Deep Venous Thrombosis in Children With Diabetic Ketoacidosis and Femoral Central Venous Catheters

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ABSTRACT. Objective. To describe findings of deep venous thrombosis (DVT) in association with femoral central venous catheter (CVC) placement for intensive fluid management in children with diabetic ketoacidosis (DKA) secondary to type 1 diabetes.

Design. Retrospective cohort study.

Setting. Pediatric intensive care unit (PICU) of a children’s referral medical center.

Patients. DKA patients from 1998 to 2002 of children with DKA with and without CVC placement. DKA patients were also compared with all PICU patients with CVC. CVC DVT was defined as ipsilateral leg swelling with CVC placement, confirmed by radiographic study, and persisting after CVC removal.

Measurements and Main Results. Of 113 DKA PICU patients, 6 (5.3%) required femoral CVC for initial management. Three of these DKA/CVC patients developed ipsilateral DVT within 48 hours of CVC placement. All 3 patients required long-term therapy with low molecular weight heparin for persistent leg swelling. DKA/CVC patients with DVT were younger (median age: 10.5 months) than DKA/CVC patients without DVT. The number of DKA/CVC patients with DVT (1.4%) was significantly greater than for all femoral non-DKA/CVC patients. DKA/CVC patients were also significantly more likely to have DVT than age-matched shock/CVC patients. They also had significantly higher glucose, corrected sodium concentrations, and lower pH and serum bicarbonate than did age-matched shock/CVC patients.

Conclusions. Femoral CVC placement is infrequently needed in pediatric DKA patients but can be associated with DVT. Femoral CVCs should be avoided in DKA patients or removed as soon as possible. DVT prophylaxis should be considered if a CVC is required. PEDIATRICS 2004;113:e57–e60. URL: http://www.pediatrics.org/cgi/content/full/113/1/e57; diabetes, diabetic ketoacidosis, thrombosis, deep venous thrombosis, central venous catheter, children.

ABBREVIATIONS. CVC, central venous catheter; DVT, deep venous thrombosis; PICU, pediatric intensive care unit; DKA, diabetic ketoacidosis.

CENTRAL VENOUS CATHETER (CVC)placement can be essential for providing fluids and medications in the treatment of the child with hypoperfusion and difficulty obtaining adequate peripheral access. CVCs, however, are associated with a variety of infectious and noninfectious complications.1,2 Both percutaneous and chronic indwelling CVCs are a significant risk factor for deep venous thrombosis (DVT) in children.1,2 Pediatric venous thromboembolism registries have reported that 28% to 50% of DVT episodes in children occurred in the presence of an acute or chronic CVC.3,4 The reported incidence of DVT in pediatric intensive care unit (PICU) patients with a CVC ranges widely depending on whether clinical or radiographic evidence of DVT is evaluated.1,5–8 One prospective study of acute CVC placement in PICU patients found a 7.5% incidence of symptomatic DVT but an incidence of 18.3% based on radiographic evidence.1

Previous experience has demonstrated increased incidence of DVT in children with chronic conditions such as malignancy or congenital heart disease or with acute infection, surgery, trauma, or hypovolemia.9,10 Diabetes mellitus has not been described as a specific isolated risk factor for DVT in children, although a propensity for hypercoagulability has been noted in diabetic adults.11

Despite growing experience regarding CVC-related thrombosis in children, increased risk of CVC-associated DVT in children with diabetic ketoacidosis (DKA) was not described until a recent case series.12 Consistent with that study, we identified 3 patients with DKA who developed clinically significant DVT after femoral CVC placement. We reviewed our experience with DVT in DKA patients and hypothesized that DKA would be associated with a higher number of CVC-associated DVTs than in non-DKA patients in our PICU.

METHODS

Billing database records from children admitted to the PICU at Children’s Health Care of Atlanta at Egleston, GA were searched for all patients admitted with DKA between the years 1998 and 2002 using International Classification of Diseases diagnosis codes for DKA (250.1) and diabetes with other coma (250.3). Patients with DKA are generally managed with insulin infusions at our institution in non-intensive care unit floor settings. PICU admission criteria include initial serum pH < 7.0, significant alteration in mental status, or persistent signs of hypovolemic shock after initial DKA resuscitation. Intravenous access in our PICU for management of DKA is obtained peripherally. CVCs are only placed if the medical staff is unable to obtain or maintain adequate peripheral access.
Table 1. Characteristics of DKA Patients With CVC Placement and Subsequent DVT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>16</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Initial glucose concentration (mg/dL)</td>
<td>986</td>
<td>776</td>
<td>814</td>
</tr>
<tr>
<td>Initial serum pH</td>
<td>6.85</td>
<td>7.07</td>
<td>7.12</td>
</tr>
<tr>
<td>Time to CVC placement; site</td>
<td>3 hours; left femoral vein</td>
<td>2 hours; right femoral vein</td>
<td>2 hours; right femoral vein</td>
</tr>
<tr>
<td>Venous catheter size</td>
<td>5-French (× 8 cm), triple lumen</td>
<td>4-French (× 5 cm), double lumen</td>
<td>5-French (× 12 cm), triple lumen</td>
</tr>
<tr>
<td>Hours CVC in place before symptoms</td>
<td>36</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>Radiographic confirmation of DVT</td>
<td>Magnetic resonance venography</td>
<td>Ultrasoundography</td>
<td>Ultrasoundography</td>
</tr>
<tr>
<td>Treatment</td>
<td>CVC removed, unfractionated heparin infusion, then LMWH (3 mo)</td>
<td>CVC removed, LMWH (3 mo)</td>
<td>CVC removed; LMWH (3 mo)</td>
</tr>
</tbody>
</table>

LMWH indicates low molecular weight heparin.

All DKA patients with DVT developed signs or symptoms within 48 hours of CVC placement with lower extremity edema and swelling, decreased extremity temperature, and difficulty with aspirating or flushing the CVC. All DVTs were confirmed by radiographic imaging (Table 1).

During the same time period, CVCs were placed in 486 patients (including DKA patients); 413 of these (85% of CVCs) were femoral catheters. Clinically recognized DVTs were reported in 6 patients (including DKA patients). All documented DVTs were found in patients with femoral CVCs. DVTs occurred in 6 of 486 (1.2%) patients with CVCs and 6 of 413 (1.5%) patients with femoral CVCs (0.7% in non-DKA femoral CVCs) compared with 3 of 6 (50%) DKA/CVC patients with DVTs ($P < .001$ by $\chi^2$).

CVCs were removed in all 3 patients at the time of DVT diagnosis. As therapy (Table 1), one patient received unfractionated heparin infusion that was changed to low molecular weight heparin after 24 hours. All patients received low molecular weight heparin that was continued at home until ultrasound confirmation of DVT resolution. Coagulation profiles were performed on all 3 patients. Studies included serum prothrombin time, antithrombin III, homocysteine, protein C, protein S, lipoprotein a, and factor VIII concentrations. All values were within normal limits except that protein S activity was slightly decreased in patients 1 (40%; reference range: 65–140%) and 2 (44%). Protein S activity was increased to normal range on follow-up measurement (107% and 114%, respectively). Patient 2 was also found to be heterozygous for factor V Leiden activity, but this was not considered to be clinically significant.

Age-matched control patients were diagnosed with shock (7: 3 hypovolemic, 2 septic, 2 cardiogenic, and 5 hypovolemia/respiratory failure). The median patient age in controls was 2.5 years (range: 1–16 years). CVC duration was significantly shorter in DKA patients (median 2 days [range: 1.5–4] vs 7 days [1–16] in control patients; $P = .05$). Clinical evidence of DVT was not reported in any non-DKA shock patient. Laboratory values in DKA/CVC patients and age-matched controls are shown in Table 2. DKA patients with CVCs had significantly greater glucose concentrations ($P < .001$) and serum osmo-
Follow-up. Low molecular weight heparin was continued for 6 months after hospitalization and then discontinued without further problem.

DISCUSSION

Our report mirrors the experience recently reported by Gutierrez et al.12 In their series, 4 of 8 DKA patients that required a femoral CVC developed symptomatic DVT. As with our study, serum glucose was significantly higher and serum pH was significantly lower than in age-matched control patients with shock and CVC. None of the control patients in that study demonstrated DVT.12 We also reviewed a larger cohort of non-DKA/CVC PICU patients to provide a more extensive comparison to DKA/CVC patients.

Several potential mechanisms could account for the increased tendency for CVC-related thrombosis with hyperglycemia11 and DKA. An acute increase in platelet aggregability has been demonstrated in adult volunteers undergoing oral glucose challenge.14 Red blood cell rigidity increases with elevated blood glucose and decreased pH, increasing viscous resistance and impairing blood flow.15,16 Acute hyperglycemia may create these platelet and blood-flow changes by reducing nitric oxide availability.17 Dehydration associated with DKA could be a contributing factor to enhancing venous stasis as part of Virchow’s triad of pathogenesis of DVT. Although suggested, dehydration alone has not been specifically isolated as a causative factor in either adults or children.18,19

Both series showed a higher percentage of CVC-associated DVT in younger DKA patients. Combining both patient series, the median age of DKA/CVC patients with DVT was 18 months (range: 1–18 months) compared with 10 years (range: 16 months to 13 years) in DKA/CVC patients without DVT (P = .002). This is probably due to the smaller femoral vessel diameter of toddlers and greater risk for occlusion and intimal damage. Another possibility is that recognition of new-onset diabetes mellitus could be delayed in young children, leading to increased hyperosmolarity and venous stasis at the time of presentation. Unfortunately, younger DKA patients are also more likely to have difficulty with obtaining peripheral catheters and thus to require central access.

Underlying thrombophilia syndromes could place pediatric cancer patients at higher risk for DVT20 but

<table>
<thead>
<tr>
<th>Laboratory Value (serum)</th>
<th>DKA/CVC Patients (n = 6)</th>
<th>Age-Matched Control CVC Patients (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>874 (520–1290)</td>
<td>80 (58–201)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Serum pH</td>
<td>7.09 (6.85–7.12)</td>
<td>7.34 (7.16–7.48)</td>
<td>.001*</td>
</tr>
<tr>
<td>Carbon dioxide (mmol/dL)</td>
<td>6 (2–15)</td>
<td>18.5 (13.4–39.0)</td>
<td>.002*</td>
</tr>
<tr>
<td>Calculated serum osmolarity (mOsm)</td>
<td>312 (291–356)</td>
<td>291.5 (277–313)</td>
<td>.013*</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>131 (113–145)</td>
<td>136 (131–146)</td>
<td>.169</td>
</tr>
<tr>
<td>Corrected sodium (mmol/L)</td>
<td>141 (140–159)</td>
<td>136.5 (131–146)</td>
<td>.027*</td>
</tr>
</tbody>
</table>

* Statistically significant difference between median values.
have not been reported in diabetes mellitus. Two of our 3 DKA/DVT patients had mildly decreased protein S activity that later resolved. This could be a result of factor consumption with critical illness and thrombosis rather than a cause of DVT in these patients.

CVCs are used infrequently in our PICU for DKA patients and are placed only when adequate peripheral access can not be obtained or maintained for acute resuscitation and medication. We primarily place femoral catheters for central venous access. The femoral site offers potential ease of placement in critically ill children without risk of mechanical pulmonary complications.6,8 Our predominant use of femoral catheterization is in contrast to the lower percentage choice (41% and 42%) in 2 previous prospective studies.12

Elevated venous pressures (4 mmHg) diagnosed by signs and symptoms may be 2 to 3 times higher than DVT diagnosed by signs and symptoms alone. Several studies found no increase in complications with femoral sites in children.1,6,7 A recent prospective study in adults found greater risk of femoral vein infectious and thrombotic complications than for subclavian catheterization.21 The significance of these findings for children is uncertain.

The current study is limited by its retrospective nature and the absence of routine radiographic evaluation of all patients with CVCs. Several studies found the incidence of DVT determined by ultrasound1,5 or venography to be 2 to 3 times higher than DVT diagnosed by signs and symptoms alone. It is likely that we significantly underestimated the incidence of symptomatic DVT and did not recognize all asymptomatic DVTs. However, this limitation also applies to both DKA and non-DKA patients and to the other recent series.12

CONCLUSIONS

Children with DKA are at greater risk for femoral CVC-associated DVT than other pediatric patients with circulatory shock. Use of CVCs should be avoided in DKA patients. If absolutely necessary, femoral CVCs should be removed or replaced as soon as possible after immediate resuscitation. If continued use of a CVC is required, prophylaxis with low molecular weight heparin should be considered given the documented risk for DVT.

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REFERENCES

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