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Central Line Associated Thrombosis in Pediatric Oncology Patients: Single Center Experience

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Abstract

Background: Central venous lines are important part in management of pediatric oncology patients, in spite of that, obtaining these access carry risk of complication. Central Venous Catheter-related Thrombosis (CVCT) is one of the major complications.

Methods: This is a single-center retrospective study; we analyzed all pediatric oncology patients with a Central Venous Catheter (CVC) over 3 years period, focused on the CVCT risk factor and its outcome. Data were retrieved from patients' hard and electronic medical records and collected in the Redcap system.

Results: A total of 323 CVCs were inserted in 266 pediatric oncology patients, 14 CVCT episodes were discover (4.33%) which was occurred in 13 patients. The incidence of CVCT was highest among hematological malignancy 10 out of 13 patients. Using steroid as part of chemotherapy was recognized as significant risk for CVCT (P value: 0.019), having a peripherally inserted central catheter PICC or femoral line compared with an implantable port Cath were associated with increased risk of CVCT (P value <.001) besides of that the risk of thrombosis increased with subsequent insertions of the central line compared with a single central line insertion (P value: .004). 50% of CVCT were asymptomatic, LMWH was used in 9 episodes and line removed in 7, complete resolution occurred in 10 episodes.

Conclusion: The use of CVC is a crucial corner in managing pediatric oncology patients and improves their quality of life, yet it is associated with significant complications, such as infection, thrombosis, and dysfunction.

The pediatric oncologists and pediatric surgeons should pay special attention to ensure optimal and appropriate CVC placement methods and post-insertion care which may play an essential role in minimizing CVC-associated complications.

Prospective studies are crucial to evaluate the clinical significance of CVC-dysfunction and its impact on the development of thrombosis, infection, or outcome of children with cancer. And to provide recommendations to improve the preventive strategies for such events.

Keywords: Thrombosis • Central Venous Catheter (CVC) • Pediatric • Oncology • Deep Vein Thrombosis (DVT)

Introduction

Central venous lines are used in critically ill children and children with chronic conditions to administer intravenous therapy, such as fluids, medications, total parenteral nutrition, and blood products. Although using central venous lines has dramatically improved the quality of care in these children, these catheters may cause mechanical obstruction, severe infectious and thrombotic complications [1].

CVCs raise the risk of thrombosis, through a variety of mechanical and biochemical processes, such as modifications to the venous flow, damage to the endothelium, or the infusion of hyperosmolar substances [2].

Despite of that, obtaining reliable central venous access remains a necessity for many patients with malignancy and is a significant decision in management.

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A range of primary venous access devices (CVADs) exists, including implantable ports and Peripherally Inserted Central Catheters (PICCs).

Over the past decade, an increase in the occurrence of Deep Vein Thrombosis (DVT) in pediatric patients has been reported, with an incidence rate of 0.07 to 0.14 per 10,000 children per year in the general pediatric population and 4.9 to 21.9 per 10,000 children in the hospitalized pediatric population every year. Although this may be attributed to increased recognition of DVT occurrence in children [3].

Vein thrombosis is a multifactorial disease influenced by various risk factors. Patients with a history of the previous thrombosis, current systemic or catheter-related infection, and inherited or acquired thrombophilia disorders, such as protein C and S deficiency are at higher risk of thrombosis. Having a PICC, larger or multi-lumen catheter, and catheter located in the femoral or cephalic veins has been associated with an increased risk of CVCT [4].

Some therapies are also prothrombotic, including medications such as asparagine, steroids, immunomodulatory agents, and previous CVAD insertion. Besides what was mentioned, an active malignancy is one of the most vital risk factors for venous thrombosis, conferring a seven-fold increased risk compared with those without malignancy.

We conducted a retrospective single-center study to analyze all patients having a CVC in the department of pediatric oncology of king Fahd specialist hospital Dammam over three years period and to determine the prevalence of CVC-related thrombosis and to characterize the risk factor of central line-associated thrombosis among pediatric oncology patients and outcome of these patients.

Materials and Methods

Our study is a retrospective study conducted at king Fahad specialist hospital, Dammam. This is tertiary care hospital located in the eastern province of Saudi Arabia.

We include all pediatric oncology patients diagnosed between January, 2017 and the end of December, 2019 and have central line catheter placed at the beginning or during their management.

Catheter-related thrombosis was defined as thrombosis associated with the vein(s) that the catheter was located in and confirmed radiologically ether by ECHO, Doppler US or CT angiograph.

After obtaining the IRB approval in king Fahad specialist hospital Dammam, all the data were retrieved from patients' hard and electronic medical records and collected in the Redcap system. Data analysis was done by using Statistical Package for the Social Sciences (SPSS) program.

Results

During study period from 1st January 2017 till the end of December 2019, we had 295 new patients belong to our paediatric hematology oncology department; we exclude 29 patients from our study (15 patient's benign hematology cases, 14 patients no CVC inserted).

We studied the clinical characteristic of 266 patient who met the inclusion criteria, we got 158 male (59.4%) and 108 female (40.6%), we found that most of our papulation age between 1-4.9 years 46.2%(123 patients). And the most common diagnosis was leukaemia 108 patients (40.6%).

Total of 323 central venous catheters were inserted in 266 patients, as 222 patients (83.5%) need only one CVC, 31 (11.7%) patients need two CVC and 13 patients (4.9 %) need three CVCs. Most of the CVC inserted were ports Cath 267 (83%) compare with PICC line 19 (6%) which was similar to Hickmann line.

35 patients (13.1%) out of 266 patients were found to have thrombosis, 62.8% (22 patients) of them were with none CVCs related thrombosis (17 patients tumour/disease related thrombosis, 5 patients due to septicaemia/DIC) and 37.1% (13 patients) were with CVC related thrombosis CVCT (Figure 1).

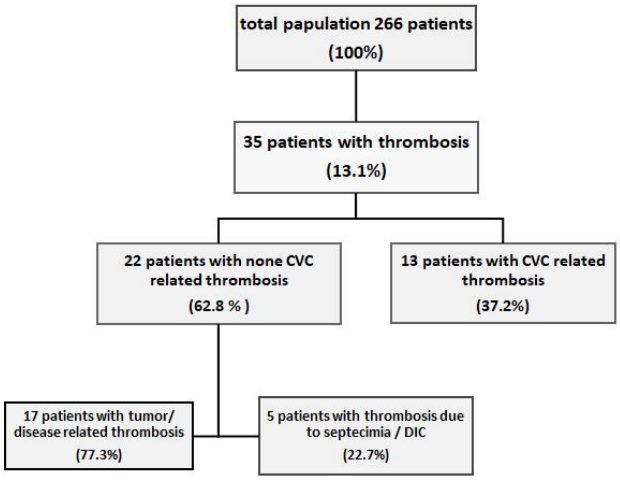

Figure 1. Explain about the total population and % of the patients.

Interestingly, among the 17 patients with disease/tumour related thrombosis we found 50% of hepatoblastoma 2 out of 4 patients with tumour related portal vein thrombosis at diagnosis and 30% of Wilms tumour patients 4 out of 13 with extended inferior vena cava thrombosis found during screening at diagnosis (Table 1).

Type of cancer (total N)	Thrombosis (N=17) (%)
Leukaemia (108)	3 (2.77%)
Lymphoma (43)	1 (2.3%)
Brain tumor (21)	2 (9.5%)
Neuroblastoma (17)	1(5.9%)

Wilm tumour (13)	4 (13.7%)
Rhabdomyosarcoma (13)	1 (7.6%)
Ewing sarcoma (9)	1 (11.1%)
Germ cell tumor (7)	1(14.3%)
Hepatoblastoma (4)	2 (50%)
Rhabdoid tumor of kidney (1)	1 (100%)

Table 1. Tumor/disease related thrombosis.

Regarding CVCs related thrombosis which was occured in (4.88%) 13 patients of our papulation, there is one patient with recurrent episode of thrombosis in 2 different lines. So, from total of 323 CVCs the overall incidence of CVCs related thrombosis is 4.33% (14/323).

Regarding the characteristic of our papulation, we analysed the risk factor for thrombosis, including BMI, age, type of cancer, use of thrombogenic medications (peg asparagine and steroid), family history of thrombosis, comorbidity, and type of line and frequency of line insertion (Table 2).

Variables	Total number (N=266)	No thrombosis (N= 253)	Thrombosis (N= 13)	p-value
Gender				
Male	158 (59.4%)	151 (95.6%)	7 (4.4%)	.676*
Female	108 (40.6%)	102 (94.4%)	6 (5.6%)	
Primary diagnosis				
Leukaemia	108	101 (93.5%)	7 (6.5%)	.380*
Lymphoma	43	40 (93.0%)	3 (7.0%)	
Brain tumor	21	20 (95.2%)	1 (4.8%)	
Neuroblastoma	17	17 (100.0%)	0	
Wilms tumor	13	13 (100.0%)	0	
Osteosarcoma	10	10 (100.0%)	0	
Ewing sarcoma	9	9 (100.0%)	0	
Hepatoblastoma	4	4 (100.0%)	0	
Retinoblastoma	1	1 (100.0%)	0	
HLH	6	6 (100.0%)	0	
LCH	3	3 (100.0%)	0	
Germ cell tumor	7	5 (71.4%)	2 (28.6%)	
Rhabdomyosarcoma	13	13 (100.0%)	0	
Other	11	11(100.0%)	0	
Age at diagnosis				
<1	9 (3.4%)	9 (100.0%)	0	.512*
1–4.9	123 (46.2%)	119 (96.7%)	4 (3.3%)	
5–8.9	49 (18.4%)	46 (93.9%)	3 (6.1%)	
9-12.9	42 (15.8%)	38 (90.5%)	4 (9.5%)	
13–16	43 (16.2%)	41 (95.3%)	2 (4.7%)	
Comorbidity				
Diabetes yes	1	0	1 (100%)	.049**
No	265	253 (95.5%)	12 (4.5%)	

Sickle cell disease yes	5	4 (80.0%)	1 (20.0%)	.223**
No	261	249 (95.4%)	12 (4.6%)	
Congenital heart disease yes	2	1 (50.0%)	1 (50.0%)	.096**
No	264	252 (95.5%)	12 (4.5%)	
BMI				
Less 20	211 (79.3%)	201 (95.3%)	10 (4.7%)	.119*
20-25	34 (12.8%)	34 (100.0%)	0	
25- 30	15 (5.6%)	13 (86.7%)	2 (13.3%)	
More 30	6 (2.3%)	5 (83.3%)	1 (16.7%)	
Use of peg asparaginase				
Yes	108	101 (93.5%)	7 (6.5%)	.319*
No	158	152 (96.2%)	6 (3.8%)	
Use of steroid				
Yes	163	151 (92.6%)	12 (7.4%)	.019*
No	103	102 (99.0%)	1 (1.0%)	

HLH-Hemophagocytic Lymphohistiocytosis, LCH-Langerhans Cell Histiocytosis *- Pearson *Chi-Square*, **Fisher's exact test

Table 2. Demographic, clinical characteristics of pediatric oncology patient with central line. Total number of patients: 266.

There was no significant difference in the incidence of CVC related thrombosis either across genders (4.4% males, 5.6% females) or across different age groups. Despite the non-significant difference in CVC related thrombosis incidence across different age groups; it is worth noting that highest percentage (9.5%) among patient between 9 and 13 year (4/38).

Most of our total papulation were none obese with BMI <20 in (79.3%) 211 patients, although there is no significant different in incidence of CVCT between BMI groups, but we notice that higher percentage among overweight and obese patient with BMI>25, compared with patient with BMI <25 (14.2%, 3/21 *vs.* 4%, 10/245, respectively).

Concerning the type of cancer and risk of CVCT we found highest percentage of CVCT in patient with GCT (28%, 2 out of 7 cases) and interestingly, 10 out of 13 patients with CVCT were belonging to haematological malignancy (7 patient's leukaemia and 3 lymphoma).

For comorbidity, we have only one patient with diabetes type 1 and he got CVCT, although it is statically significant with (P value=0.049) because of low number we cannot comfortably say that there is correlation between DM and CVCT. Similarly, out of 5 patients with SCD who have concomitant malignancy, only 1 has CVCT. As well for congenital cardiac disease 1 out of 2 patients get CVCT due to small number of this comorbidity we cannot conclude the correlation between these comorbidities and CVCT.

Evaluate the use of thrombophilic medications, we found the use of steroid is significant risk for CVCT (P value= 0.019), and it is worth notice that almost half of patients with CVCT received peg asparaginase in spite it is statistically not significant.

Apropos of noting line characteristics, Figure 2 explains the different type of line inserted at each time, at initial diagnosis we saw that majority of patients >90% the port Cath insertion was the 1st option while the 2nd line inserted after removal of 1st, we saw both Hickmann and porta cath with similar incidence and finally for 3rd line insertion after removal of 2nd one the PICC line was the major incidence.

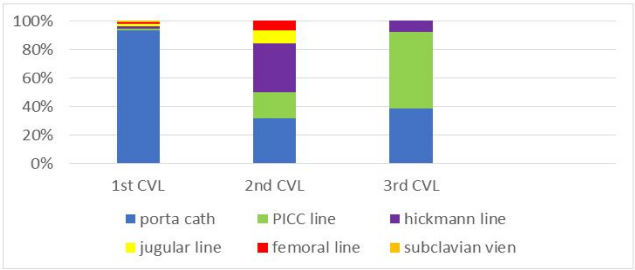

Figure 2. Type of CVL each time.

Among line characteristics, type of the line was noted to be of significance with a higher risk of CVCT in femoral and PICC line (P value<.001) in addition, to that the frequency of line insertion, we found that thrombosis occurs in 2nd and 3rd line inserted more than the 1st line inserted (P value=0.004) (Table 3).

Variable	Total 323	No thrombosis (n: 309)	Thrombosis (n:14)	p-value
Type of line				

Port Cath	267 (82.7%)	260 (97.4%)	7 (2.6%)	<.001*
PICC	19 (5.9%)	14 (73.7%)	5 (26.3%)	
Femoral line	6 (1.9%)	4 (66.7%)	2 (33.3%)	
Hickmann line	20 (6.2%)	20 (100.0%)	0	
Jugular line	8 (2.5%)	8 (100.0%)	0	
Subclavian line	3 (0.9%)	3 (100.0%)	0	
Line number				
1st	266 (82.4%)	259 (97.4%)	7 (2.6%)	.004*
2nd	44 (13.6%)	39 (88.6%)	5 (11.4%)	
3rd	13 (4%)	11 (84.6%)	2 (15.4%)	

Note: PICC-Peripherally Inserted Central Catheter *-Pearson *Chi-Square*

Table 3. CVCs related risk factor: Total number of lines: 323.

From the 14 episodes of CVCT we found only one patient with CVCT had family history in his father with CNS thrombosis before age 40. And 2 out of 14 episodes were associated with central line infection both was positive catheter tip culture with staphylococcus aureus.

Almost half of the episodes were asymptomatic all of them port Cath associated thrombosis with incidental discover during ECHO screening.

9 out of 14 episodes treated with LMWH (enoxaparin) with mean duration 4.7 months (SD=2.167) and the mean for anti X level was 0.87 (SD=0.178). 5 episodes of CVCT had no treatment given one of them had femoral line related thrombosis in APL patient with coagulopathy later he died with disease complication, other 3 episodes were subclinical, asymptomatic port cath related small, calcified non occlusive thrombus in the right atrial that was discovered accidently during routine echocardiogram studies, and the 5th case was PICC line related thrombosis discovered because of line dysfunction and doppler US done accordingly and showed non occlusive thrombosis, this line was removed without anticoagulant therapy.

There was no usage of warfarin or antifibrinolytic treatment in any one of our patients.

Furthermore, 7 out 14 episodes CVLs were removed 2 of them due to central line infection, other with line malfunction or occlusive and symptomatic limb swelling.

Concerning the outcome of our 14 episodes of CVCT, 10 episodes of thrombosis were resolved in mean duration 3.9 months (SD=2.2), one episode regress in size, while 2 remain same size and 1 no follow up (mortality case).

Additionally, in our study we noted that the occurrence of CVCT was at a mean of 4.7 months following line placement but differed drastically between types of lines. The femoral lines had the shortest duration from insertion time to thrombi formation (4 d), whereas the port caths had the longest period (342 d) (Table 4).

Variables	N=14 (%)
Symptom	
Asymptomatic	7 (50%)
Lower limb sweeling	5 (35.7%)
Line not working	2 (14.2%)
Occlusive	
Yes	6 (42.9%)
No	8 (57.1%)
Diagnostic tool	
ECHO	7 (50%)
Doppler US	6 (42.8%)
CT scan	1 (7.2%)
Use of anticoagulant	

LMWH	9 (64.3%)
Not used	5 (35.7%)
Duration of anticoagulant (months), mean ± SE	4.78 (SD=2.1)
Anti X level, mean ± SE	0.87 (SD=0.178)
Removal of line	
Yes	7 (50%)
No	7 (50%)
Out come	
Complete resolve	10 (71.4 %)
Regress in size	1 (7.1%)
Same size	2 (14.2%)
No follow up	1 (7.1 %)
Duration to resolve (months), mean ± SE	3.9 (SD= 2.2)
Associated CVC infection	
Yes	2 (14.3%)
No	12 (85.7%)
Positive family history of thrombosis	N=13 (%)
Yes	1 (7.7%)
No	12 (92.3%)
Duration between line insertion and thrombosis (days) mean ± SE	
Port Cath	342.3 (SD=353.9)
PICC line	30.60 (SD=30.6)
Femoral line	4 (SD=0.00)
All line (months) mean ± SE	4.7 (SD=2.16)

Table 4. Characteristic of CVCT and outcome.

Discussion

In a multicenter study from the children's hospital-acquired thrombosis consortium for the evaluation of venous thromboembolism risk factors among hospitalized children with central venous catheters: The study ran on >1000 participants and identified those with a PICC, a femoral vein as a placement site, frequent CVC insertions, and a CVC with a malfunction requiring tPA as having increased odds of developing CRT compared with non-CRT.

Thromboembolism (TE) is a frequent and potentially fatal complication in pediatric patients with cancer [5]. Malignancy was linked to the occurrence of coagulation disturbances and thrombosis and was believed to be associated with a four to seven fold increase in the risk of Venous Thromboembolism (VTE) [6].

Besides the effect of cancer on the coagulation system, specifically solid tumors with the mass effect, can impair the blood flow and lead to stasis, which increases the risk of VTE. Additionally, the direct invasion of cancer cells into blood vessels might raise the risk of thrombosis.

The surgical interventions in such patients that involve biopsies or tumor resections also had its impact on increasing the risk of thrombosis due to endothelial damage, reactive thrombocytosis, and immobility [7].

For example, Wilms tumor is one of the known solid tumors that have a propensity to invade blood arteries, causing tumor thrombus to form in the renal veins, inferior vena cava, and even the right atrium. Up to 10% of patients have an extension of the tumor thrombus along the renal vein into the inferior vena cava.

In our study, 6.3% of our population they have tumor-related thrombosis, with a higher incidence was among hepatoblastoma and renal tumors, which is 50% and 13.7%, respectively.

Symptomatic CVAD-related thrombosis has been reported to be very high (30%–68%) in children with lymphoma, while the incidence of CRT was 10.2% in children with leukemia and PICCs.

Pediatric patients with acute leukemia are typically prone to infectious or hemorrhagic complications that could be serious and life

threatening. Yet, thrombosis has been repeatedly described as possibly complicating the course of the disease.

Mitchel et al. [8] found that natural coagulation inhibitors such as protein C were decreased in patients with leukemia even before starting chemotherapy. On the other hand, coagulation factors VIII, IX, and von Wille brand factor were significantly elevated, promoting hypercoagulability [7]. In lymphoma cases, mediastinal tumors may compress the blood vessels in the upper part of the body and lead to thrombosis. Interestingly, 92.7% of patients with thrombosis in Hodgkin lymphoma cases had a mediastinal mass [9].

Our current data showed that most patients with CVCT are among the group of hematological malignancy (leukemia and lymphoma) (10 out of 13 patients with CVCT).

Clinical evidence has supported a causal relationship between Chemotherapy and thrombosis for over three decades. Chemotherapy is capable of inducing thrombogenic effects through multiple different mechanisms independent of underlying malignancy [10].

Asparaginase is an essential medication in pediatric Acute Lymphoblastic Leukemia (ALL) treatment regimens, and it is very well known to be associated with improved long-term outcomes and survival [11].

One of the most significant asparaginase-related toxicities impacting morbidity and mortality is Venous Thromboembolism (VTE).

Asparaginase can cause impairment of anticoagulant and fibrinolytic mechanisms, producing a prothrombotic state that lead to overt thrombosis in 2%–10% of the patients [5]. The impaired synthesis of antithrombin and plasminogen and the depletion of protein C and S are thought to be responsible for the thrombotic tendency in patients treated with asparaginase.

A large meta-analysis by Caruso et al. reported a 5.2% incidence rate of symptomatic thrombotic complications in 1752 pediatric ALL patients treated with asparaginase [12]; however, a lower incidence of severe thrombosis and hemorrhages that is around 1 to 2% reported in a similar study [13] for children undergoing induction therapy which includes asparaginase.

In another multicenter review of pediatric patients treated with asparaginase-containing regimens between 1976 and 1980, 18 children out of 1547 (1.2%) studied developed a 'severe' thrombotic, or hemorrhagic complication.

Our current result showed that asparaginase-containing regimens were used in 7 out of 13 (53.8%) patients with CVCT.

Steroids play an essential role in treating pediatric Acute Lymphoblastic Leukemia (ALL) and are regularly incorporated into treatment regimens for hematologic malignancies (*i.e.*, Leukemia, lymphoma).

The increased risk of VTE secondary to exogenous steroid use was confirmed in a large case-control study that included patients with malignancy; this study demonstrated an Incidence Rate Ratio (IRR) of 2.31 for DVT/PE in patients actively taking corticosteroids compared to controls [14]. On the other hand, the concomitant administration of *Escherichia coli* asparagine/prednisone to leukemic children with a prothrombotic risk factor was found to increase the risk of thrombosis (odds ratio: 34.5; 95% confidence interval: 4.39–271.42; P=0.0008) [15].

In our study showed that in 12 out of 13 patients with CVCT, steroids were used as part of their chemotherapy regimens, and the results were statically significant with (P=0.019) compared with those patients who did not use steroids.

Besides that, pediatric cancer patients are at an increased risk of Venous Thromboembolism (VTE) due to their cancer. Central Venous Catheters (CVCs) are known to increase that risk further [16].

Catheter-related thrombosis is not an infrequent occurrence in pediatric oncology patients. According to study design, patient selection, catheter type, follow-up time, and detection method, reported rates of catheter-related thrombosis vary widely [12]. In a revision by Ramsus, Hansen et al. of Fifteen studies (n=1,551) described CVC-related VTE, the reported rate is 11% for CVC-related VTE [17].

In another large retrospective study over nine years for 296 pediatric oncology patients, thrombosis occurred in 2.4% of patients. Data from another study with a total of 4920 central lines that were inserted into 3130 patients found that the incidence of CVCT was 3.6% [4], interestingly; our data showed a similar incidence of CVCT 4.33% in a total of 323 lines inserted. However, it is still less than what was reported in another national study from Saudi Arabia on the PICU population, in which the incidence of thrombosis among temporary central line insertions over two years was 8.5%. In this study, most lines were short term, like the femoral lines [18].

Age was addressed in some studies as an important factor that has an impact on thrombosis incidence in small children; specifically, NICU patients have a risk for CVCT. Additionally, adolescents with age >11 years are at increased risk for DVT [19]. Another study conducted at a pediatric tertiary care hospital in the United States in 2011 by Bhuvana A. Setty et al. reveals a bimodal distribution, with the majority of VTE occurring in children >15 years old at admission and another lower peak in children one year of age at admission [20]. However, we did not observe a similar impact of the age factor on the risk of CVCT in a statistically significant way. Despite that, we got a little higher incidence among patients related to the age group between 9 to 12 years. On the other hand, since there is no neonatology service in our centre, we had no single case for this age group.

Clinical and epidemiological studies support a relationship between obesity and thrombosis, involving elevated expression of the prothrombotic molecules plasminogen activator inhibitor-1 and Tissue Factor (TF) and increased platelet activation [21].

A relevant study [33] addressed the effects of Body Mass Index (BMI) on the risk of Thromboembolism (TE) in children (<18 years) with hematological malignancies during the period 1990-2009 and included 359 patients. Obesity was prevalent in 12% of patients: 6%versus 17% prior to and after the year 2000 (P=0.02), they found that increasing BMI was associated with an increased but statistically insignificant risk of TE adjusted Odds Ratios (OR): 0.75 (95%CI 0.32-1.77), 0.93 (95% CI 0.38-2.30), and 1.01 (95% CI 0.42-2.41) for underweight, overweight, and obese group [22].

A cross-sectional study conducted among hospitalized patients demonstrated that obesity was significantly associated with DVT (PR, 2.1; 95% CI, 1.5-2.8). While another retrospective research indicates that there is no difference in the incidence of central venous line-associated DVT between BMI groups (p-value: 0.23) [23], our current data did not prove an association between BMI groups and line related thrombosis. (p- value:.119)

The literature has described various acquired and hereditary risk factors for pediatric VTEs and CVCs. Multifactorial etiologies were found in over 90% of cases [24-26]. Sepsis, malignancy, congenital heart disease, and surgery; were among the most common concomitant risk factors for thrombosis in the presence of CVCs [27].

Systemic infection has been identified as a risk factor for thrombosis. In cases of severe sepsis, hemostatic system dysregulation can result in disseminated intravascular coagulation and micro-vascular thrombosis, contributing to CVCT [28].

Moreover, there is accumulating evidence that CVCT and CVC-related infections are not separate entities, but seem to have a bidirectional relationship [29].

Exit-Site Infection (ESI) (P value=0.001), catheter-related blood stream infection (P value=0.001), and coagulase-negative staphylococci infection (P value=0.002) were all identified as significant risk factors for central line thrombosis.

In our study, we have 2 out of 14 episodes of CVCT with documented catheter infection. And 1.8% of our population (5/266) with septicemia-related thrombosis, which is less than what are reported from other previous studies. One study observed that the second most frequent underlying risk factor for CVCT was infections (15/78, 19%) [30]; another study reported that 46% (24/52) of children (aged one month to 18 years) with venous thrombosis were due to infection, this incidence increases in the neonatal age group to 60% (28/47) [31].

Children with Congenital Heart Disease (CHD) are the largest pediatric patient group, accounting for one-third of children suffering from venous thromboembolism [32]. The CHD frequently disrupts the balance of hemostasis, which paradoxically may lead to bleeding, thrombosis, or both. Abnormalities in coagulation proteins, platelet quantity, and function, and red cell number and function that affect hemostasis are just a few of the reported discrepancies. These abnormalities can result in bleeding and/or thrombosis, with many having more than one abnormality [33].

In a prospective, observational cohort study published in blood 2016, 883 CVCs were placed, with a total of 43 CVCTs (4.9%), and they found that congenital heart disease was a significant risk for CVCT with OR=2.8 (CI 1.3-6.0) [23].

In our population, we had only two patients with CHD, and one (50%) of them got CVCT; but due to the very small number, we could not significantly conclude the risk of CHD and CVCT.

Central Venous Access Devices (CVAD) provides essential benefits in treating pediatric oncological patients for long-term chemotherapy administration or transfusion of blood and blood products and laboratory tests [34].

Three main types of central venous catheters are used in pediatric cancer patients: The Peripherally Inserted Central Catheter (PICC line), tunnelled central line, and the subcutaneous port. Multiple factors determine what type of catheter is best for each patient, like the type of therapy, the needed duration of treatment, the child's age, health status, and the risk of infection and other complications [35].

Implanted ports, compared to the externalized tunnelled catheters, have a decreased risk of infection, minimal maintenance requirement, and flexibility with clothing, bathing, and daily living activities. Because of that, it results in a high level of patient acceptability and makes it the best type of device for outpatient oncology treatment [36]; they are also known to have a reduced DVT risk than other forms of central catheters. Because PICCs begin in a small vein, which creates stagnant blood flow, patients with it are more susceptible to catheter-related thrombosis than patients with other kinds of central venous catheters [37].

Wang, et al. addressing a large meta-analysis of 22 studies concluded that the Port-related VTE was lower than those PICC-related in cancer patients (OR=0.38, 95% CI: 0.25-0.58) [38].

Data from another retrospective study that involved 376 CVLs in 325 pediatric patients support the above findings in which the incidence of DVT was 5.1%. The type of CVL was a statistically significant risk factor for DVT, with 10.9 times higher odds of thrombosis in tunneled CVLs than in ports and 12.2 times higher odds compared to PICCs [3].

These studies support our finding of a significantly lower risk of catheter-related thrombosis in port Cath compared with femoral lines and PICCs (p-value: <.001).

So far, the presence of an IV catheter is considered the most common cause of upper extremity DVT. More than doppler ultrasound, venography had a chance to pick more asymptomatic cases. Among 25 studies addressing the issue of central venous line associated thrombosis, the rates of asymptomatic DVT were 41% when Venography was used to screen patients and 19% with Doppler ultrasound [39]. The median times to symptomatic and asymptomatic CVCT were 17 (range 1–49) and 8 (range 1–16) catheter days, respectively as in one study involved 104 patients with 200 insertions of central venous catheters [8].

Our study also noticed the most prolonged duration between line insertion and thrombosis was in port A Cath. In contrast, shortest with a femoral line, this finding was similar to another observation study in which they found the median time to development of DVT from CVL placement for ports was a significantly longer time to thrombi occurrence than PICCs (P=0.019) and tunneled catheters (P<0.001) [3].

On the other hand, in a multi-center retrospective cohort study with a total of 402 cases of central line insertion (165 PICC and 236 port), there was no significant difference in time until onset of thrombosis between catheter types (median=58.5, range=21.9-91.6 days for implantable ports *vs.* 42.5, 13-77.8 days for PICCs; P=.35) [4].

The long period in our study between port insertion and occurrence of thrombosis could be because most port-associated thrombosis were right atrial thrombi which were subclinical and asymptomatic, and a small thrombus was found by accident while evaluating heart function by echocardiography.

The subsequent CVC placements after the initial inserted ones can lead to more damage to the endothelium. And one crucial study by Monika Joks, et al. [40] found a statistically significant increased incidence of central line-related thromboses in patients who underwent two or more central lines insertion with the comparison to those treated with only one line inserted (P=0.033). Multivariate analysis confirmed treatment with more than two prior chemotherapy lines is an independent risk factor for CVCT, increasing the risk of CVCT more than threefold.

Many studies addressed the number of subsequent central line insertions as a significant risk factor. In a Local single center study, retrospective in nature done by Ruqaiah AlTassan, et al. that was conducted on pediatric ICU patients. Its result showed that the subsequent central line insertions carried a 6.76-fold higher risk for thrombosis than those who required only one line (95% Confidence Interval (CI): 2.339-16.667; p=0.0003) [18]. Our current data support similar results the incidence of CVCT is significantly higher after the second and third lines than in patients with only one line inserted, with a p-value of 0.004.

The main goals of CVCT treatment are reducing symptoms, preventing the extension of thrombosis, and preventing chronic venous blockage. The first two things to decide in patients with CVCT are whether to utilize thrombolytic therapy to restore central venous flow or to remove the CVC [29].

The 2019 international clinical practice guidelines for treating and preventing venous thromboembolism in patients with cancer recommend keeping CVC in place if it is functional, well positioned, and not infected, with a good resolution of symptoms under close surveillance while anticoagulation therapy is administered [28].

In patients with malignancy, LMWH is the preferred anticoagulant, with warfarin being an alternative in patients without malignancy once their critical illness has resolved [41].

Moreover, CHEST guidelines recommend that children with CVCT receive therapeutic low molecular weight heparin. They suggest that the drug be monitored to a target level between 0.5 to 1.0 units/mL in a sample taken at 4 to 6 h after subcutaneous injection [42]. However, almost 65% of our patients with CVCT were treated with LMWH, with mean of anti X level was 0.87 (SD=0.178). While catheter removal was performed in 50% of episodes; most of them were occlusive thrombus, line malfunction or infected lines [43].

CVCT confers significant acute and chronic morbidity and mortality. Sequels to that thrombosis include Catheter occlusion, loss of venous access, and disrupting tightly planned treatment schedules; furthermore, the presence of thrombosis on a catheter provides a fertile microenvironment for bacteria to grow, increasing rates of bacterial colonization and catheter-related sepsis, infection, embolism to other vessels, including Pulmonary embolism, right heart thromboembolism, superior vena cava syndrome, and paradoxical embolism to the systemic circulation are other uncommon yet potentially life-threatening complications [35,4].

Patients may also suffer from chronic pain secondary to the post-thrombotic syndrome that impairs their daily routine activities.

Fortunately, in our study we got no reported post-thrombotic complication in any of the 14 episodes.

The following are some of our study's limitations: Being a study of a single institute, the relatively small sample size of our population, the retrospective nature of a study in addition to lack of documentation of some important data such as a family history of inherited thrombophilia.

This study cannot rule out that there may be additional asymptomatic thrombosis cases among our population that are not detected, as we did not do routine imaging for surveillance of thrombosis in all our patients.

Conclusion

Over the past two decades, although the use of CVCs has increased dramatically, the risk of Catheter-related thrombosis per catheter has decreased, perhaps related to fewer thrombogenic catheters and improved insertion techniques. Meticulous attention must be given to clinicians, particularly in cases with more than risk factors or concurrent use of thrombogenic medications. Given that the majority of cases occur asymptomatically, a high index of suspicion is required for diagnosis to allow for the timely administration of treatment.

Further adjusted recommendations focusing on technique of insertion and avoidance of femoral lines, if possible, in addition to decreasing the number of PICCs placed, maybe help to decrease the incidence of CRT in children, the improvement of planning the treatment for CVC-related thrombosis, whether short vs. long-term anticoagulant therapy, needs an extensive multicenter collaboration. Besides that, each treating center should develop a local CVC practice guideline and implement active quality improvement strategies to prevent CVC complications and reduce its burden on patient care.

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