The Art and Science of Infusion Nursing

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Catheter-Associated Thrombosis in Children

Single-Institution Experience and Review of Pediatric Venous Thromboembolic Disease

ABSTRACT

Central venous catheters and peripherally inserted central catheters are widely used in children with serious chronic diseases. In this report, data about catheters and venous thromboembolic disease (VTE) in children will be reviewed, and the experience of a single academic children's hospital will be described. Two separate data sets that examine overlapping subpopulations will be reported: (1) the proportion of pediatric patients with catheters who develop VTE and (2) the proportion of patients referred to pediatric hematology for VTE who have catheters. The limitations of current pilot data and the authors' approach to better define this problem and its prevention are discussed.

Key words: central venous catheters (CVCs), deep vein thrombosis (DVT), peripherally inserted central catheters (PICCs), pulmonary embolism (PE), venous thromboembolism (VTE)

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More than 5 million central venous catheters (CVCs) are placed each year in the United States and are necessary in the treatment of seriously ill patients.[1] Central venous access is often required in children to provide total parenteral nutrition, prolonged antibiotics, and chemotherapy.

Various types of central venous lines have been developed to provide access for rapid infusion of fluids or medicines, prolonged medication administration, frequent blood draws, or recurring transfusions. Peripherally inserted central catheters (PICCs) are a frequently used means for providing prolonged fluid and medicine administration, especially for ambulatory patients. Typically, these lines are inserted in an upper extremity vein (median cubital, basilic, or cephalic) and advanced to the atrio-caval junction, where the rate of blood flow limits irritation of the vein by the infusate. PICCs may have multiple lumens if a patient requires more than 1 therapy simultaneously—for instance, parenteral nutrition and antibiotics. CVCs can be tunneled or nontunneled. Whereas tunneled lines (often called Hickman or Broviac lines) may be used for ambulatory infusion, nontunneled lines typically are removed before a patient's discharge from a health care facility. A wide range of sizes and lumen numbers are available. CVCs are generally placed in the internal jugular, subclavian, or femoral vein.

Although these devices are essential in the care of patients, their use is not without risk. Such complications as infection, dysfunction, or obstruction have been reported in as many as 65% of central lines in pediatric patients.[2] More than 50% of venous thromboses in children have been related to CVCs, making catheter placement the single most significant risk factor for thrombus formation in children.[3,4] The rate of catheter-associated venous thromboembolic (VTE) disease in pediatric patients has been observed to be between 7%

and 14%.[5-8] Differing rates of thrombosis have been reported with PICCs (10%) compared with CVCs (2%).[9] Deep vein thrombosis (DVT) is subsequently associated with the risk of developing serious complications, such as pulmonary embolus or postthrombotic syndrome.[3,10]

The pediatric pilot studies described here form an effort to better understand the rate of VTE associated with central line placement and the consequences that follow. In a retrospective analysis, we reviewed the charts and billing data of pediatric patients who had undergone central line placement during the time period of interest. The primary outcome of the study was to define the rate of catheter-associated DVTs among pediatric patients at our institution. Secondarily, we compared rates of thrombosis between PICCs and CVCs. We then examined a different denominator—pediatric patients referred to hematology for VTE—to look at catheter-associated events and underlying risk factors.

METHODS

In the first pilot study, we performed a retrospective chart review of pediatric patients who had undergone central line placement at our institution between January 1, 2007, and August 31, 2011. Billing data were used to identify the patients—current procedural terminology codes for line placement and International Classification of Diseases (ICD-9) codes for DVT. These 2 cohorts were collated and queried for temporal relationships indicating the presence of a line-associated thrombus. Comparisons were then made between the rates of thrombus formation with PICCs and CVCs using rate of occurrence.

In the second pilot study, a thrombosis and thrombophilia referral patient database was created to track cases of thrombosis. Both inpatient and outpatient hematology consults were followed, with referrals occurring at the authors' institution between January 1, 2007, and August 31, 2011. Characteristics associated with thrombus formation—such as underlying medical condition, thrombophilia evaluation, and line placement—were tracked through the database.

Approval for this study was granted by the University of North Carolina's institutional review board.

RESULTS

Nine hundred twenty-two lines were identified as having been placed in pediatric patients during the specified time period, an average of 16.5 lines placed a month. One hundred one CVCs and 821 PICCs were placed. Fifty-three central line-associated DVTs were observed in our study population, yielding a rate of 5.7% (53/922). Thirteen DVTs were associated with CVCs (12.9%, 13/101), and 40 thromboses were reported with PICCs (4.9%, 40/821).

Over the same 4 years, 164 patients were referred for hematology consultation for thrombosis or thrombophilia evaluation (an average of 41 referrals a year); they were included in the referral database. One hundred twenty-six patients referred for consultation had a thrombosis (77%). Fifty-three patients had a line-associated VTE (42%). Forty-four of the 126 patients with documented thrombus had an underlying thrombophilia (35%). Ten of the 53 with a line-associated thrombus (19%) were also determined to have a concomitant thrombophilia. Seventeen of the patients with thrombosis also developed pulmonary embolism (13%); 5 patients (4%) died as the result of complications associated with a thrombus.

DISCUSSION

Catheter-Associated Thrombosis

We present a retrospective pilot study that was performed to better understand the rate of catheter-associated venous thrombosis at one tertiary care pediatric institution. The total rate of symptomatic catheter-associated DVT of 5.7% observed at our institution is similar to previously reported rates (7%-14%).[5-8] Rates as high as 18.3% among critically ill patients have been observed.[11] Prospective studies evaluating patients for both symptomatic and asymptomatic venous thrombosis associated with central line placement have reported rates as high as 35%.[12-14] The rate observed in our study is certainly lower than these because we considered symptomatic thromboses only.

In prior studies, the rate of thrombosis associated with PICCs has been observed to be higher than the rate observed with CVCs—10% compared with 2%.[9] We observed a higher rate of VTE associated with CVCs as opposed to PICCs. The increased rate observed with CVCs may be due in part to their typically larger diameter compared with PICCs and the smaller caliber of pediatric veins in which they have been placed. An increased rate of thrombus formation with increasing catheter diameter (number of lumens) and an inverse correlation to the size of the vein accessed has been reported.[14-17] CVCs are often used for patients with higher acuity of disease, which may explain a higher rate of thrombosis with their use compared with PICCs. The higher rate of thrombosis seen in our analysis with CVCs may also be related to an underrepresented sample population. CVCs are often placed in the critical care unit and may be billed in a bundle of other charges. For this reason, some short-term, nontunneled CVCs may not have been identified in our study. It is not clear whether these missed cases would increase or decrease

the CVC clot rate. Additional studies comparing thrombosis rates between PICCs and CVCs are needed, and they need to include duration of catheter exposure.

Upper extremity DVTs account for about 10% of all DVTs, and most are associated with central catheters. The diagnosis of upper extremity thrombosis may be more challenging than in lower extremities. Doppler ultrasound is less sensitive in the upper central veins, and further evaluation with additional imaging is often necessary. The risk of associated pulmonary embolus and clot recurrence is lower than the risk with lower extremity DVTs. Previous studies have demonstrated increased rates of thrombosis related to the location of line placement. Higher rates have been observed with internal jugular placement as opposed to subclavian[18,19]; however, contradictory results have also been reported, with higher rates seen with subclavian placement.[8,12] At this time, the question of optimal location for central line placement remains unanswered.

Advancement of a line's tip has also been associated with varying risk of thrombus formation. In one series, all cases of PICC-associated thrombosis were related to the distal migration of the line from the superior vena cava (SVC) into a vessel with lower flow velocity.[9] Tip placement at the SVC-atrial junction has been associated with lower rates of thrombosis compared with placement in the axillosubclavian-inominate vein.[20,21] These studies indicate that proper placement of a PICC tip is important to reduce the risk of clot formation.

Additional factors such as catheter composition may also contribute to the risk of thrombus formation. Older lines were made from stiffer materials that carried a higher risk of clot formation.[16] In this current study, the authors did not record the location of line placement, diameter (French) of the line, or number of lumens. Nor did we distinguish among tunneled, nontunneled, and implanted CVCs. Future studies comparing these variables will be informative.

Although the incidence of DVT is much lower in pediatric patients compared with adults (as many as 10 to 100 times fewer cases), the rates among children are increasing.[22] Rates are thought to be higher among patients cared for in tertiary care centers because of the increased prevalence of children with CVCs, chronic illnesses, and higher acuity of illness. As noted above, the majority of pediatric patients who develop a DVT have a concurrent CVC, making line placement the single largest risk factor for clot formation among children. More than 50% of thromboses noted in some pediatric studies have been attributed to central lines.[3,4] From the authors' database, 42% of clots were line associated, making lines the most significant risk factor seen in our patient population. Additional acquired risk factors associated with clot development included infection, inflammation, malignancies, dehydration, immobility, surgery, obesity, and medications. At the authors' institution, 10% of pediatric patients referred with VTE have a BMI greater than 30, which may be low compared with other data sets.

Inherited thrombophilias contribute to DVT formation among pediatric patients; however, these alone are generally less common than other risk factors. In pediatric patients, there is usually a combination of factors (temporary and permanent; acquired and underlying) that leads to thrombus formation.[23] In our patient population, more than one-third (35%) of pediatric patients with a thrombosis had an underlying thrombophilia. More than half of these patients had both a central line and a thrombophilia. The decision for pursuing a thrombophilia evaluation depends on whether other potential etiologies have been identified, the severity of the thrombosis, whether a patient experiences subsequent thrombus formation, and the response of the VTE to therapy. However, the prevalence of thrombophilia in these data is high, suggesting that pediatric patients with line thrombosis should be evaluated for underlying risk factors.

In reviewing the referral database, 17 (13%) patients developed the complication of pulmonary embolus, and 5 (4%) patients died as a result of complications associated with their thrombosis. The morbidity from pulmonary embolism or postthrombotic syndrome has been reported by the Canadian Registry of Venous Thromboembolic Complications to be 6.5% to 9.4%, and there is a mortality of 2.2% associated with VTE.[3,10] The higher percentages of patients with a thrombophilia and pulmonary embolus seen in our institution are likely due to selection bias of referrals made to a tertiary care center.

Diagnosis

The diagnosis of catheter-associated VTE in children is most frequently obtained using Doppler ultrasound studies because they are noninvasive, although the technique has a poor sensitivity for the central veins of the upper extremities. Additional studies such as computed tomography angiogram, magnetic resonance angiogram, echocardiogram, or site-directed venogram can be used if the diagnosis remains uncertain. Venography is often considered the gold standard study for diagnosis of catheter-associated thrombosis because of its high sensitivity and specificity; however, it requires exposure to radiation and contrast.[14] Venograms can be used in concert with thrombolysis to provide both diagnostic and therapeutic benefit. Studies comparing Doppler ultrasound and venography for the diagnosis of line-related thrombosis in children are needed.

Treatment and Prevention

Therapy for DVT in children is similar to therapy in adults, and evidence-based guidelines have been published.[24] Removal of any possible risk factors is

often the initial step. Whenever possible, CVCs should be removed. Anticoagulation is often achieved initially with a continuous heparin infusion or low-molecular-weight heparins, such as enoxaparin (Lovenox) or fundaparinux (Arixtra). Argatroban has been employed in the setting of heparin-induced thrombocytopenia. Coumadin remains the most commonly used method for oral anticoagulation. Newer oral agents such as dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) have been used effectively in adults and are showing promise for use in older children. Although there is a risk of bleeding with anticoagulation therapy, in this patient series the rate of anticoagulation-associated bleeding was 2%. Methods for thrombosis prevention include risk factor modification (hydration, activity, weight loss, smoking cessation), treatment of underlying medical conditions, using smaller-gauge lines, choosing sites associated with lower rates of clot formation, and intermittently infusing line with antithrombotic agents, such as heparin. Catheter surface modifications have been used as well. Heparin-bonded catheters have been associated with lower rates of thrombosis but may lead to the development of antiplatelet antibodies and thrombocytopenia.[14] Systemic antithrombotic administration for prophylaxis in children with central lines has been shown to be safe with unclear efficacy.[25]

Education and proper patient selection are factors that may decrease the rates of complications with central venous lines. At the authors' institution, a pediatric nursing specialty team is available for PICC placement and support. Patients must meet certain criteria for PICC placement to avoid unnecessarily exposing them to the risks of the intervention. Patients must require prolonged IV medications (>5 days) or parenteral nutrition. PICCs are placed in the median cubital, cephalic, or basilic veins with the tip advanced to the SVC-atrial junction. The basilic and cephalic sites are preferred to the median cubital site to promote movement of the arm. Lines may remain in place for as long as 1 year, if properly maintained. All families are required to watch a video describing proper care of the line before its placement, and before discharge, all families and patients are instructed by nurses on proper care and maintenance of the line (dressing changes, flushing with normal saline and heparin). Families must demonstrate proficiency in line care before discharge. Further investigation of thrombosis rates between families receiving education and those not receiving education is needed. Once a thrombosis has occurred, an entirely different set of educational materials is required, and education about anticoagulation and secondary prevention becomes necessary.

Monitoring Therapy

An underused but simple method for monitoring anticoagulation therapy is the evaluation of serial d-dimer levels. D-dimers are the degradation products formed from the proteolysis of a fibrin clot by plasmin and are a marker of endogenous fibrinolysis.[26,27] The diagnostic negative predictive value for d-dimer measurement in a patient determined unlikely to have a DVT has been well established.[27] Additionally, measuring d-dimer levels 1 month after discontinuation of anticoagulation has been useful in guiding duration of treatment. An elevated d-dimer level 1 month after anticoagulation discontinuation has been associated with increased risk of thrombus recurrence and indicates a need for resumption of anticoagulation.[28,29] Optimal duration of therapy remains uncertain, and the available data addressing this question are largely from adult studies. Three and 6 months of anticoagulation were shown to be equivalent in the treatment of proximal DVTs or pulmonary embolus.[30] A subsequent study has demonstrated a slight but statistically significant increase in risk of DVT recurrence in the setting of anticoagulation for less than 6 months.[31] Three months of therapeutic anticoagulation is often recommended for most pediatric patients, followed by a possible longer course of prophylaxis based on prior history of thrombosis, underlying risk factors, severity of thrombosis, response to therapy, and whether a provoking line (eg, the line that was in place at the time of thrombus formation and is associated with its formation) is still in place.[24]

FUTURE STUDIES

The studies reported here are limited by the methods in which the study populations were determined. In using billing data, there exists the potential to fail to capture portions of the study population. For example, critical care billing can be bundled so that individual codes for line placement may not be used. The current study underestimates the number of lines placed in the critical care setting and likely underestimates the rate of associated DVTs, although the duration for which those lines remain in use is probably a modifier. The number of catheter-associated clots would likely be higher among the critically ill patient population because of their underlying illness; however, this increased risk is often outweighed by the benefit of secure venous access in this closely monitored population. The current study does not identify the underlying reason necessitating central line placement, nor are line characteristics, such as location of placement, recorded. For the hematology referral database, selection bias is a given. Future studies to compare rates of line-associated clots among children with various medical conditions, various locations of placement, and different catheter sizes and types will be informative.

These data show an overall rate of central line-associated venous thrombosis similar to what has been reported previously in the pediatric literature. However,

the rate for CVC-associated thrombosis is higher in our population than the rate associated with PICCs, which is the opposite of what has been previously observed. A study including a larger patient population is in progress to better elucidate the relative risks of thrombosis among PICCs, CVCs, and implanted ports. In addition, referrals to pediatric hematology for VTE in patients with CVCs and PICCs show a relatively high rate of underlying thrombophilia (19%), notwithstanding the common acquired risk factors. Whether these underlying risks affect future treatment and prevention in patients with CVCs and PICCs will need to be studied further in pediatric populations.

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