Venous Thromboembolic Complications (VTE) in Children: First Analyses of the Canadian Registry of VTE


Deep vein thrombosis (DVT) and pulmonary embolism (PE) occur in pediatric patients; however, the incidence, associated morbidity, and mortality are unknown. A Canadian registry of DVT and PE in children (ages 1 month to 18 years) was established July 1, 1990 in 15 tertiary-care pediatric centers. One-hundred thirty-seven patients were identified prospectively and are the subject of this report. The incidence of DVT/PE was 5.3/10,000 hospital admissions or 0.07/10,000 children in Canada. Infants under 1 year old and teenagers predominated with equal numbers of both sexes. DVT were located in the upper (n = 50) and lower (n = 79) venous system, or as PE alone (n = 8). Central venous lines (CVLs) were present in approximately 33% of children with DVT (n = 45). Associated conditions were present in 96% of children and 90% of children had two or more associated conditions for DVT. DVT was diagnosed by venography (n = 83), duplex ultrasound (n = 37), and other combinations (n = 17). Twenty-two of the 31 ventilation/perfusion scans were interpreted as high-probability scans for PE. Therapy consisted of heparin (n = 115), thrombolysis (n = 15), surgical removal of a CVL or thrombus (n = 22), and oral anticoagulant therapy (n = 103). Significant bleeding complications did not occur. However, three (2.2%) children died as a direct consequence of their thromboembolic disease; DVT occurred in 23 children and postphlebitic syndrome (PPS) occurred in 26. In conclusion, DVTs occur in a significant number of hospitalized children with a mortality of 2.2%. Complications are not hemorrhagic, but thrombotic, and characterized by PE, recurrent disease, and PPS. In contrast to adults, the upper venous system is frequently affected because of the use of CVLs. The frequency of DVT/PE justifies controlled trials of primary prophylaxis in high-risk groups, and therapeutic trials to determine optimal treatment.

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MATERIALS AND METHODS

Participating Centers

The Canadian pediatric registry was initiated at two pediatric tertiary-care centers, McMaster University Medical Centre (Hamilton, Ontario) and the Hospital for Sick Children (Toronto, Ontario), on March 1, 1990. After evaluation of case registry forms and an initial organizational meeting on June 19, 1990, the other 13 tertiary-care pediatric centers in Canada joined the registry for a total of 15 centers. Patients in this report were entered from July 1, 1990 to December 31, 1992 for a total of 30 months. The centers included British Columbia Children's Hospital (Vancouver, British Columbia); Alberta Children's Hospital (Calgary, Alberta); University Hospital (Edmonton, Alberta); University Hospital (Saskatoon, Saskatchewan); Children's Hospital (Winnipeg, Manitoba); Children's Hospital of Eastern Ontario (Toronto, Ontario); Children's Hospital of Eastern Ontario (Ottawa, Ontario); Hotel Dieu (Kingston, Ontario); Hospital Ste-Justine (Montreal, Quebec); Montreal Children's Hospital (Montreal, Quebec); Le Centre Hospitalier Universitaire (Quebec City, Quebec); Izaak Walton Killam Children's Hospital (Halifax, Nova Scotia); and Janeway Child Health Centre (St John's, Newfoundland).

A designated pediatric hematologist at each center maintained a prospective list of consecutive children with documented DVT referred to their service. In addition, medical records in each institution used specific codes for thrombotic complications and were used to cross-check the list of children with DVT. A monthly mailing was instituted to ensure children were entered in a prospective manner. The research assistant (M.A.) for the registry site visited each center initially to organize patient entry and subsequently to cross-check data collection on each patient. At Ste-Justine's Hospital, an on-site research assistant ensured the quality of data collection.

Patient Population

Children from 1 month to 18 years old were eligible for entry if a DVT was objectively documented in the upper or lower venous system. Newborns and infants less than 1 month old were entered into a separate international registry and are not included in this analysis. Children with thrombotic occlusion of the venous system in the central nervous system, portal system, renal veins, or other nonextremity venous systems were not included in this registry. There were no other restrictions for entry into the registry.

Data Collection

Comprehensive clinical data forms were completed for each child and included the following information.

Age and sex distribution. Weight, gender, and the age at time of the diagnosis were recorded for all children.

Associated conditions. A comprehensive history and appropriate laboratory tests were performed to determine if any of the following conditions were present: inherited prethrombotic disorder, systemic infection, recent abortion or pregnancy, birth-control pill usage, congenital heart disease (CHD), drug usage, central venous catheters (CVLs), shock, systemic lupus erythematosus (SLE), nephrotic syndrome, dehydration, obesity, recent surgery or trauma, cancer, short gut syndrome requiring home total parenteral nutrition (TPN), and others.

Diagnosis and location. For inclusion in the registry, all DVT had to be confirmed by an objective radiographic test. The type of test used and the location of the DVT were recorded.

Initial therapy. Details of initial management with the anticoagulant heparin and/or thrombolytic therapy were recorded. This included amounts of drug administered per kilogram, use of bolus doses, duration of therapy, and choice of laboratory test to monitor therapy.

Maintenance therapy with oral anticoagulant therapy. The institution of treatment with warfarin, duration of therapy, and tests used to monitor therapy were recorded.

Complications of treatment. Bleeding complications were considered to be significant if the hemoglobin decreased by 20 g/L or more, a transfusion with red blood cells was administered to a patient in the absence of surgery or trauma, and/or if anticoagulant therapy was stopped because the responsible physician assessed the bleeding as excessive.

Complications related to the primary thrombotic event. Complications related to DVT were diagnosed when there was objective evidence that the initial lesion extended, a new thrombotic complication occurred, and/or there was evidence of postphlebitic syndrome (PPS). The latter was diagnosed in the presence of swelling, discoloration, obvious collateral circulation, and/or pain in the affected limb 3 months or more after the initial diagnoses.

RESULTS

Incidence of DVT in Children In Canada

One-hundred thirty-seven consecutive children were entered into the registry. The distribution of patients by province is shown in Table 1. The majority of patients were from Hospital for Sick Children and Hospital Ste-Justine. The distribution of patients reflected both the size of these institutions and centralization of resources in Canada. The total number of admissions per center during the time of the registry was used to calculate both institutional incidences and a combined incidence in Canada of 5.3 per 10,000 hospital admissions (Table 1). The incidence in children in Canada was 0.07/10,000.

Age and Sex Distribution of DVT in Children in Canada

The age distribution of all children is shown in Fig 1. The frequency of DVT was highest in children less than 1 year old (n = 25; 18%) and in children ages 11 to 18 (n = 69; 50%). The sex distribution was even with 69 males and 68 females.

Associated Conditions

Associated conditions with DVT/PE were identified in 132 (96%) of the 137 children (Table 2). Many children had multiple associated conditions with their thrombotic dis-
Fig 1. The age distribution of 137 consecutive children (1 month to 18 years) with DVT in Canada from July 1, 1990 to December 31, 1992. Infants, from 1 month to 1 year old, constituted the single largest age group of children. Teenagers were the second largest group with the decreasing numbers in the late teen years reflecting referral to adult programs.

ease. There were 5 children with no associated condition or idiopathic DVT (3.6%), 17 (12.4%) with only one condition; 54 (39.4%) with two conditions; 48 (35%) with three conditions; and 13 (9.6%) with four conditions. The presence of CVLs was the single most important predisposing cause of DVT in children (n = 45; 32.8%). In contrast, inherited prethrombotic disorders were documented in 12 children (8.8%). However, only 45 children were evaluated suggesting that a prethrombotic disorder may be more common. Inherited deficiencies of Protein C (n = 6) and Protein S (n = 6) were the disorders identified. A family history was present in 9 of the 12 cases and all but 2 children with an inherited prethrombotic disorder also had an acquired condition that predated the thrombotic event.

Diagnosis and Location of Peripheral Thrombotic Events

The objective tests used to confirm the diagnosis of DVT and/or PE are shown in Table 3. Venography alone or in combination with other tests was the most frequently used modality. Duplex ultrasonography alone was the second most commonly used test (Table 3). DVT in the upper system was present in 50 children (36.3%), and in the lower system in 79 (57.7%). CVLs were associated with 39 (28.5%) DVT in the upper system and 6 (4.4%) in the lower system. The distribution of DVT and/or PE was not affected by age or sex.

Diagnosis and Distribution of Pulmonary Embolism

Twenty-two of the 31 ventilation/perfusion (VQ) scans (71%) performed were reported as high probability for PE, 3 were low probability and 6 were normal. PE alone, without documented DVT, occurred in 8 of the 22 (36.4%) children. Of these 8 children, 3 occurred after ventriculo-peritoneal shunt changes for hydrocephalus; 5 were related to CVLs, 2 for the treatment of acute lymphoblastic leukemia, 2 for dialysis in children with nephrotic syndrome; and 1 in a child with multiple abscesses. PE was documented in 3 of 50 children with DVT in the upper system and in 11 of 79 children with DVT in the lower system.

Treatment

Children with DVT received a variety of therapeutic interventions including anticoagulation therapy with heparin, thrombolytic therapy, oral anticoagulation therapy, and other therapy (Table 4).
Heparin therapy. Anticoagulation therapy with heparin (usually porcine) was the most common form of initial treatment, and was used in 115 (85%) patients (Table 4). An initial bolus of heparin was administered in 101 children, most commonly at 50 to 75 U/kg/bolus. Maintenance therapy was administered to 115 (74%) of children with a starting dose most commonly of 20 to 24 U/kg/h. The length of therapy varied considerably from 1 to 62 days (median = 14).

Heparin therapy was monitored by the activated partial thromboplastin time (APTT) for all children. APTT assays were performed with four different reagents across the country. The therapeutic range for APTT values varied from center to center and was determined by heparin levels in only two centers.

Thrombolytic therapy. Thrombolytic therapy was administered to 15 children for extension of their original thrombus (12) or to clear blocked CVLs (3) (Table 4). The agents used were streptokinase (9); urokinase (5); and tissue plasminogen activator (tPA) (3). Two children received two agents. No uniform-dosage schedule was followed. The duration of therapy ranged from 1 hour to 6 days with a median of 48 hours. One of the 15 children had a complete resolution, 9 showed partial resolution and 5 had no resolution of the thrombus. Twelve patients were subsequently treated with heparin and the three with central venous catheters had their catheters removed.

Oral anticoagulant therapy. Maintenance therapy with oral anticoagulants was administered in 103 (75.1%) children, usually overlapping with heparin therapy for a few days. The duration of treatment varied with the majority of children receiving more than 3 months of therapy (Table 4). Children treated for more than 3 months had persistent underlying risk factors (ie, cancer plus a CVL). Oral anticoagulant therapy was uniformly monitored by the prothrombin time (PT) assay. In thirteen centers, PT values were reported as International Normalized Ratios with a therapeutic range of 2 to 3.

Other therapy. Nineteen children did not receive anticoagulant or thrombolytic therapy. One child was diagnosed with PE at autopsy. One child with a femoral-vein thrombus after cardiac catheterization was diagnosed 8 weeks later at a subsequent catheterization. Three children had their thrombi surgically removed. The remaining 15 children (10.9%) had their CVLs removed when a related DVT was found. Five of these 15 had subsequent CVLs placed and were treated with oral anticoagulants at that time.

Outcome

Mortality. By the time of submission, the follow-up period ranged from a minimum of 6 months to a maximum of 3 years with a median of approximately 18 months. Thirteen of the 137 (9.5%) children died; 10 from their underlying disease and 3 (2.2%) as a direct result of their thrombotic complications. Two died of PE, one of which was secondary to a CVL and only diagnosed at autopsy, whereas the second died of PE while receiving anticoagulant therapy. The third child died of an extending thrombus in the inferior vena cava while receiving heparin therapy.

Recurrent thromboembolic disease. Of the remaining 124 children, 23 (18.5%) developed recurrent DVT and/or PE. 16 (70.0%) of which occurred on anticoagulant therapy. This group was comprised of 16 males and 7 females with a median age of 12 years (range 1 to 17 years). The underlying disorders were diverse and consisted of cancer (n = 4), CHD (n = 4), trauma/surgery (n = 8), nephrotic syndrome (n = 2), and 5 other disorders. Ten of the 23 children had CVL-related DVT and 4 were Protein C deficient. The recurrent disease was either local in the upper or lower system, or in the form of new PE.

Resolution of disease. Seventy-two children had follow-up diagnostic tests with a variety of radiographic tests (Table 5). Based upon all techniques, complete resolution occurred in 42 children, partial resolution in 21% and no resolution in 37% (Table 5). However, the proportion of resolved and unresolved DVT was not consistent between radiographic tests (Table 5). With venography, 56% of children had no resolution whereas the other tests combined reported that only 15% of children did not have at least some resolution. PPS was diagnosed based on clinical features of pain.

Table 4. Treatment of DVT in Children

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin therapy</td>
<td></td>
</tr>
<tr>
<td>Bolus (N)</td>
<td>101 (73.7)</td>
</tr>
<tr>
<td>Bolus (U/kg)</td>
<td>50-75</td>
</tr>
<tr>
<td>Maintenance (N)</td>
<td>115</td>
</tr>
<tr>
<td>Initial dose (U/kg/h)</td>
<td>20-24</td>
</tr>
<tr>
<td>Duration (median [range])</td>
<td>14 [1-62]</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>15</td>
</tr>
<tr>
<td>Duration (median [range])</td>
<td>48 h [1-6 d]</td>
</tr>
<tr>
<td>Complete resolution (N)</td>
<td>1</td>
</tr>
<tr>
<td>Partial resolution (N)</td>
<td></td>
</tr>
<tr>
<td>No resolution</td>
<td>5</td>
</tr>
<tr>
<td>Oral anticoagulation therapy</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>103 (75%)</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>&gt;3 mos (N)</td>
<td>60</td>
</tr>
<tr>
<td>3 mos (N)</td>
<td>24</td>
</tr>
<tr>
<td>1-2 mos (N)</td>
<td>19</td>
</tr>
</tbody>
</table>

All 15 children were treated with heparin after thrombolytic therapy.

Table 5. Assessment of Outcome of DVT in Children by Radiographic Evaluation

<table>
<thead>
<tr>
<th>Radiographic Test</th>
<th>Complete</th>
<th>Partial</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venography</td>
<td>9 (23%)</td>
<td>8 (21%)</td>
<td>22 (56%)</td>
<td>39</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>14 (82%)</td>
<td>1 (6%)</td>
<td>2 (12%)</td>
<td>17</td>
</tr>
<tr>
<td>Other*</td>
<td>7 (44%)</td>
<td>6 (37%)</td>
<td>3 (19%)</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>30 (42%)</td>
<td>15 (21%)</td>
<td>27 (37%)</td>
<td>72</td>
</tr>
</tbody>
</table>

* Other forms of radiographic tests included echocardiography and heart catheterization.
swelling, discoloration, and ulceration. At the time of this report, 26 children (21%) had evidence of PPS. Seven of the children with PPS also had recurrent thromboembolic disease.

Bleeding complications. In contrast with the complications secondary to the primary disease, there were no children who had any evidence of serious hemorrhagic complications secondary to therapy. There were no children with central nervous system hemorrhagic complications and no child required blood transfusions because of excessive bleeding.

DISCUSSION

The Canadian registry of pediatric patients with DVT was established in 1990 to determine the epidemiologic features of this entity. The first 137 consecutive patients entered into the registry are the subject of this report. The registry established the incidence, age distribution, associated conditions, diagnostic modalities, location, treatment patterns, and short-term outcomes of DVT in pediatric patients in Canada. Many epidemiologic features of DVT in children differ significantly from adults suggesting that optimal intervention strategies for children may also differ. In addition, the incidence of DVT in children in Canada is similar to some forms of childhood cancer and justifies clinical intervention trials with the objectives of optimizing prevention and treatment.

The incidence of DVT in hospitalized Canadian children was 5.3/10,000 per year and in the general population of children, 0.07/10,000. The latter incidence is significantly lower than that reported for adult patients, which is estimated at 2.5 to 5% of the adult population. The only previous estimates of the incidence of DVT in children were based on retrospective studies in single institutions. Mechanisms that may protect children from DVT have only recently been explored and include a decreased capacity to generate thrombin caused by decreased plasma concentrations of prothrombin, an enhanced capacity to inhibit thrombin reflecting increased plasma concentrations of α2M, and differences in platelet/vessel-wall interaction. These and other, yet unidentified mechanisms likely provide protection to most pediatric patients from DVT.

Infants less than 1 year old and teenagers constituted the age groups at greatest risk for DVT. The vast majority of children had serious associated conditions. Idiopathic DVT occurred in only 4% of children in the Canadian registry and 2% of pediatric patients reported in the literature (1975 to 1992). In contrast, approximately 30% of DVT in adults are idiopathic. The most common associated conditions in the registry were cancer, CHD, trauma, short gut syndrome requiring TPN administered through CVLs, nephrotic syndrome, and surgery. The frequency of these disorders was similar to the more recent literature, but differed considerably from the older literature. For example, before the early 1970s, ventriculo-atrial (VA) shunts, infection, and CHD were the leading causes of thromboembolic complications in children. VA shunts are rarely used now because they caused right-atrial thrombi and continuous microembolization to the lung with subsequent pulmonary hypertension. Before the late 1960s, children with cancer, the largest single group of children with DVT in the Canadian registry, rarely survived long enough to develop DVT.

One of the goals of the Canadian registry was to identify patient groups at high risk for DVT and/or PE. Our analysis showed that CVLs were the single most important association for DVT in pediatric patients. CVLs contributed directly to one third of all DVT in children and 78% of DVT in the upper extremity. The incidence of CVL-related DVT at 1.7 per 10,000 admissions can be considered a minimum estimate because children with blocked CVLs and no other clinical symptoms are rarely evaluated with venographic studies. Indeed, the reported frequency of CVL-related DVT in pediatric patients ranges from 2% to 32% reflecting, in large part, whether subjective or objective tests were used for screening. One particularly high-risk group of patients with CVLs is comprised of children receiving long-term home TPN. The immediate ramifications of CVL-related DVT in the upper venous system include loss of venous access in children who are completely dependent on CVLs for specific forms of therapy, superior vena cava syndrome, chylothorax, hydrocephalus, PE, and death. The long-term ramifications include PPS and pulmonary hypertension. Identification of CVL-related DVT as a serious entity facilitates trials testing the potential role of prophylactic therapy. Initial studies show that low-dose warfarin therapy is successful in preventing CVL-related thrombi in adults and children. Identification of other high-risk groups is imperative so that they may also benefit from early diagnosis, treatment, and potentially, prophylactic therapy.

There is a group of specific inherited coagulation disorders that predispose to thrombotic complications in adults. The contribution of these disorders to thrombotic disease in pediatric patients has not been determined previously. Twelve or 8.8% of children were diagnosed with either protein C deficiency (6), or protein S deficiency (6). However, only one third of children were tested, suggesting that the true frequency of affected children was higher. All but 2 of the 12 affected children had separate acquired problems that temporarily increased their risk of thrombotic complications. Case reports in the literature also describe the unmasking of inherited hemostatic prethrombotic defects by acquired disorders. Although the short-term management of these children is relatively straightforward, the long-term management of these children presents a dilemma. Specifically, is long-term full-dose therapy with full-dose warfarin necessary if the acquired disorder resolves? The majority of children in the registry with congenital prethrombotic disorders were treated with warfarin (full dose or low dose) on a long-term basis.

The diagnosis of DVT in the registry was based on objective tests for all children. Venography with or without duplex ultrasonography comprised the most common radiographic test used. Duplex ultrasonography alone was used in 20% of children and in combination with other tests in 55% of patients. The ease and lack of invasiveness makes duplex ultrasonography an attractive alternative to venog-
raphy. However, there are no studies evaluating the sensitivity and specificity of duplex ultrasonography compared with venography in children. Although the positive and negative predictive ability of duplex ultrasonography is excellent for proximal DVT in adults, these results cannot be simply extrapolated to children for many reasons. First, the location of DVT is diverse in children with at least one third of DVT occurring in the upper system where the reliability of duplex ultrasonography has never been compared with venography in well-designed trials. Second, the size of the vessels is usually smaller in children, which may pose a further problem. Finally, the effect of the primary disorders, which differ in children from adults, is not known. A study to determine the reliability of duplex ultrasonography compared with venography in pediatric patients is urgently needed.

Postmortem and clinical studies of DVT in adults have documented a clear association between DVT and PE. PE is one of the most important causes of sudden and unexpected death in hospitalized adult patients. In the Canadian registry, PE was diagnosed in 22 of 31 children based on high-probability VQ scans, for an incidence of 0.86 per 10,000 admissions. This incidence is slightly lower than that previously estimated in adolescents (7.8 per 10,000) and significantly lower than for hospitalized adults. However, only 23% of children were evaluated by VQ scan for PE. The true incidence of PE is likely greater than that documented in the registry reflecting the low index of suspicion of PE in pediatric patients. PE occurred secondary to DVT in the lower or upper system. The long-term consequences of PE in children are unknown.

The reasons for treating patients with DVT are to prevent PE, local extension of the thrombus with its associated morbidity, and PPS. Treatment of children in the registry with anticoagulant and thrombolytic therapy followed conventional guidelines for management of adult patients with DVT. An initial course of heparin followed by 3 to 6 months of oral anticoagulant therapy was the most common treatment plan administered. Thrombolytic therapy was used in only 11% of children following a variety of protocols and with variable success. Although no children had clinically important bleeding, 19% had well-documented extensions of their thrombotic process, most commonly in the form of a PE. Further, 67% of the recurrences manifested while the patient was receiving anticoagulant therapy, a pattern clearly different from adults in whom approximately 20% also reoccurs, but while off therapy.

The long-term outcome of DVT and PE in children remains to be determined. With a follow-up of 6 months to 3 years in the Canadian registry, the majority of children had incomplete resolution of their thrombotic event by objective testing and 20% had clinical evidence of PPS. Although exact comparisons with adult patients with DVT and PE are not feasible, the available clinical information suggests that further thromboembolic complications and PPS are at least as frequent in children as in adults. In vitro studies show that endogenous fibrinolysis may be impaired in children. Plasma concentrations of tPA are decreased and plasmino-

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