

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.

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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 for fluid resuscitation, insulin infusion, and access for other intravenous medications such as antibiotics.

This group was subsequently cross-matched with procedure codes for CVC placement and confirmed by using a critical care procedure database. Medical records were reviewed for patients identified with DKA that required a CVC for volume resuscitation. Calculation of serum osmolality and correction of serum sodium concentrations for hyperglycemia were performed by using standard formulas.¹³

Degree of dehydration, type of fluids, and fluid administration rate were obtained. DVT was defined as leg swelling and edema, with thrombosis confirmed by radiographic study. CVC-associated DVT was defined as ipsilateral leg swelling with CVC placement, with thrombosis confirmed by radiographic study, and symptoms persisting after CVC removal.

For comparison, the PICU database was also reviewed for all non-DKA patients undergoing CVC placement during the same time period. Two age-matched non-DKA PICU patients with a diagnosis of circulatory shock and placement of a femoral CVC were located for each DKA/CVC patient to provide comparison data. Clinical findings and admission laboratory values were compared with similar information from consecutive DKA/CVC patients. Comparison patients were excluded if concomitant coagulopathy was noted.

Data were analyzed by using standard statistical software (Sigma Stat 2.0). Differences in laboratory and physiologic variables were compared between groups by using a standard *t* test for parametric data and Mann-Whitney rank sum test for non-parametric data. Differences in the incidence of DVT between populations were evaluated by using Fisher's exact test. Statistical significance was determined by a *P* value < .05.

RESULTS

During the study period, 113 patients with DKA were admitted to the PICU. The median age of all DKA patients was 11 years (range: 1 month to 23 years). Of those admissions, only 6 (5.3%) required CVC placement. The median age of DKA patients with CVC was 2.5 years (range: 14 months to 12 years). The median time of CVC placement was 2.7 hours after PICU admission. All CVCs in DKA patients were placed in the femoral vein (4 on the right and 2 on the left).

Of 6 DKA patients with CVC, 3 developed clinical evidence of DVT (all in the extremity of CVC placement) (Table 1). All 3 were female. The median age of DKA patients with CVC and DVT was 16 months, compared with a median of 10.5 years in DKA patients with CVC without DVT (*P* = .067). The median age of DKA patients with CVC/DVT was also not significantly different from all DKA patients without CVC (*P* = .10).

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 χ^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-

TABLE 1. Characteristics of DKA Patients With CVC Placement and Subsequent DVT

	Patient 1	Patient 2	Patient 3
Age (mo)	16	14	18
Initial glucose concentration (mg/dL)	986	776	814
Initial serum pH	6.85	7.07	7.12
Time to CVC placement; site	3 hours; left femoral vein	2 hours; right femoral vein	2 hours; right femoral vein
Venous catheter size	5-French (× 8 cm), triple lumen	4-French (× 5 cm), double lumen	5-French (× 12 cm), triple lumen
Hours CVC in place before symptoms	36	48	24
Radiographic confirmation of DVT	Magnetic resonance venography	Ultrasonography	Ultrasonography
Treatment	CVC removed, unfractionated heparin infusion, then LMWH (6 mo)	CVC removed, LMWH (3 mo)	CVC removed; LMWH (3 mo)

LMWH indicates low molecular weight heparin.

TABLE 2. Comparison of Laboratory Values (Expressed as Median [Range]) Between DKA Patients With CVC and Age-Matched Patients (Median 2.5 years) With Shock and CVC (2 Controls for Each DKA Patient)

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

* Statistically significant difference between median values.

larity ($P = .013$) than control patients. Serum pH ($P = .001$) and serum CO_2 ($P = .002$) were also significantly lower in DKA/CVC patients than their age-matched CVC controls. Corrected serum sodium values were significantly higher in DKA/CVC patients ($P = .027$). Serum blood urea nitrogen, platelet counts, and hematocrit and platelets were not significantly different between groups. No age-matched shock/CVC patients had clinical evidence of DVT. DKA/CVC patients were significantly more likely to have DVT than age-matched shock/CVC patients ($P = .025$).

Illustrative Case Report

A 16-month-old previously healthy African American female (patient 1) was evaluated after 2 weeks of polydipsia and polyuria followed by vomiting and lethargy. She was obtunded with initial serum glucose of 986 mg/dL and serum pH 6.85, and DKA was diagnosed. She received normal saline and insulin and was transferred to the PICU.

Within 3 hours of PICU admission, a 5-French, 8-cm, triple-lumen catheter was placed in her left femoral vein due to difficulties obtaining adequate peripheral intravenous access and ongoing need for aggressive fluid and insulin therapy. Hypotension persisted despite administering a total of 60 mL/kg normal saline, and she transiently received a dopamine infusion for several hours. Empiric antibiotic therapy was given, but no organism was isolated. The CVC was also used for insulin infusion and intravenous fluids for maintenance and deficit fluid requirements.

On PICU day 2, 30 hours after CVC placement, significant left lower extremity edema was noted. The CVC was removed and the patient was started on low molecular weight heparin at 1 mg/kg per dose twice daily. Ultrasonographic examination done on day 3 did not demonstrate DVT. Because of persistent extremity edema, magnetic resonance venography was done 2 days later, which confirmed the presence of a near-completely occlusive thrombus within the inferior aspect of the left external iliac vein. She was discharged from the hospital on hospital day 7 on subcutaneous insulin and low molecular weight heparin. At follow-up 1 week after discharge, her leg edema had improved noticeably, and it was almost completely resolved 7 weeks later at follow-up. Low molecular weight heparin was con-

tinued 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 a 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 hyperosmolality 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

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.^{1,6} Although 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 ultrasonography^{1,5} 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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