Role of serial ultrasound screening of venous thrombosis in oncologic children with central lines

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ABSTRACT

Objective: Pediatric oncology patients are more likely to develop venous thromboembolic events related to central venous catheter (CVC). Study aim was to determine the incidence of catheter related thrombosis (CRT) in a cohort of pediatric oncology patients using vascular ultrasound (US).
Methods: Consecutive children of a single cancer referral center, requiring medium to long term CVC implantation, were screened for CRT, using serial ultrasound exams.
Measurements and main results: US examinations were taken 15, 30 and 90 days after CVC implantation. A total of 113 catheters were studied in 103 patients (median age 10.5 years old). Ultrasound screening was completed in 80.5% patients. Apart from three subjects, US investigations were well tolerated. Patients were followed for a median of 87 days. No symptomatic CRT was recorded throughout. Three cases of asymptomatic thrombosis were identified with early US screening; incidence of CRT events for 1000 catheter-days was 0.11. The presence of previous catheter-related infection and an history of one or more previous CVC placement were identified as risk factors.
Conclusions: In our pediatric patients the incidence of CRT is low. Ultrasound monitoring is well tolerated and allows detecting asymptomatic CRT. Patients with previous CVC infection or insertion seem to have a higher risk of CRT (p =0.003 and p = 0.043 respectively).

1. Introduction

In recent years, medium and long term central venous catheters (CVC) have been increasingly used to administer chemotherapy and any other intravenous drug in pediatric patients with cancer.

Totally implantable central venous access ports, tunneled central venous catheters and Peripherally Inserted Central Catheters are among the most used medium to long term CVC in children [1].

Pediatric oncology patients are at increased risk of developing venous thromboembolic events due to their malignant disease, the related chemotherapeutic treatment [2] and the presence of CVC, which is one of the most important risk factors [3]. Data about the incidence of catheter related thrombosis (CRT) vary among studies between 4 and 50% [4–6]. This gap is caused by the differences in the definition of CRT, the method used for diagnosing thrombosis, CVC subtype and the population enrolled [4–6].

Venography is considered the reference method for diagnosis of deep venous thrombosis [7–9]. Nevertheless, venous ultrasonography is a noninvasive, more practical and more economical tool to perform CRT diagnosis. In our Institution, we usually perform vascular ultrasonography in case of malfunctioning catheters or in presence of signs or symptoms of thrombosis, both in adults and children. Venography is used in doubtful cases or when the exact thrombus extension cannot be reliably predicted with ultrasonography, i.e in case of thrombus in the mediastinal vessels.

Abbreviations

CVC	Central Venous Catheter
CRT	Catheter Related Thrombosis
US	Ultrasound
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico
BSA	Body Surface Area
INT	Istituto Nazionale dei Tumori
PAC	Port-a-cath
PICC	Peripherally Inserted Central Catheter
PNX	Pneumothorax
IR	Incidence Rate
CIs	Confidence Intervals
IJV	Internal Jugular Vein
PTS	Post Thrombotic Syndrome

The early detection of CRT permits immediate treatment to reduce the CVC malfunctioning, thrombosis symptoms and the thromboembolism risk [10]. To our knowledge, only few pediatric studies include a prospective US evaluation for CRT detection [4,11–14]. These studies have strong limitations, such as few enrolled patients [11–13] or US exam performed only once during the CVC life [4,14].

Based on this data, we decided to prospectively investigate the incidence of CRT in our pediatric oncologic population, using the noninvasive serial ultrasound (US) surveillance, performed after CVC insertion. Unlike recent literature, we chose a sequential evaluation, characterized by 3 assessments distributed in the first three months post CVC placement, to allow the early detection of asymptomatic thrombi.

2. Materials and methods

2.1. Patients

Oncology patients younger than 18 years old, who had medium to long term CVC inserted by the Vascular Access Implantation Service of the Fondazione IRCCS Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, between October 2015 and December 2016, were enrolled.

Exclusion criteria were: lack of parental consent, continuation of care in another hospital or patient or parents opposition to undergo the scheduled ultrasound examination. The demographic variables, recorded for each patient, were: age, sex and body surface area (BSA).

We also recorded the presence of known thrombosis risk factors, classified as "patient-related" and "catheter-related" [2,13,15–17]. Patient-related risk factors included: family history of venous thrombosis, type of tumor (lymphomas and thoracic/mediastinal tumors vs. others) [18], previous major surgical procedures, prolonged bed rest. Catheter-related risk factors were: multiple venipunctures and arterial punctures during the positioning procedure, CVC type, positioning site, previous CVC insertion, previous CVC infection or previous CVC occlusion.

The study was approved by the local ethics committee after a retrospective analysis of CVC-related complications (INT 65/14). All parents signed informed consent.

2.2. CVC selection and implantation

Three different CVC-types were used: totally implantable central venous access ports (PAC. Celsite, BRAUN), Peripherally Inserted Central Catheters (PICC. MedCOMP) and tunneled central venous catheters (Groshong®, Bard). The choice of the CVC-type was related to the patient's age and size and to the expected duration of therapy. Catheters were implanted by trained and qualified staff, in a dedicated operating room. The cannulation sites were the venous vessels of the superior district. The catheter-size ranges between 3 and 7 Fr, chosen according to the US vessel diameter: the external diameter of the catheter should not exceed 45−50% of the vessel diameter [19]. Venous punctures were ultrasound-guided and CVC tip position was checked by X-ray. CVC-related data collected were: catheter type and size, site of venous puncture, duration of the procedure, number of vein punctures performed and complications occurred during the procedure (arterial puncture, PNX). The CVC insertion's data were collected by an independent observer.

2.3. CVC ultrasound surveillance

Ultrasound surveillance was performed sequentially, 15, 30 and 90 days after implantation. These time frames were chosen for the higher CRT prevalence in the first period after CVC implantation, mainly due to the vessel trauma at insertion [16,17,20,21]. The US exam was performed earlier than that scheduled by the study in case of clinical symptoms of thrombosis.

Venous ultrasonography was performed with ESAOTE MyLab 30 Gold ultrasound machine with linear probe (until 15 MHz). B-mode US, combined with color flow Doppler imaging, was used. The finding of a thrombotic event determined the end of the US surveillance. US monitoring was carried out mainly in an outpatient setting, during ambulatorial chemotherapy infusion.

The vein district where CVC was placed was analyzed, and suggestive signs of thrombosis were considered: non-compressibility of the vessel lumen, an intraluminal hyperechoic formation and the partial or total absence of venous flow with Color- Doppler [8,21]. All the exams were performed by two anesthesiologists, expert in vascular ultrasound. Doubtful cases were reevaluated by an expert sonographer.

If a CRT was diagnosed, a prompt treatment with subcutaneous enoxaparin was initiated (1 mg/kg every 12 h, for 3 months) [22].

During the ultrasound follow-up we also evaluated the onset of other major CVC related complications (such as infections, malfunction for any reason, accidental removal, fissuring).

Moreover, all the causes of CVC removal (end of treatment, any case of displacement/damage, thrombosis or infection) were recorded.

In our center, in case of CVC infection or thrombosis, CVC management and eventual removal follow local protocols based on recent guidelines [23−25]. In particular, in case of thrombosis, CVC is removed only if there is a malfunction due to occlusion, which cannot be treated with thrombolytics. If, despite the associated thrombosis, the catheter is functional, well positioned, and there are no signs of thrombophlebitis, it can be left in place and used.

2.4. Statistical analysis

Study patients and CVC characteristics were expressed as frequency and percentage for categorical variables and as median, IQR and range for continuous variables.

The exposure time, from CVC insertion to the last ultrasound exam or to CRT diagnosis, and CVC life, from CVC positioning to removal, were calculated and expressed in days.

Incidence Rates (IR) with 95% Confidence Intervals (CIs) were calculated to evaluate the incidence of thrombosis overall. IRs were expressed in 1000 catheter-days. A post hoc analysis was conducted to test the association between previous CVC infection or insertion and the occurrence of CRT. This analysis was performed

using the Fisher's exact test for proportions.

All analyses were carried out using the SAS™ software (SAS Institute. Version 9.4).

3. Results

During the enrollment period, 103 patients with a known diagnosis of cancer, underwent medium to long term CVC implantation for chemotherapy infusion.

The patient's median age was 10.5 years old (IQR 10, range 0.4–17 years old), 56.6% was male. The prevalent types of cancer were central nervous system malignancies (33.9%), followed by sarcomas (Ewing Sarcoma, Rhabdomiosarcoma and non-Rhabdosarcomas soft tissue sarcoma) (27.2%) and lymphomas (10.7%).

Five patients had a central cannulation in the year before the beginning of the study: two CVC were removed because of end of therapy, one CVC for infection, one for malfunction and the last one for unknown cause. For the other 98 patients it was the first placement.

Patient-related and catheter-related risk factors for venous thrombosis were frequent in enrolled patients (Table 1).

All CVCs were placed in the superior district veins: the internal jugular vein (IJV) was the most frequent cannulated vessel for PAC and Groshong® catheters, while PICC were preferentially positioned in brachial and basilic veins. The most frequently placed CVC type was Port-a-cath (65.5%), followed by PICC (24.8%) and Groshong® (9.7%) (Table 2). PICC was the catheter preferentially chosen for eldest subjects (median age 15 years old, IQR = 5.5) while Groshong® for the youngest (median age 2 years old, IQR = 3). A total of 113 catheters were subjected to ultrasound screening: 91 CVC (80.5%) completed the 90-days US follow up. In the other 22 cases US monitoring was concluded earlier: 14 CVCs were removed for complications, while it was impossible to perform all the US evaluations with three patients (median age 4.5 years old) because of their refusal; two patients continued treatment in other hospitals, two patients died during follow up and one patient removed CVC before the 90 days of study because of completion of treatment plan (Flow diagram). The median duration of US follow up for single catheter was 87 days (IQR 12.5, range 0–164 days), One patient's data were excluded at the end of the study based on parents' request. With patients transferred to other

Table 1
Risk factors associated to thrombosis.

	N	%
Patient-related (103 patients)		
Family history of venous thrombosis	1	0.9
Major surgery	43	41.7
head and neck	15	14.6
upper and lower limbs	13	12.6
abdominal	10	9.7
thoracic	2	1.9
vertebral paravertebral	2	1.9
hip	1	1.0
Tumors with higher thrombotic risk	16	15.5
lymphomas	14	13.6
thoracic/mediastinal tumors	2	1.9
Prolonged bed rest	1	0.9
CVC-related (113 CVC)		
Multiple venipuncture (>2)[a] during insertion procedure	18	15.9
Arterial puncture during insertion procedure	3	2.6
CVC with higher thrombotic risk (PICC) [24]	28	24.8
Previous CVC insertion	15	13.2
Previous CVC infection	18	16.0

[a] We considered a number of attempts >2 as sign of difficult insertion. No CVC required a number of attempts >5.

Table 2
Central Venous Catheter types and insertion's sites.

	All N (%)	PAC N (%)	PICC N (%)	Groshong® N (%)
Total	113 (100)	74 (65.5)	28 (24.8)	11 (9.7%)
Divided by Insertion's site				
IJV	80 (70.7)	70	0	10
Brachial	16 (14.1)	0	15	1
Basilic	10 (8.8)	0	10	0
Subclavian	5 (4.4)	4	1	0
Axillary	2 (1.8)	0	2	0

hospitals, and with those who refused US examination after enrollment, clinical monitoring continued until the expected date of the study's completion, in order to evaluate the onset of major CVC related complications.

Between the 14 patients who required CVC removal for complications, seven patients needed a second CVC. Three of these patients had problems also with a second CVC and required a third device.

The median life of CVC until removal was 134 days (IQR = 187, range = 3–491 days).

We found three cases of thrombosis during US follow up (2.7%% of enrolled CVCs). All the CRTs were asymptomatic. They were detected in three different patients.

The three diagnosis were confirmed by standard venography. None of the other patients underwent venography during the study period.

The overall incidence rate of CRT was 0.11 (0.03–0.33) events for 1000 catheter-days.

Table 3 reported the thrombosis' risk factors for the three patients.

The analysis of the three asymptomatic thrombosis' cases suggested a relationship between CRT and 2 specific risk factors: a previous CVC infection and a previous CVC insertion. In fact, all had a previous catheter-related infection, as defined by international guidelines [26,27]; in all three cases, the infected CVC was the same that developed thrombosis. Additionally, two cases had an history of a previous CVC insertion.

We conducted a post hoc analysis to test the association between these two risk factors and CRT (Table 4). This analysis seems to indicate a significant correlation between previous CVC infection or insertion and the occurrence of CRT in our pediatric population (p = 0.003 and p = 0.043 respectively).

After 1 month of anticoagulant therapy, an ultrasound scan showed the disappearance of the thrombus in all patients. Despite the resolution of thrombosis, in 2 cases CVC was removed 1 month after CRT diagnosis, because of a CVC related infection. The other one had no other major complications and it was retained and used until the end of therapy. No patient developed symptoms of thromboembolism or other post thrombotic complications. During the study period, we also evaluated the onset of other major CVC related complications besides thrombosis. Complications during placing (early complications) were rare, while we found numerous late complications (Table 5). The most frequent late complication was CVC infection: it occurred in 16.8% of CVC monitored.

4. Discussion

This is the first perspective and sequential ultrasound evaluation study of symptomatic and asymptomatic CRT incidence focused on a large cohort of pediatric oncology patients from a single tertiary oncologic center. US procedure was well tolerated by all 103 patients, with the exception of 3 (median age 4.5 years old).

Asymptomatic CRT was detected in three patients, 2.7% of the

Flow chart study
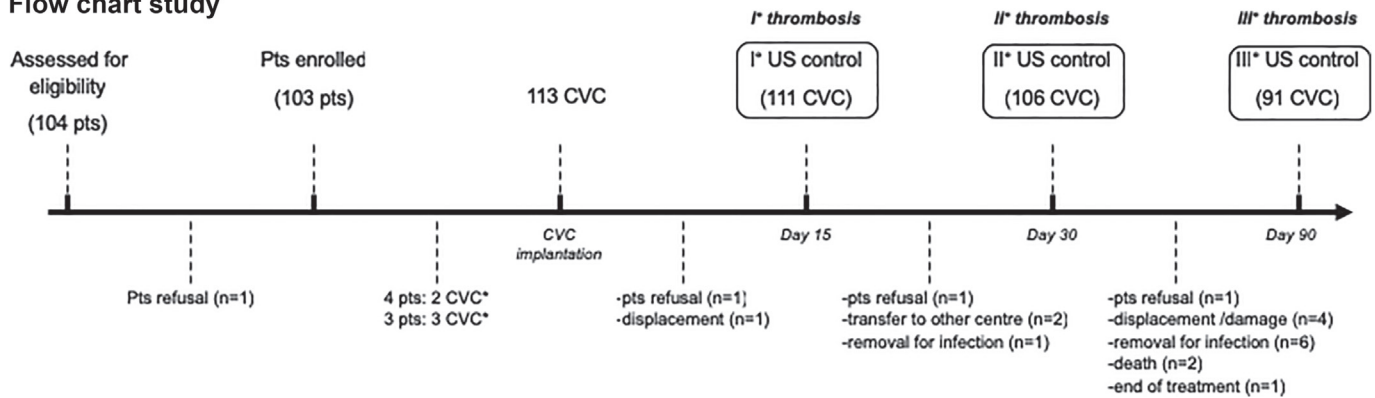
Flow diagram. Timeline of study design reporting the number of patients included, the number of patients excluded and why and the number of thrombosis detected at any ultrasound check.

Table 3
Asymptomatic Thrombosis's Cases. Patients and thrombosis' data and thrombotic risk factors.

	Case 1	Case 2	Case 3
Patients's data			
Sex	M	M	F
Age	17	3	6
Patient-related risk factors			
Type of tumor	Lymphoma	Neuroblastoma	Glioma
Family history	No	No	No
Recent major surgery	No	No	No
CVC related risk factors			
CVC type	PICC	PAC	PAC
Left site	Yes	No	No
Previous CVC	Yes	Yes	No
Previous infection	Yes	Yes	Yes
Previous occlusion	Yes	No	No
Thrombosis' data			
Δt days cannulation-diagnosis[a]	6	89	29
Thrombosed vein	Subclavian	Jugular	Jugular

[a] Δt days: time (days) between cannulation and diagnosis.

Table 4
Correlation between CRT and previous CVC infection (A) or previous CVC insertion (B).

(A)		
Previous CVC infection	No CRT N (%)	CRT N (%)
No	95 (100)	0
Yes	15 (83.33)	3 (16.67)

(B)		
Previous CVC insertion	No CRT N (%)	CRT N (%)
No	97 (98.98)	1 (1.02)
Yes	13 (86.67)	2 (13.33)

Table 5
Early and late Central Venous Catheter related complications.

	N	%
Early Complications		
Difficult guide progression	11	9.7
Multiple veins attempts[a]	18	15.9
Arterial puncture	3	2.6
Late complications		
CVC related infection[b]	19	16.8
Infection of puncture site/ports	3	2.6
Accidental removal	2	1.8
Malfunction	11	9.7
Port overturning	2	1.8
Catheter dislodgment	5	4.4
Fibrin sheat	2	1.8

[a] We considered a number of attempts >2. No CVC required a number of attempts >5.
[b] 7 cases required catheter removal to resolve sepsis.

113 catheters studied. This corresponds to an incidence rate of 0.11 events for 1000 catheter-days (95% CI 0.03−0.33), which is much lower than the values reported in different cohorts of patients [6,28]. In our population, nobody had symptomatic CVC-related thrombosis, that in literature have an incidence between 12 and 28% [6,16,28,29]. One explanation of this discrepancy could be the recent introduction of measures to reduce the incidence of CRT, such as US-guided vascular line placement, the choice of the correct device diameter in relation to the vessel size, the intra-procedural fluoroscopic control of tip position to reduce misplacements, the routine maintenance and dressing from qualified nursing staff. This lower rate could be also explained by the use of tunneled CVCs that reduces complication compared to non tunneled CVCs, the inclusion of patients with solid tumors whose treatments seem less thrombogenic that those used in haematological tumors (eg. asparaginase and prolonged high-doses steroid treatment for acute lymphatic leukemia) [18]. No patients with acute leukemia have been enrolled in our cohort because this haematological disease is not treated in our center. Other possible explanations are the shorter follow-up compared with similar studies [4,21] and US imaging technique which fails to detect the thrombus in the large central veins (eg. Superior Vena Cava). Our results are in line with two recent studies with a similar ultrasound monitoring [4,30].

The early diagnosis of the three asymptomatic thrombosis allowed prompt treatment.

In most published pediatric studies report case series of treating asymptomatic thrombosis [28,31], there is no evidence that anticoagulation improves outcome in this population. A recent study demonstrated a low risk of short and long term sequelae among cardiopathic children with asymptomatic CRT, despite the absence of any therapeutic anticoagulation [32]. The American Society of Hematology [33] suggests to choose either anticoagulation or no anticoagulation treatment, based on the individual patient's factors (the perceived risk of local and embolic complications, the overall state of the child and the risks of therapy) until better evidence becomes available. The British Society of Hematology (2018) recommends, instead, to monitor incidental thrombosis, particularly when the age of the event is unclear. However, it admits that the risk of Post Thrombotic Syndrome (PTS) in childhood cancer survivors with previous asymptomatic CVC-related thrombosis may favour treatment if the thrombosis is thought to be a recent event

[22].

We decided to treat asymptomatic CRT in our oncological population, because of the possible risks of thrombus extension and complications (e.g. the removal and repositioning of a malfunctioning catheter due to an extensive thrombosis, often in deep sedation or under general anesthesia, with a possible delay of cancer treatments). Moreover, considering the timing of the ultrasound screening, the CRT were likely to be recent events and therefore could benefit from the anticoagulation therapy.

Despite the low number of asymptomatic thrombosis cases, a post-hoc analysis seems to highlight a significant association between a previous CVC infection or a previous CVC insertion and CRT. All three patients had a history of previous CVC infection (p = 0.003). The relationship between thrombosis and infection is probably bi-directional: CVC thrombi, favoring the adhesion of microorganisms, seems to facilitate bacteremia. On the other hand, CVC-related infection induces an inflammatory response that could lead to coagulation derangement with further formation or progression of thrombi in at risk areas (vein where CVC is placed). Two out of three subjects had, instead, a story of previous CVC (p =0.043), removed less than 1 year before. A previous CVC insertion is a known risk factor for CRT [34] probably because of the trauma on the vein endothelium, one of the three components of Virchow's triad.

We have found no other risk factors in common.

We used a bivariate testing to explore the relationship between a history of previous CVC infection or previous CVC insertion and thrombosis. The low number of events recorded in our cohort did not permit to carry out a more informative multivariate analysis.

Anticoagulant therapy with heparin, started soon after diagnosis, allowed a complete resolution of CRT after one month. However, two out of three CVC had to be removed within a month due to a subsequent infection. This may be explained by the possible infectious risk induced by thrombosis. The removal of the infected CVC was justified by the lack of clinical response after 72 h of adequate antimicrobials [24]. No CVC was removed due to the thrombosis itself; in fact they remained always patent and well-functioning. CVC removal was always based on clinical signs and was not based on ultrasound findings.

In conclusion we believe that, given the low incidence of the CRT in our pediatric population, the yeld of screening the entire sample of children with CVC is too low, and too expensive in terms of time and planning. A serial US examination would be, instead, cost-effective and well tolerated on a targeted risk population with previous CVC infections and several placements. Furthermore, we think that the early diagnosis of asymptomatic CRT with US screening is useful because it permits prompt treatment.

However, more data about the benefits of LMWH on medium to long CVC related asymptomatic thrombosis in oncologic children, would be necessary to justify its use. These data would support the use of ultrasound screening for CRT.

The main limitation of US follow-up is the restricted access that avoids a complete outline of all portions of the subclavian veins. However, sonography has the advantage over CT scan, magnetic resonance imaging and venography of being less expensive, portable, nonionizing and requiring no intravenous contrast.

Nevertheless, the outcome and timing of such a strategy is currently unknown and clearly needs to be explored prospectively.

5. Conclusions

A serial Ultrasound monitoring of CVC thrombosis is well tolerated by a pediatric oncological population, and allows an early detection of asymptomatic CRT. A history of previous CVC infection and of previous CVCs place patients at higher risk of developing thrombosis. In this subgroup of oncological children, serial ultrasound exams should be scheduled at the CVC's placement to permit early diagnosis and treatment of CRT.

Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

Financial disclosure

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