Increased Risk of Thrombosis Associated with Peripherally Inserted Central Catheters Compared with Conventional Central Venous Catheters in Children with Leukemia

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Objective To study the risk of catheter-associated thrombosis (CAT) between peripherally inserted central catheters (PICCs) and tunneled central venous catheters in children with leukemia.

Study design We analyzed all PICCs and conventional tunneled catheters placed in patients aged <18 years and admitted to our institute for leukemia treatment between February 2008 and April 2014. Cases of symptomatic CAT were confirmed by ultrasound and treated with low-molecular-weight heparin.

Results During the study period, 157 PICCs and 138 conventional tunneled catheters were placed in 192 patients with leukemia. CAT incidence was 1.5% (n = 2) in the conventional tunneled catheter group and 10.2% (n = 16) in the PICC group. The OR for CAT occurrence after PICC vs conventional tunneled catheter placement was 5.6 (95% CI, 1.2-26.5).

Conclusion Our results suggest that the use of PICCs in children with leukemia increases the risk of CAT in comparison with the use of conventional tunneled catheters. Further randomized controlled studies are needed to characterize this risk and to better define indications. *(J Pediatr 2018;■■:■■-■■).*

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Central venous lines (CVLs) are important in the treatment of children with cancer, but have been shown to be strongly associated with venous thromboembolic events (VTEs) in both solid tumor[1-4] and hematologic[3-8] malignancies. For example, Piovesan et al reported that 30% of VTEs in children with cancer were associated with CVLs and that these events most frequently manifested as deep vein thrombosis in the extremities.[3]

Peripherally inserted central catheters (PICCs) are increasingly used in patients with hematologic malignancies, both adults and children.[9,10] PICCs are inserted into a peripheral vein and advanced to place the catheter tip in the superior vena cava. This insertion mode causes fewer immediate complications than conventional tunneled catheters.[9,11,12] PICCs are, however, associated with thrombosis at the insertion site,[10,13,14] particularly in patients with cancer.[13,15,16] The authors of a meta-analysis published in 2013[13] reported that the rate of VTEs in adult patients with cancer with PICCs ranged from 4.69% to 8.64% and that the probability of developing a VTE was significantly higher when PICCs were used compared with conventional tunneled catheters (OR, 2.55). In the general pediatric population, there seems to be no significant difference in the incidence of thrombosis between these 2 methods for establishing venous access.[10] However, to the best of our knowledge, no studies have compared PICCs with conventional tunneled catheters as concerns thrombosis development in children undergoing treatment for leukemia.

Since 2008, the use of PICCs has increased in our pediatric hematology and oncology institute, with a concomitant decrease in that of conventional tunneled catheters. We took advantage of this evolution in practices to compare retrospectively the risks of thrombosis associated with PICC and conventional tunneled catheter placement in children diagnosed with leukemia.

Methods

We conducted a single-center, retrospective study at the Pediatric Hematology and Oncology Institute in Lyon, France. Children diagnosed with hematologic cancer between February 1, 2008, and December 31, 2013, were identified using the

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CAT	Catheter-associated thrombosis
CVL	Central venous line
L-ASP	L-asparaginase
LMWH	Low-molecular-weight heparin
PICC	Peripherally inserted central catheter
VTE	Venous thromboembolic event

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The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.03.026

hospital's database and medical records. Data collected for all patients included cancer type, leukemia type (acute lymphoblastic leukemia [ALL] or acute myeloid leukemia [AML]), CVL characteristics (conventional tunneled catheter or PICC, number, site implantation), patient characteristics (age, sex), and chemotherapy administration (L-asparaginase [L-ASP] or not). The catheters analyzed in this study were placed in the included patients between February 1, 2008, and April 27, 2014. Patients who received low-molecular-weight heparin (LMWH; the only anticoagulant used by the institute) during the study period were identified using the database of the hospital's pharmacy department. The indications for LMWH use were analyzed in the hospital's database.

Study Population

The study population included all patients <18 years of age with newly diagnosed or relapsed leukemia (ALL or AML). Exclusion criteria were hematologic cancer other than leukemia, care started in another hospital, no CVL use, and LMWH prescription for an indication other than CAT Only PICC-type and conventional tunneled catheter-type lines were analyzed. Conventional tunneled catheters included implanted ports and Broviac, Hickman, and similar types of catheters with a subcutaneous tunnel. Vascular access ports without a short subcutaneous tunnel are rarely used for leukemia treatment in our center and were, thus, excluded from the study. All catheters inserted between February 1, 2008, and April 27, 2014, were analyzed. We assessed all events occurring during the time from insertion to removal.

Patients were grouped according to the type of CVL deployed in their case (PICC group or conventional tunneled catheter group).

All chemotherapy protocols and the use of L-ASP were as per international protocol guidelines. The dosing and rhythm of L-ASP administration depended on the type of leukemia, the risk group and the treatment phase (induction, consolidation, etc).

Definition of Outcomes

The primary outcome was the occurrence of symptomatic catheter-associated thrombosis (CAT) after PICC or conventional tunneled catheter insertion. We defined CAT as thrombosis involving the deep veins of the arm (brachial, axillary, subclavian, or internal jugular veins). CAT was suspected when patients had symptoms (upper extremity edema, pain, or erythema) on the same side as the catheter, and confirmed by a radiologist using ultrasound imaging (Aplio 500, Toshiba Medical Systems, Otawara, Japan) with a valid quality control. Diagnostic criteria were noncompressibility of the vein, visible thrombus, or lack of Doppler-detected flow.

Catheter Insertion

All CVLs were placed by anesthesiologists according to international guidelines. PICCs were inserted under sterile conditions into peripheral veins (brachial, basilic, cephalic) and advanced to the vena cava; conventional tunneled catheters were placed in the internal jugular or subclavian vein. Some patients received several catheters (after intentional or accidental removal of an initial catheter); all subsequent catheters were inserted into a new vein. All PICCs and conventional tunneled catheters were made of silicone or polyethylene. Catheter size varied according to the age and weight of the patient. The final position of the intrathoracic catheter was verified at the end of the procedure by chest radiograph in the anesthesiology department. The implantation was considered successful when the catheter tip was placed at the junction of the superior vena cava and the right atrium.[17]

CAT Management

CATs were treated systematically with LMWH, namely, tinzaparin sodium (INNOHEP, 10 000 IU anti-Xa/0.5 mL) administrated subcutaneously (LEO Pharma, Ballerup, Denmark). A therapeutic dose of 175 IU/kg/day was administered for 3 months (minimum) according to international guidelines.[17,18] Central catheters were not removed upon CAT diagnosis. Clot resolution was confirmed by a new ultrasound examination.

Statistical Analyses

The probability of CAT in each group was assessed with Kaplan-Meier analysis and compared with the log-rank test. Multivariate and Cox analyses were used to screen for potential CAT risk factors. These latter were selected according to previously published data: sex, age (<12 or ≥12 years of age and <18 years of age), type of leukemia (ALL or AML), characteristics of the central catheter (vein used, type of catheter), and chemotherapy including L-ASP or not. Because none of the catheters were removed after the diagnosis of CAT, catheter removal could not be related to the statistical event. As mentioned, any subsequent catheters were always inserted in another vein. Thus, every catheter could be considered independent of the patient in terms of CAT occurrence. Statistical significance was set at $P < .05$ and all statistical analyses were performed with SPSS version 24.0 (SPSS Inc, Chicago, Illinois).

Results

During the 74-month study period, there were 216 patients diagnosed with hematologic malignancies. Twenty-one of those patients were excluded for lymphoma (n = 6), care started in another center (n = 8), incomplete data (n = 3), or other diseases (n = 4, ie, chronic myeloid leukemia [n = 1], severe aplastic anemia [n = 2], and myelodysplastic syndrome [n = 1]). Three of the remaining 195 patients died before central catheters were placed. Thus, for the present study, 192 patients with leukemia (28 with AML and 164 with ALL) were analyzed.

The analysis of the pharmacy database found 50 children treated with LMWH, 16 of whom had leukemia. Three of these 16 patients were treated for cerebral venous thrombosis and, thus, excluded, leaving 13 patients with leukemia who received LMWH for an upper extremity CAT. A further search of the hospital database found 4 additional LMWH-treated patients who were not in the pharmacy database. One of these 17 patients had 2 CATs at 2 different times. Thus, in all, 18 CATs occurred during the study period.

FLA 5.5.0 DTD ■ YMPD9875_proof ■ April 27, 2018