, to determine optimal timing and modality of neuroimaging surveillance for this group of patients while they are on anticoagulation with LMWH.

**CONCLUSIONS**

Infants at risk for cerebral atrophy, whether from a diffuse ischemic insult or another cause, are vulnerable to clinically significant SDH when treated with LMWH. Comorbid diffuse brain injury may be a relative contraindication to anticoagulation for small, non-progressive CVST or DVT.
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