CENTRAL VENOUS LINE-RELATED THROMBOSIS IN CHILDREN: ASSOCIATION WITH CENTRAL VENOUS LINE LOCATION AND INSERTION TECHNIQUE

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Running title: RISK FACTORS OF CENTRAL VENOUS LINE-RELATED THROMBOSIS

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ABSTRACT

Background: Venous thromboembolic events (VTE) in children are associated with central venous lines (CVL). The study objective was to assess whether CVL location and insertion technique are associated with the incidence of VTE in children. We hypothesized that VTE would be more frequent with i) CVL location on the left body side, ii) CVL location in the subclavian compared to the jugular vein, and iii) CVL insertion by percutaneous technique compared to venous cut-down.

Methods: Prospective, multicentre cohort study in children with acute lymphoblastic leukemia during induction chemotherapy who had a CVL placed in the upper venous system. Characteristics of CVL were documented prospectively. All children had outcome assessment for VTE by objective radiographic tests including bilateral venography, ultrasound, echocardiography, and cranial magnetic resonance imaging.

Findings: Among 85 children, 29 (34%) had VTE. There were 28 VTE in the upper venous system and 1 sinovenous thrombosis. Left-sided CVL (odds ratio 2.5, 95% confidence interval 1.0-6.4, p=0.048), subclavian CVL (3.1, 1.2-8.5, p=0.025), and percutaneous CVL insertion (3.5, 1.3-9.2, p=0.011) were associated with an increased incidence of VTE. There was interaction between CVL vein location and insertion technique: subclavian vein CVL inserted percutaneously had an increased incidence of VTE (54%) compared to any other combination (p=0.07).
Conclusions: For CVL in the upper venous system, CVL placement on the right side and in the jugular vein may reduce the risk of CVL-related VTE. If subclavian vein placement is necessary, CVL insertion by venous cut-down appears preferable over percutaneous insertion.

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KEY WORDS: central venous line, cut-down, jugular vein, venous thrombosis, insertion technique, location, percutaneous, subclavian vein, upper venous system
INTRODUCTION

Venous thromboembolic events (VTE) in children occur predominantly as secondary complications of severe underlying diseases, such as cancer, congenital heart disease, prematurity, infection, and others.\textsuperscript{1-4} The major risk factor, accounting for more than two thirds of VTE in children, is the presence of a central venous line (CVL) which is frequently required for the treatment of primary disease.\textsuperscript{5,6} Venous thromboembolic events in children predominantly affect the upper body venous system reflecting the preferred location of CVL placement.

Pathogenic mechanisms of CVL-related VTE include the intravascular presence of a foreign surface, obstruction of venous flow, trauma to the venous wall at CVL insertion, and endothelial irritation by the line or by the infusate.\textsuperscript{7-9} There is biological rationale to suggest that location and insertion technique of the CVL are associated with different levels of obstruction of flow and venous trauma. Therefore, we hypothesized that CVL location and insertion technique would be associated with the risk of VTE. We hypothesized that VTE would be more frequent with i) CVL location on the left body side compared to the right, and ii) CVL location in the subclavian vein compared to the jugular vein. Based on the anatomy of the upper venous system (figure 1), venous access is more difficult and there is increased potential for obstruction to flow for CVL located both on the left side and in the subclavian vein. We also hypothesized that, in the subclavian vein, VTE would be more frequent with iii) percutaneous CVL insertion compared to surgical venous cut-down because the former may be associated with an increased risk for venous trauma.
FIGURE 1. Upper venous system.
Schematic of the central upper venous system with examples of a right internal jugular vein CVL (1), a left internal jugular vein CVL (2), and a right subclavian CVL (3).

Abbreviations: R, right; L, left; IJV, internal jugular vein; SCV, subclavian vein; BCV, brachiocephalic vein; SVC, superior vena cava.

In the literature, few studies have provided data on an association of CVL body side 8; 10-15, CVL vein location 14; 16-20, or CVL insertion technique 15; 21 with the incidence of VTE. Results from these studies are inconsistent or even contradictory, which is probably related to differences in study design, selection of study populations, and outcome assessment. Particularly, outcome assessment differed between studies
that variably used clinical endpoints, ultrasound, or venography to detect VTE. There is good evidence that CVL-related VTE frequently remain clinically undetected, therefore clinical endpoints alone are inappropriate for such a study.\textsuperscript{12; 14; 22} There is also recent evidence that ultrasound is insensitive for VTE in the subclavian vein, and venography is insensitive for VTE in the jugular vein.\textsuperscript{23; 24} Therefore, when screening for VTE in the two locations, both venography and ultrasound are required.

To date, no study has prospectively evaluated the association of CVL side, CVL vein location, and CVL insertion technique with the incidence of VTE using both ultrasound and venography. \textit{PARKAA (Prophylactic Antithrombin Replacement in Kids with ALL treated with Asparaginase)} was a multi-centre clinical trial evaluating the incidence of VTE in children with acute lymphoblastic leukemia (ALL) during treatment with asparaginase. By inclusion criteria, all patients had a CVL placed in the upper venous system, and for outcome assessment, all patients underwent screening for VTE by a panel of objective radiographic tests. The \textit{PAARKA} study presented a unique opportunity to perform a substudy designed to provide data on the association of CVL location and CVL insertion technique with the risk of VTE. Because these factors are controllable, information from this study could potentially aid in reducing CVL-related thrombotic complications.
METHODS

Study Design
The design was a prospective cohort study executed in 9 centres in North America. The study was a substudy of PARKAA which was an open label, randomized, extended phase II study designed to determine the incidence of DVT in children with ALL who received asparaginase as part of their induction chemotherapy and to explore the potential of antithrombin concentrates in preventing DVT in these children. The results from the PARKAA study are reported elsewhere.\textsuperscript{25, 26} The primary objective of the study presented here was to determine whether there is an association of CVL location and CVL insertion technique with the incidence of VTE. Central venous line-related variables were collected prospectively according to a standardized case report form. For outcome assessment, all patients were screened for VTE using a panel of objective radiographic tests after 4 weeks of induction chemotherapy.

Patient Population
Children with ALL were enrolled between July 1997 and May 1999. The study was performed in 9 pediatric tertiary care centres in Canada (Calgary, Edmonton, London, Ottawa, Vancouver) and the USA (Atlanta, Houston, Palo Alto, Syracuse). Patients were eligible for the study if they were between 6 months and 18 years of age, were receiving induction chemotherapy including Escherichia coli asparaginase, and had a functioning indwelling CVL placed within 2 week of initiating chemotherapy. Patients were excluded if they had one or more of the following conditions: had previously received asparaginase, a known
hypersensitivity to any of the ingredients in the antithrombin concentrate, other medical conditions that could have interfered with participation in the study, other investigational drugs were used within 30 days of enrolment, or they required therapeutic anticoagulation.

Patients were classified as high risk ALL in the presence of any of the following: i) age 10-18 years, ii) white blood count >50 x 10^9/L, iii) testicular leukemia, iv) central nervous system leukemia. Standard risk ALL was defined by the absence of these criteria. The study protocol was reviewed by the institutional review boards of all participating centres, and informed consent was obtained from all patients’ guardians and children of appropriate age.

Central venous line characteristics

Central venous line placement was done according to local standard of care at study centres. The body side and vein location of the CVL were the choice of the attending physician. Central venous lines were externalized tunneled silastic catheters (Broviac or Hickman) or subcutaneously implanted port systems. Catheter sizes were chosen appropriate for age (6 to 10 French diameter). All CVL were inserted under general anaesthesia in the operating room. All CVL were placed in the upper venous system, either in the subclavian vein by infraclavicular approach or in the jugular vein. Catheters were inserted either by percutaneous technique or by surgical venous cut-down. Percutaneous CVL insertion was done by use of anatomical landmarks or using ultrasound guidance. The vein was accessed by Seldinger technique, a guide wire passed into the vein, and after skin incision, the CVL was threaded into the vessel. For venous cut-down, the vein
was accessed by surgical preparation, and the CVL inserted through direct venotomy. The CVL tip was confirmed radiographically to lie in the superior vena cava or right atrium. Finally, the CVL was tunneled through the subcutaneous tissue for some distance where it was externalized or the subcutaneous port was placed. Minimum platelet counts of $50 \times 10^9$/L were generally required for CVL insertion but the decision whether to give platelet transfusions was left to the investigator. Central venous line characteristics were documented prospectively using a standardized case report form. These data included the body side of CVL location (right, left), the vein used for CVL access (subclavian, jugular vein), location of the CVL tip (superior vena cava, right atrium), and CVL insertion technique (percutaneous, venous cut-down).

As per study protocol, patients did not receive therapeutic doses of heparin or warfarin. Patients did receive small amounts of unfractionated heparin for prophylaxis of CVL-blockage either by continuous infusion (1-3 units/ml) or intermittent flushes (50-100 units/ml up to 4 times per day) according to local standard of care.

Laboratory prothrombotic markers tested included Factor V Leiden, the prothrombin gene G20210A mutation, plasma antithrombin levels, and antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies IgG and IgM). Details of the assays applied have been described in the primary study report.
**Outcome Assessment**

The primary study outcome was a VTE in any location either presenting with clinical symptoms or an asymptomatic VTE identified at exit screening. During the study period, patients were closely monitored for clinical symptoms of VTE. No definitions were stipulated for clinical presentation of VTE which was left to the judgement of the attending physician. There was one exception to this rule: if there was loss of CVL patency and local thrombolysis was unable to restore patency, or the decision was made to remove the CVL, objective testing for VTE had to be performed. Clinically suspected VTE was confirmed by objective radiographic test consisting of Color Doppler ultrasound, bilateral venography of the upper venous system (conventional or magnetic resonance venography) echocardiography, and magnetic resonance imaging of the head. Bilateral venography was performed to prevent wash-out of contrast media from the contralateral brachiocephalic vein. Patients who did not develop symptoms of VTE were screened for asymptomatic VTE by performing each of the four radiographic tests after completion of 4 weeks of induction chemotherapy.

Protocols for the performance and interpretation of radiographic tests were defined a priori. An independent Central Adjudication Committee evaluated and interpreted all radiographic tests by reviewing radiographic films and video documentations. The committee consisted of two physicians with appropriate expertise who were blinded to patient identity, treatment allocation and had no other involvement with study patients.
Statistics

Study patients were included in the primary analysis on a per-protocol basis. Reasons for exclusion were i) no exit venogram, and ii) premature withdrawal from the study unless due to a VTE. Frequencies of CVL characteristics were analyzed in relation to frequencies of patients with or without VTE using 2x2 contingency tables. Associations between CVL characteristics and the occurrence of VTE were analyzed using chi-square test or Fisher’s exact test. In addition, exact odds ratios (OR) and 95% confidence intervals (95%CI) were calculated. Multivariable analyses to test for several factors simultaneously (CVL body side, vein location, insertion type, study centre) and their interactions in association with the absolute risk of VTE were performed. A generalized linear model with an identity link and underlying Binomial structure was fit using the GMBO module of the Epicure 2.10 software. All tests were two-sided.

RESULTS

Patient Population

A total of 109 patients were enrolled in PARKAA and were randomized in a 1:2 ratio to either antithrombin or no antithrombin treatment. Twenty-four patients were excluded because of premature withdrawal from the study (n=9), or missing or inadequate exit venography (n=15). Eighty-five (78%) patients satisfied the criteria for the per-protocol analysis. Demographic information for the patients included in the study is provided in Table 1. The median number of patients per study centre was 7 and ranged between 2 and 16. The 24 excluded patients did not differ from the study cohort with respect to age, height, weight, gender, and ALL risk category.
TABLE 1. Patient Demographics.

<table>
<thead>
<tr>
<th>Demographic variable §</th>
<th>No Thrombosis</th>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>56</td>
<td>29</td>
</tr>
<tr>
<td>Age (years) *</td>
<td>4.8 (1.6 – 16.6)</td>
<td>7.3 (1.9 – 17.2)</td>
</tr>
<tr>
<td>Height (cm) *</td>
<td>106 (82 – 177)</td>
<td>127 (85 – 183)</td>
</tr>
<tr>
<td>Weight (kg) *</td>
<td>19 (10 – 83)</td>
<td>23 (11 – 71)</td>
</tr>
<tr>
<td>Gender (female) +</td>
<td>22 (39%)</td>
<td>16 (55%)</td>
</tr>
<tr>
<td>Race +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>40 (71%)</td>
<td>23 (79%)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (9%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (4%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (16%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>ALL Risk Category (high) +</td>
<td>20 (36%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>Platelet counts (x 10^9/L) *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>61 (7 – 507)</td>
<td>82 (12 – 372)</td>
</tr>
<tr>
<td>Day 15</td>
<td>102 (5 – 438)</td>
<td>104 (20 – 476)</td>
</tr>
<tr>
<td>Day 28</td>
<td>295 (24 – 740)</td>
<td>245 (101 – 543)</td>
</tr>
</tbody>
</table>

* median (minimum – maximum)
+ number (%)

§ None of the variables was significantly associated with the incidence of VTE as tested by logistic regression.

Abbreviations: cm, centimeter; kg, kilogram; L, litre; ALL, acute lymphoblastic leukemia; CVL, central venous line.
Central venous line characteristics

Central venous lines were located on the left side of the body in 42 (49%) and on the right side in 43 (51%) patients. One patient had a left-sided subclavian CVL replaced by a right-sided subclavian CVL on study day 10 because of CVL infection. All other patients had only one CVL during the study period. Catheters were located in the subclavian veins in 50 (59%) and in the jugular veins in 35 (41%) patients -- 26 (30%) in the external jugular vein and 9 (11%) in the internal jugular vein. Tips of CVL were located in the superior vena cava in 45 (53%), in the right atrium in 31 (36%), and other locations in 9 (11%) patients. Insertion of CVL was by percutaneous technique in 45 (53%) patients and by venous cut-down in 40 (47%) patients. These CVL attributes did not differ in relation to patient characteristics. One exception to this was that female patients more frequently had subclavian (56%) than jugular CVL (29%, p=0.012) which might have been for cosmetic reasons because subclavian CVL are less visible beneath the clothing. There was considerable variation in CVL characteristics across study centres, with left-sided CVL location ranging from 14-100%, and subclavian CVL location and percutaneous CVL insertion varying from 0-100%.

Incidence and Location of Thrombosis

Venous thromboembolic events occurred in 29 of 85 patients (34%). Four of the 29 patients (14%) had clinical symptoms leading to the diagnosis of VTE. Symptoms included swelling of a limb, pain, subcutaneous collateral veins, headache and eye movement abnormalities. The remaining 25 patients were clinically asymptomatic and VTE were identified by radiographic exit screening.
Twenty-eight of 29 children with VTE (97%) had VTE in the central upper venous system and one patient had sinovenous thrombosis in combination with internal jugular vein thrombosis. The subclavian vein was the most frequently affected vein (90%) with approximately half of these thrombi extending into more centrally located venous segments. Three thrombi extended into the right atrium. Twenty-one (72%) VTE were located on the left side. Venous occlusion was classified as 100% in 3 (13%), as 75%-100% in 9 (39%), 50-75% in 3 (13%), and 25-50% in 5 (22%) of the 23 VTE detected by venography. Collateral veins were present in 14 (61%) patients and were graded as major in 9 (39%) and minor in 5 (22%) of VTE identified by venography. Severe venous occlusion (more than 75%) was significantly associated with the presence of collaterals (p=0.04).

There were no significant differences in the incidence of VTE in relation to age, height, weight, gender, ALL risk category, and study centre as tested by logistic regression (table 1). Comparing patients with symptomatic VTE to patients with asymptomatic VTE, median age was 10.7 years (2.0-16.2, minimum-maximum) and 6.5 years (1.9-17.2), height 141 cm (88-166) and 120 cm (85-183), weight 43 kg (15-49) and 22 kg (11-71), and 3/4 (75%) and 13/25 (52%) and were girls, respectively. There were no significant differences in patient demographics between in patients with symptomatic and asymptomatic VTE.

**Association of CVL Characteristics with Thrombosis**

There was a close relationship between CVL location and VTE location. All VTE were located on the same side as the CVL except for 2 patients with CVL on the right side but VTE located on the left. The patient with an initial left -sided CVL
replaced by a right-sided CVL was found to have bilateral thrombotic occlusion on exit venography. All but five VTE (83%) were located in the venous segment where the CVL accessed the venous system. The patient who suffered from sinovenous thrombosis, had a jugular vein CVL located on the same side. In five patients, VTE was located not at CVL insertion site but more centrally along the course of the CVL.

Association of CVL body side with thrombosis

Patients with CVL on the left side of the body, had a 44% (19/43) incidence of VTE compared to a 24% (10/42) incidence in patients with CVL on the right side (OR 2.5, 95%CI 1.0-6.4, p=0.048) (figure 2). In the patient with a second CVL, only his right-sided CVL present at the time of exit screening was included in the analysis. There was no association between CVL side and the severity of thrombotic occlusion.

Association of CVL vein location with thrombosis

Patients with CVL in the subclavian vein had a 44% (22/50) incidence of VTE compared to a 20% (7/35) incidence in patients with jugular vein CVL (OR 3.1, 95%CI 1.2-8.5, p=0.025). There was no significant difference in the incidence of VTE between CVL located in the external or internal jugular vein. Among patients with subclavian CVL, a trend was seen for more severe thrombotic occlusion (50%, 11/22 with >75% occlusion) compared to patients with jugular CVL (14%, 1/7, p=0.095). The location of CVL tips did not show an association with the incidence of VTE.
FIGURE 2. Association of CVL body side with thrombosis.
Incidence of VTE in patients with CVL on the left compared to the right side of the body (odds ratio 2.5, 95%CI 1.0-6.4, p=0.048).

Association of central venous line insertion technique with thrombosis
Patients with percutaneously inserted CVL had a 47% (21/45) incidence of VTE compared to 20% (8/40) VTE with CVL inserted by venous cut-down (OR 3.5, 95%CI 1.3-9.2, p=0.011). There was no association between CVL insertion technique and the severity of thrombotic occlusion.

Association of both CVL location and CVL insertion technique with thrombosis
Analyzing the combined effect of CVL vein location and CVL insertion technique on the incidence of VTE by multivariable analysis revealed a strong interaction between
the two factors on an additive linear scale (p=0.07) (figure 3). Of patients with CVL in the subclavian vein inserted percutaneously, 53% (20/38) had VTE compared to 17% (2/12) VTE in patients with subclavian CVL inserted by venous cut-down, 14% (1/7) VTE with percutaneously inserted jugular CVL, and 21% (6/28) VTE with jugular CVL inserted by cut-down. These results suggest that a subclavian CVL inserted percutaneously was associated with an increased risk of VTE, compared to any other combination of location and insertion technique.

FIGURE 3. Association of CVL vein location and CVL insertion technique with thrombosis. The combination of CVL located in the subclavian vein and inserted percutaneously was associated with an increased incidence of VTE compared to any other combinations (test for interaction, p=0.07).
There was no interaction of CVL body side with either CVL vein location or CVL insertion technique or both in association with VTE. There was also no interaction of patient characteristics with CVL side, vein location, or insertion technique in association with VTE.

**Other Potential Risk Factors of Thrombosis**

Platelet counts at study entry, day 15, and study end are summarized in table 1. There was no association of platelet counts with the incidence of VTE (p=0.87). The Factor V Leiden mutation was present in 4/77 (5%) patients, 2 of whom had asymptomatic VTE (p=0.29), the prothrombin gene G20210A mutation was present in 1/74 (1%) patient who did not have VTE, and there was no patient with antithrombin deficiency. Low titre antiphospholipid antibodies were transiently positive in 3/85 (4%) patients, 2 of whom had asymptomatic VTE (p=0.23).25 There was no interaction of antithrombin treatment group with CVL characteristics in association with VTE.26

**DISCUSSION**

Venous thrombosis is a serious secondary complication in children and is frequently associated with the use of CVL. However, CVL are essential for successful treatment of children with life-threatening diseases. Therefore, identification of risk factors of CVL-related VTE is important, particularly factors that can be modified without compromising clinical care. The present study, designed to identify such factors, was a prospective cohort study of children with CVL placed in the upper
venous system who were screened for VTE using objective radiographic tests. The study results show that CVL on the left body side, in the subclavian vein, or inserted by percutaneous technique are associated with an increased risk of VTE. An increased risk of VTE was observed with subclavian CVL inserted percutaneously when compared to any other combination of location and insertion technique.

The rationale for studying CVL location in relation to the risk of VTE is based on the anatomy of the upper body venous system (figure 1). In comparison to the right side, the left brachiocephalic vein is longer with a more horizontal course, leading to a sharper angle into the superior vena cava. A CVL located in the right jugular vein represents the shortest and most direct access to the heart. In contrast, a CVL in the left jugular vein has a greater distance to the heart and passes two angles in the venous system, increasing the potential for flow obstruction and venous wall adherence causing endothelial damage. Compared to jugular CVL, subclavian CVL follow an even sharper curve into the central venous system, resulting in wall adherence. The CVL enters where the vein passes between the clavicle and the first rib, which may cause vein compression and kinking of the CVL.

In the literature, there is inconsistent information on the association of CVL body side with VTE. Four studies reported left-sided CVL to be associated with an increased incidence of VTE. However, a similar number of studies have found no significant influence of CVL side on VTE. It is unclear whether interaction from other CVL-related factors could have influenced these different findings. In the present study, left-sided CVL was associated with an increased frequency of VTE independent of CVL vein location and insertion technique.
Several studies in the literature directly compared CVL location in the subclavian or in the jugular veins but findings were contradictory. Two studies in adult patients reported incidences of VTE in 42 to 50% of patients with subclavian CVL compared to 0 to 10% with jugular vein CVL.\textsuperscript{16, 17} In contrast, Tinsit et al. observed 42% VTE with jugular CVL compared to 10% VTE with subclavian CVL.\textsuperscript{14} These discrepancies may be related to differing outcome assessment which was by venography only in the first two studies and by ultrasound only in the latter study. Venography is not sensitive for detection of VTE in the jugular veins and ultrasound is not sensitive for VTE in the subclavian veins.\textsuperscript{23, 24} The current study, which demonstrates a significantly increased incidence of VTE with subclavian (44%) compared to jugular CVL (20%), provides the most objective information as both venography and ultrasound were used to screen for VTE.

In the present study, the majority of VTE (83%) were located close to the CVL entry site rather than the CVL tip. Moreover, there was no association between various CVL tip locations and the incidence of VTE. These findings support the concept that endothelial disruption at CVL insertion is an important risk factor for the development of VTE and may be more relevant than endothelial irritation at the CVL tip.

Insertion technique may be associated with development of VTE because of the relative trauma both to the venous wall and perivascular tissue.\textsuperscript{7} A study on percutaneous CVL reported that the number of punctures required to correctly place CVL was significantly correlated with the incidence of VTE, providing indirect
evidence that venous trauma influences the development of VTE. Two studies in patients with cancer that directly compared percutaneous CVL insertion with venous cut-down had contradictory results: One pediatric study observed CVL failure, ie. loss of patency, to be less likely with percutaneous CVL compared to surgically inserted CVL. However, loss of CVL patency does not necessarily correlate with large vessel thrombosis. In contrast, a recent study in adults observed an increased frequency of VTE with CVL inserted by radiologists, ie. percutaneously, compared to CVL inserted by surgical cut-down.

In the present study, percutaneous CVL insertion was the factor most strongly associated with an increased risk of VTE. It is important to emphasize that the increased risk of VTE was only seen with subclavian CVL inserted percutaneously as compared to subclavian venous cut-down and jugular CVL inserted by either technique. Several factors may be responsible for this interaction. First, percutaneous CVL insertion into the subclavian vein is considered technically more difficult than into the jugular vein. Second, ultrasound guidance of CVL insertion into the subclavian vein is hampered by the presence of the clavicle. Third, because the subclavian vein takes a sharp curve at the site of CVL entry, endothelial damage at the opposite wall of the vein may occur when introducing the dilatator or catheter sheath. In contrast, the jugular vein is more easily accessible for puncture and ultrasound guidance, and because of the vein’s straight course, is less susceptible to trauma. Consistent with these considerations, we observed no significant difference between percutaneous CVL insertion and venous cut-down in the jugular vein.
A limitation of the present study is that the various modes of CVL placement were the choice of attending physicians and were not compared in a randomized fashion. Therefore, the results must be considered preliminary and need to be confirmed in future randomized clinical trials. Other limitations of the study are that a number of CVL-related factors with potential influence on the incidence of VTE were not assessed, such as the experience of the physician inserting the CVL, the time required for CVL insertion and immediate complications, type of CVL, and the number of CVL lumen. Previous reports have suggested the operator’s experience, CVL insertion time and complications to be associated with VTE, although a recent well-designed study did not observe any of these associations. No association was reported between CVL type or the number of CVL lumen and the incidence of VTE. Also the time of CVL insertion was not recorded, restricting the ability to assess whether duration of CVL placement was associated with VTE. Although the study period was fairly uniform, duration of CVL placement may have varied from about two to four weeks, as CVL were allowed to be inserted up to two weeks after study entry. However, based on previous studies, most VTE occur early and duration of CVL placement is not associated with the incidence of VTE. Finally, the present study was not designed to assess the effect of heparin prophylaxis on CVL-associated VTE as there was no standardization of dose and mode of heparin prophylaxis.

The issue of the risk of CVL-related VTE in relation to congenital prothrombotic markers is controversial in the literature. In the current study, Factor V Leiden mutation was present in 4 (5%) patients, 2 of whom had asymptomatic VTE, the prothrombin gene G20210A mutation was present in 1 patient (1%) who did not
have VTE, and no patient had antithrombin deficiency. Compared to the effect of CVL-related factors on the risk of VTE, congenital prothrombotic disorders had minor, if any, influence on the incidence of VTE. However, the present study was not powered to assess whether there was a statistically significant association between prothrombotic conditions and CVL-related VTE.

A definition for the clinical presentation of VTE was not stipulated because clinical symptoms are both insensitive and nonspecific. This lack of definition may have influenced the proportion of symptomatic VTE among all VTE detected in this study. However, outcome screening using multiple objective tests guaranteed that no VTE were missed. Asymptomatic VTE were included as outcome because there is good evidence that the majority of CVL-related VTE remain clinically undetected. Development of CVL-related DVT is usually gradual, permitting collaterals to form, thereby minimizing typical symptoms of acute VTE. Subtle symptoms of DVT are frequently not recognized in children with severe underlying disease. The asymptomatic DVT observed in PAARKA were clinically significant with two thirds occluding more than 50% of the vessel and having collateral veins. Short term complications of CVL-related DVT, both symptomatic and asymptomatic, are pulmonary embolism, chylothorax, embolic stroke via intracardiac right-to-left shunting, CVL-related sepsis, and repeated loss of CVL patency requiring local thrombolytic therapy or CVL replacement. A limitation of the present study is that follow-up was only a few weeks, therefore, the long-term outcome of VTE is unknown. The reported long term consequences of CVL-related DVT in children are post-thrombotic syndrome, recurrent DVT, and loss of future venous access.
In conclusion, the risk of CVL-related VTE was significantly increased with CVL on the left side, in the subclavian vein, and inserted percutaneously. Subclavian CVL inserted percutaneously were associated with the highest risk of VTE. The study results suggest that CVL in the upper venous system should be placed on the right side and in the jugular vein to minimize the risk of CVL-related VTE. If subclavian vein placement is necessary, CVL insertion by venous cut-down appears preferable over the percutaneous approach.
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APPENDIX

The investigators and institutions participating in the PAARKA study were:

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