Anticoagulation Therapy in Pediatric Patients With Sinovenous Thrombosis

A Cohort Study

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Objective: To assess the use of anticoagulant therapy in a consecutive cohort study of children with sinovenous thrombosis (SVT).

Methods: A single institutional pilot study of anticoagulant therapy was conducted from January 1992 to December 1996 at the Hospital for Sick Children, Toronto, Ontario. Consecutive children with the diagnosis of SVT, made by computed tomography, magnetic resonance imaging (MRI), MRI with venography, ultrasonography, nuclear brain scanning, or conventional angiography were eligible for anticoagulant therapy.

Radiographic Evaluation: Most children underwent multiple radiographic tests for evaluation of the central nervous system. Of the 32 episodes of SVT, CT was performed in 30, MRI with or without venography in 26, ultrasonography in 11, and nuclear brain scanning in 5. The majority of the SVTs were located at the superior sagittal sinus (50%) and right lateral sinus complex (44%).

Results: There were 30 consecutive children with 32 episodes of SVT during the 5-year study (2 girls had recurrent SVT). The median age was 6.2 years (age range, 3 days to 18 years), and the sex of the patients was evenly distributed (15 girls and 15 boys). The primary associated clinical conditions consisted of systemic lupus erythematosus (n = 5), renal disease (n = 3), perinatal distress (n = 2), congenital heart disease (n = 1), cerebral arteriovenous malformation (n = 1), and neurosurgery for refractory seizures (n = 1). The remainder were previously healthy children older than 1 month (n = 10) and newborns (n = 7). Eight children were ineligible for anticoagulant therapy because of an associated intracranial hemorrhage (n = 6), a postoperative bleeding risk after neurosurgery (n = 1), or a prolonged delay from the diagnosis to the time of referral (n = 1). Ten children received standard heparin, and 12 children received low-molecular-weight heparin (LMWH) (enoxaparin sodium). Eighteen children were treated with oral anticoagulants for 3 months after initial heparin therapy, and 4 patients received LMWH for the entire course of treatment. There was no intracranial hemorrhage in the 12 patients treated with LMWH, but there was 1 case of clinically silent bleeding in the standard heparin group.

Conclusions: The results of this pilot study suggest that anticoagulant therapy, in particular LMWH, is safe and may have a role in the treatment of children with SVT. A randomized controlled trial is warranted.

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PEDiatric ISCHEMIC stroke is increasingly recognized as an important disease but is still likely underdiagnosed. This is particularly true for sinovenous thrombosis (SVT). Clinically unsuspected SVT has been found in neonates with asphyxia, lethargy, or seizures and in 25% of children with pseudotumor cerebri undergoing angiography. No systematic studies evaluating potential therapies in pediatric SVT have been published, to our knowledge.

In response to the frequency, seriousness, and lack of information on thrombotic disease in children, institutional, collaborative thrombophilia and cerebrovascular programs were instituted at the Hospital for Sick Children, Toronto, Ontario, in 1990 and 1994, respectively. One of the initial goals of these programs was to conduct cohort studies of children with specific thrombotic complications to evaluate the epidemiological features of the disease and to assess the potential benefits of intervention with anticoagulants. One component of the Hospital for Sick Children’s Thrombophilia and Cerebrovascular programs focused on SVT.

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A review of the literature in 1994 revealed that the outcome from SVT included 16% mortality and approximately 22% of children with serious long-term neurologic deficits. At the same time, a randomized controlled trial of anticoagulant therapy with heparin in adults with
PATIENTS, MATERIALS, AND METHODS

From January 16, 1992, to December 2, 1996, consecutive pediatric patients at the Hospital for Sick Children with the diagnosis of SVT were evaluated for potential treatment with anticoagulants. The following demographic information was collected prospectively for all patients: age at the time of diagnosis, sex, underlying risk factors or associated clinical conditions, and clinical presentation. In all patients, the presence of SVT was confirmed by radiographic testing, which included computed tomography (CT), magnetic resonance imaging (MRI) with or without venography, ultrasonography, nuclear brain scanning, and/or conventional angiography.

ANTICOAGULATION THERAPY

Treatment with standard heparin sodium was initiated with a bolus of 50 to 75 U/kg administered over 10 minutes, followed by maintenance therapy initiated at 20 to 28 U/kg per hour.12 Standard heparin therapy was adjusted according to activated partial thromboplastin time (APTT) values following a nomogram.12 The APTT therapeutic range corresponded to an anti–factor Xa heparin level of 0.35 to 0.70 U/mL.13 Treatment with LMWH consisted of enoxaparin, which has an anti–factor Xa–antithrombin ratio of more than 4.0. Enoxaparin sodium therapy was initiated at a dosage of 1 mg/kg every 12 hours for patients older than 2 months14 and 1.5 mg/kg for patients younger than 2 months.15 Subsequent dosages were adjusted according to anti–factor Xa levels 4 hours after the subcutaneous dose was administered.15,16 The therapeutic range for anti–factor Xa levels was 0.50 to 1.0 U/mL.13,14 Treatment with warfarin sodium (Coumadin, DuPont Merck Pharmaceutical Co, Wilmington, Del) was monitored by prothrombin times expressed as international normalized ratios. Warfarin sodium therapy was initiated at a dosage of 0.2 mg/kg per dose for 2 days. Subsequent loading doses were dependent upon the international normalized ratio values, which were measured daily for the first week of treatment.13 The target international normalized ratio range was 2 to 3.

COAGULATION ASSAYS

Platelet-poor plasma for coagulation studies was obtained from whole blood anticoagulated with sodium citrate (1 part anticoagulant to 9 parts blood), followed by centrifugation at 3000g for 20 minutes at 4°C. Coagulation tests for the purpose of monitoring anticoagulant therapy consisted of 1 of the following, depending on the anticoagulant: the prothrombin time (Precision Biologicals Inc, Dartmouth, Nova Scotia), the APTT (Precision Biologicals Inc), and anti–factor Xa heparin assay.14

OUTCOME

The clinical outcomes of our study were death, neurologic deficit (minor, moderate, and severe), and normal neurologic development. Clinical outcome was assessed by standardized neurologic examination in the Stroke Clinic by 3 study pediatric neurologists. The radiological outcomes were the number and extent of parenchymal lesions and the extent of vessel occlusion more than 4 weeks after diagnosis. Radiological outcomes were evaluated by comparison of follow-up MRI or CT scans obtained more than 4 weeks after diagnosis with initial scans obtained at diagnosis. All CT and MRI scans were reviewed by the study staff neuroradiologist at the Hospital for Sick Children, and each scan was carefully compared with earlier scans to assess whether there was a change in vessel occlusion and/or in parenchymal lesions. Each patient was then categorized into an overall classification for parenchymal lesion change (improved, no change, worse) and for extent of sinovenous occlusion (improved, no change, worse).

RESULTS

PATIENT POPULATION

Thirty consecutive pediatric patients with SVT, 15 girls and 15 boys, were treated at the Hospital for Sick Children over the 5-year study period. Two female patients had 2 episodes of SVT, resulting in a total of 32 episodes. The Figure gives the age distribution of the 30
children. Approximately one third of children were younger than 1 year, and one third were teenagers. The mean age was 6.7 years, and the median age was 6.2 years. In the nontreated group, there was a predominance of newborns (7 of 8) compared with the treated group (3 of 22).

**CLINICAL PRESENTATION**

The clinical presentation of the 32 SVT events consisted of signs and symptoms of increased intracranial pressure (n = 22, 69%), dehydration (n = 9, 28%), fever (n = 5, 15.6%), and otitis media/mastoiditis (n = 3, 9.4%). Sixteen children also presented with seizures (63%). Previously recognized risk factors in the 30 children consisted of systemic lupus erythematosus (n = 5, 17%), renal disease (n = 3, 10%), perinatal distress (n = 2, 7%), congenital heart disease (n = 1, 3%), cerebral arteriovenous malformation (n = 1, 3%), and neurosurgery for seizures (n = 1, 3%). The rest were previously healthy children older than 1 month (n = 10, 33%) and healthy newborns (n = 7, 23%). The distribution of risk factors in the 22 children receiving anticoagulant therapy differed from that in the nontreated children in that all patients with systemic lupus erythematosus (n = 5), renal disease (n = 3), or iron deficiency anemia (n = 3) were in the treated group. Also, there was a decreased proportion of previously healthy infants and children in the treated group (12 of 22) compared with the nontreated group (6 of 8). Many patients (10 of 22 treated and 2 of 8 nontreated) had 2 or more risk factors. Dehydration was frequent in both the treated (7 of 22) and the nontreated (4 of 8) cohorts, and prothrombin testing revealed acquired abnormalities in both treated (11 of 22) and nontreated (2 of 8) patients.

**INITIAL RADIOGRAPHIC EVALUATION**

All children had SVT confirmed by a radiographic test. Of the 32 episodes of SVT, a CT scan was performed in 30, MRI with or without MR venography in 26, ultrasonography in 11, and nuclear brain scanning in 5. Four children older than 1 year underwent only CT and 2 underwent only MRI. Multiple tests were used to diagnose the remaining events. Only 12 children had thrombosis of a single venous sinus. The remaining 18 children had thrombosis of multiple venous sinuses. The most common areas involved were the superior sagittal sinus and the right lateral sinus complex. In terms of parenchymal lesions related to SVT, 15 of 22 patients receiving anticoagulant therapy had no parenchymal lesions, and the remainder had parenchymal lesions consisting of bland infarcts (n = 4), hemorrhagic infarcts (n = 2), intracerebral hemorrhage (n = 2), and subarachnoid hemorrhage (n = 2). Seven of the 8 children who did not receive anticoagulant treatment had parenchymal lesions, which consisted of hemorrhagic infarcts (n = 6) and intracerebral hemorrhage (n = 3). Also, 6 children had multiple, small, bilateral white matter abnormalities on MRI.

**TREATMENT WITH ANTICOAGULATION**

Of the 30 consecutive children, 8 did not receive anticoagulant therapy because of a significant intracranial hemorrhage (n = 6), a postoperative bleeding risk after neurosurgery (n = 1), or an extensive delay prior to referral to the Hospital for Sick Children (n = 1). Initial anticoagulant therapy in the 22 treated children consisted of standard heparin in 10 patients and LMWH in 12 patients. Eighteen children received warfarin and 4 received LMWH as maintenance therapy for approximately 3 months.

Maintenance doses of heparin sodium for children older than 2 months ranged from 12 to 34 U/kg per hour administered by intravenous infusion, with a median of 20 U/kg per hour. There were no patients younger than 2 months who received standard heparin. Maintenance doses of LMWH for children older than 2 months ranged from 0.35 to 1.12 mg/kg every 12 hours administered subcutaneously (median dose, 1 mg/kg every 12 hours). Maintenance doses of LMWH for patients younger than 2 months ranged from 0.97 to 1.48 mg/kg every 12 hours (median dose, 1.45 mg/kg every 12 hours).

**OUTCOME**

Three children died, none of whom had received anticoagulant therapy. The 2 recurrent SVTs occurred in 2 girls initially treated with LMWH. One girl with systemic lupus erythematosus had a recurrence while she was receiving prophylactic therapy with warfarin, and 1 with renal disease had a recurrence when she was not receiving anticoagulant therapy. The 2 children with recurrence are currently receiving warfarin therapy indefinitely. Neurologic follow-up is available for 21 of the remaining 25 patients. The median length of follow-up is 1 year (range, 1 month to 3.2 years). Nineteen patients (90.5%) are seizure free, and 2 patients have persistent seizures requiring medication. Fourteen patients (66.7%) are neurologically normal; 6 patients (28.5%) have minor neurologic deficits; and 1 patient (4.8%) has a moderate neurologic deficit.

Twenty of 22 children who received anticoagulant therapy underwent follow-up CT and/or MRI after the initiation of therapy. The first follow-up scans were obtained 3 to 6 days (4 children), 7 to 28 days (7 children), 6 weeks to 3 months (5 children), or more than 3 months (4 children) after the initiation of therapy. There
were no cases with new or increased bleeding in the children treated with LMWH. There was 1 patient who had clinically silent bleeding into a previously bland infarct during standard heparin therapy.

Among the cohort of 22 patients treated with anticoagulants, follow-up radiological studies were obtained 4 or more weeks after diagnosis in 19 patients: 18 undergoing MRI alone and 1 undergoing CT alone. The mean interval from diagnosis to last follow-up scan was 11.2 months (median, 6 months; range, 1-36 months), and 58% of the scans were obtained between 3 and 9 months after initial diagnosis. Four of the 8 patients treated without anticoagulants underwent follow-up CT and/or MRI more than 4 weeks after diagnosis. When the last follow-up scan for each patient was compared with the earlier scans, the 11 patients with parenchymal lesions showed either no change (n = 5) or improvement (n = 6). Nearly all patients showed some improvement in the extent of sinovenous vessel occlusion, regardless of whether they received anticoagulant therapy (17 of 19 patients) or no anticoagulant therapy (3 of 4 patients). Ten children had complete recanalization between 2 and 17 months after diagnosis. The recanalization occurred within 4 months in 4 patients. No patient had worsening of their radiological findings during this period.

COMMENT

Ischemic cerebrovascular diseases occur in at least 1.2 per 100 000 children per year,2 and SVT constitutes approximately 25% of these events, with an estimated incidence of 0.29 per 100 000.16 Although relatively rare, SVT in infants and children causes death and long-term neurologic deficits, resulting in a significant burden of illness to patients and society. A recent randomized controlled trial in adults with SVT assessed the potential role of anticoagulant therapy and reported a significantly positive effect.10 However, for many age-related pathophysiological reasons, results from studies in adults cannot simply be extrapolated to children. Before initiating a similar multicenter randomized controlled trial in children with SVT, we performed a single-center cohort study to provide preliminary information on the safety and potential efficacy of anticoagulant therapy in children with SVT. Our study showed that, despite diverse ages and risk factors, initial anticoagulant therapy, in particular the use of LMWH, did not result in significant bleeding and may have improved survival.

The clinical presentation of SVT in children was dependent on age, which was linked to the underlying risk factors. Infants and young children most commonly presented with seizures, while older children most commonly presented with headache and vomiting. In contrast, adults usually present with isolated intracranial hypertension, focal neurologic signs, or cavernous sinus syndrome.17 Dehydration was the predominant risk factor in infants, while systemic lupus erythematosus with an associated antiphospholipid antibody was the most common risk factor in older children. The risk factors in older children are similar to those seen in adults, in whom the most frequent causes are hypercoagulable states, systemic infections, and inflammatory diseases.17

In 1991, Einhaupl et al10 published the results of a randomized placebo-controlled trial of heparin in adults with aseptic cerebral SVT. The study was conducted between 1982 and 1984 and had a planned sample size of 60. However, an interim analysis of clinical outcome, consisting of complete recovery, neurologic deficit, and death, was conducted with results from the first 20 patients, 10 receiving heparin and 10 placebo, and the study was discontinued owing to a significant increase in survival and decrease in neurologic deficit in the treated group. In the same article, the authors descriptively compared the incidence of intracranial hemorrhage and death in 102 adults with SVT treated with or without heparin. They reported that mortality due to intracranial hemorrhage was 15% in the standard heparin–treated group compared with 69% in the untreated group. The study by Einhaupl and colleagues, despite its methodological limitations, has established the use of anticoagulants as therapy for adults with SVT.

The different epidemiological features of SVT in children compared with adults, as well as the ontogenic differences in both the neurologic and hemostatic systems, makes simple extrapolation of the results of trials in adults to children unlikely to be valid. To our knowledge, however, there are no randomized trials of anticoagulant therapy in children with SVT. A comprehensive review was conducted of the literature published between 1980 and 1996. Articles involving 150 children were identified with adequate information on the use of anticoagulants and clinical outcome, which was classified as death, normal, or residual neurologic deficits (reference list available on request). There were 136 children who did not receive anticoagulants and 14 children who did receive standard heparin and/or oral anticoagulants. There was no difference in mortality rates between the nontreated and treated children (16% and 14%, respectively). However, the frequency of residual neurologic sequelae was strikingly different, with a neurologic morbidity rate of 21.5% in nontreated children and 0% in treated children. While no definitive conclusions can be drawn from the literature review of SVT in children, the results, in combination with Einhaupl and colleagues’ trial, provide a compelling rationale for a clinical trial assessing anticoagulant therapy in children with SVT.

Clearly, multicenter, multinational clinical trials are required to assess the role of anticoagulant therapy in children with SVT. The initiation of the International Children’s Thrombophilia Network in 1995 has made feasible the level of international collaboration necessary to accomplish this goal. However, before such a complex trial can be undertaken, preliminary information on the potential safety and efficacy of anticoagulant therapy is critically important.

We initiated a cohort study of anticoagulant therapy in children with SVT in 1992, following the publication of the article by Einhaupl et al.10 Initially, we aimed to assess treatment with standard heparin with or without warfarin. However, when LMWHs became available in Canada in 1994, we chose to switch
from standard heparin to LMWH in our pilot study because of the many potential advantages of LMWH therapy for children. Low-molecular-weight heparins are prepared from standard heparin by a variety of methods and have a mean molecular weight of approximately 5000 kd, compared with 15 000 kd for standard heparin.\textsuperscript{18,19} Similar to those of standard heparin, the anticoagulant activities of LMWH are dependent on binding to, and enhancing the activities of, antithrombin, an important physiological inhibitor of coagulation. While standard heparin equally inhibits 2 critically important enzymes in coagulation, factor Xa and thrombin, LMWH preferentially inhibits factor Xa.\textsuperscript{20-23} The specificity of LMWH for factor Xa necessitates monitoring using an anti–factor Xa heparin assay, because LMWH does not prolong the APTT, except when excessive levels are present. The advantages of using LMWH instead of standard heparin are as follows: consistent pharmacokinetics that minimize the need for monitoring; subcutaneous administration that eliminates the need for continuous intravenous access; fewer complications, which include bleeding, heparin-induced thrombocytopenia, and osteoporosis; and equal or increased efficacy.\textsuperscript{13} For invasive procedures during LMWH therapy, including angiography, doses should be held for at least the preceding 24 hours in light of recent reports of spinal epidural hematoma in adults who undergo epidural anesthesia while receiving LMWH therapy. Eight children in our study did not receive anticoagulant therapy. Three (38%) of them died. However, these 3 patients may have represented more severe disease, as the majority had intracranial hemorrhage at presentation. No patients who received anticoagulant therapy died. One patient treated with standard heparin had a small intracranial hemorrhage into a previous infarct, but there were no clinical sequelae. No children treated with LMWH bled, and no bleeding was documented during warfarin therapy. Treatment with LMWH has demonstrated a reduced bleeding risk compared with standard heparin therapy, and our results are consistent with this, although not conclusive. Further studies are required to determine whether subsets of patients can be identified in whom the risks of anticoagulation are increased. There were 2 recurrent SVTs, 1 in a child who had completed anticoagulant therapy and 1 in a child who was receiving low prophylactic doses of warfarin. Recurrent thrombosis, in general, is due to the presence of ongoing risk factors or inadequate treatment. The former seems likely in these 2 cases.

The results of our pilot study suggest that the use of anticoagulants, particularly LMWHs, is safe in children with SVT. Our sample size and study design do not allow conclusions to be made about the efficacy of anticoagulation in terms of mortality and long-term neurologic impairment. This information can only be determined in large multicenter randomized controlled trials. The results of our study, in conjunction with results of previous adult trials and the available literature, suggest that an intervention trial to examine the efficacy of LMWH therapy in children with SVT is now appropriate.

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REFERENCES


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