Central Venous Catheter-Associated Deep Venous Thrombosis in Critically Ill Children in Tanta Pediatric Intensive Care Unit

Abstract

Background: The largest prevalence of CVC-related thrombosis occurs in infants under the age of one year, which is likely due to the infant's smaller diameter vessels. In addition, CVC-related thromboses are more likely to occur in patients with malignancy, critical illness, congenital heart disease, systemic infection, total parenteral nutrition, trauma, and in patients admitted to the Neonatal Intensive Care Unit. Central line occlusion or frequent central line infections are sometimes the first sign of thrombosis and should increase suspicion of a VTE. In neonates with catheter-related thrombosis, thrombocytopenia may be the presenting sign. At least 18% of critically ill children with a CVC develop radiologically confirmed catheter-associated thrombosis (CAT). Clinically apparent thrombosis occurs in 17.5% of critically ill children with a CVC .

Methods: This prospective observational study was carried out on 55 pediatric patients admitted to PICU, Tanta University Hospital. The duration of research was conducted from December 2020 to December 2022. They were subdivided into:

Group I: Fifteen patients with Factor VIII (FVIII) activity <100 %

Group II: Twenty patients with FVIII activity from 100 % to 150 % (high normal)

Group III: Twenty patients with FVIII activity >150 %.

After correction of dehydration (if present); All patients in the three groups: FVIII and D-dimer, were collected on the day of insertion of central venous line (all patients from the start received thromboprophylaxis in the form of (Enoxaparin Sodium ®) with dose (0.5 mg/kg subcutaneous every 12 hours) and after one week of enrollment. Twenty patients **received Alteplase®** dosing for CVC occlusion based on patient weight category and the volume of the affected catheter lumen.

Results: FVIII activity was a significant predictor for central venous line thrombosis with cut-off value>152, sensitivity100, specificity 80, PPV 93.7, and NPV 100.

Conclusion: F VIII activity was a significant predictor for central venous line thrombosis.

Enoxaparin sodium® was effective as thromboprophylaxis with a dose (of 0.5 mg/kg subcutaneously every 12 hours) within the normal range of factor VIII (up to 150%).

Alteplase® dosing for CVC occlusion based on patient weight category and the volume of the affected catheter lumen with an efficacy of 73.33%.

Key words: Deep Venous Thrombosis, Pediatric, central venous catheter

Introduction

"Deep venous thrombosis is a significant problem in critically ill children. The most important risk factor for DVT is the presence of a CVC. The risk for CVC-related DVT is low within 24 hours after insertion of the CVC but significantly increases thereafter. Although routinely used in critically ill, pharmacologic thromboprophylaxis is not recommended in children with CVC due to the paucity of studies to support this practice. It would be ideal to provide thromboprophylaxis only to critically ill children at high risk for CVC-related DVT. No test has been known to identify these children" [1].

"The no tunnelled type of CVC is usually inserted when children are critically ill and likely hypercoagulable. Coagulation factors, particularly factor VIII, increase during critical illness. Factor VIII activity >150 IU/dL is associated with 2.6 to 4.8-fold odds of developing DVT in adults" [2].

"Numerous risk factors contribute to the development of an abnormal thrombus. Identification of the causative factors of VTE as well as determining the reversibility of these factors is very important in planning the therapy, in terms of length and intensity of the interventions, and assessment of the risk of recurrence of the thrombosis" [3].

“The goals of VTE therapy are to prevent clot extension, prevent embolism, restore venous patency, limit the long-term sequelae, and reduce the risk of recurrence. These goals are achieved by rebalancing the hemostatic system with anticoagulant and thrombolytic therapy and, when possible, reversal of the causative factors” [4].

Aim of the work

This work aimed to identify critically ill children at risk for central venous catheter-associated thrombosis to target them for thromboprophylaxis.

Methods

This prospective observational study was carried out on 55 pediatric patients admitted to PICU, Tanta University Hospital.

The duration of research was conducted from December 2020 to December 2022. Written informed consent was obtained from the guardians of all patients included in the study. The study was approved by the ethics committee of the Faculty of Medicine, Tanta University.

Inclusion criteria: Patients with a no tunneled CVC inserted within the previous 24 hours were enrolled. Patients on mechanical ventilation and Patients with hemodynamic instability.

Exclusion criteria :Children with documented thromboembolic events within the past 3 months. Children received anticoagulants within the past 3 months. Children who received hemostatic support, particularly fresh frozen plasma or cryoprecipitate.

Patients were divided into 3 groups:

Group I: Fifteen patients with FVIII activity <100 % (low normal)

Group II: Twenty patients with FVIII activity from 100 % to 150 % (high normal)

Group III: Twenty patients with FVIII activity >150 %.

All patients received thromboprophylaxis in the form of (Enoxaparin Sodium ®) with a dose (of 0.5 mg/kg subcutaneously every 12 hours).

All patients enrolled in this study were evaluated by history taking including Presence of significant immobility (limitation in independent purposeful physical movement of body or one or more extremities from baseline > 48 hours). Presence of chronic VTE risk factors during major surgery, major injury, or during periods of infection and inflammation, Inflammatory bowel disease., Nephrotic syndrome. Cystic fibrosis., Need for PICU., Need for mechanical ventilation.

Scoring systems for patients: Pediatric Risk for mortality scoring III: obtained within 24 hr. of admission [7]. Pediatric Sequential Organ Failure Assessment scoring: obtained from each patient daily and recorded on 1st day and after one week of admission [8].

All patients enrolled in this study after correction of dehydration (if present): FVIII and D-dimer, were collected on the day of insertion of CVL [9].

On the day of enrollment, Ultrasound imaging was performed on the central vein where the CVC was inserted and on both lower extremities, the most common sites of non-CVC-related DVT [10]. The US was repeated on the site of insertion of the CVC within 24 hours of its removal or one week after insertion of the CVC when the clinical team suspected CVC-related DVT, or when the subject was unlikely to survive for the next 24 hours.

Blinded, certified radiology technicians at each hospital performed the US using the EDAN model (DUS 60) ISO 9000, ISO 13485 Origin: CHINA Ultrasound Imaging Platform with 7-15 MHz linear transducers [11].

Statistical analysis of the data

"Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). (128) Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. The significance of the obtained results was judged at the 5% level" [12].

The used tests were: Chi-square test (For categorical variables, to compare between different groups). Student t-test (For normally distributed quantitative variables, to compare between two studied groups). ANOVA with repeated measures (For normally distributed quantitative variables, to compare between more than two periods or stages, and Post Hoc test (LSD) for pairwise comparisons). Mann-Whitney test (For abnormally distributed quantitative variables, to compare between two studied groups). Linear correlation coefficient (r): For detection of correlation between two quantitative variables in one group. The power of significance was evaluated as follows: Probability level (P-value) >0.05=Non significant (NS). P-value <0.05=Significant.

Results

The demographic and anthropometric data of the studied patients was presented in Table (1): There was no significant difference throughout the study between the studied groups.

Regarding the comparison of US between the studied groups: There was a significant increase in the incidence of IV echoic material in group III compared with groups I, and II. Otherwise, there was no statistically significant difference throughout the study figure (1).

Regarding the Comparison of D-dimer between the studied groups: There was a significant decrease of D-dimer on the 7th day compared with the 1st day in groups I, and II compared with group III.

Regarding the Comparison of FVIII activity between the studied groups: There was a significant increase in FVIII activity in group III compared with groups I, and II on 1st day. Also, there was a significant increase in FVIII activity in group III compared with groups I, and II on the 7th day) figure (2).

Regard Effect of Enoxaparin sodium® between the Studied Groups: There was a significant increase in CVC occlusion in group III compared with groups I, and II Table (2).

Regard Effect of Alteplase® between the Studied Groups: There was a significant increase in Patients who received Alteplase® in group III compared with groups I, and II.

Regarding Pediatric Risk for Mortality III Scoring Score in Studied Groups: There was a significant increase in the risk of mortality in group III compared with groups I, and II. Otherwise, there was no significant difference throughout the study.

Regarding the correlation of FVIII with other parameters: There was a positive correlation between FVIII activity with ESR on the 1st and 7th days. There was a negative correlation between FVIII activity with PT and PTT on the 1st and 7th days Table (3).

Regarding the ROC curve for FVIII activity for predicting catheter-related thrombosis in critically ill children: FVIII activity was a significant predictor for central venous line thrombosis with cut-off value>152, sensitivity100, specificity 80, PPV 93.7, and NPV 100 figure (3).

Discussion

The present study showed that regarding age, weight, and sex there was no significant difference in age and sex throughout the study between the studied groups. The non-significant difference found in age, weight, and sex demonstrates the non-bias choice of the study cases.

The present study showed that Hb, WBCs, PLTs, PT, PTT, and ESR there was no significant difference between the studied groups during the study period.

The present study showed that ALT, AST, Albumin, and CRP there was no significant difference between the studied groups during the study period. This was in accordance with, Kamphuisen et al. [13] conducted two groups of patients with or without pulmonary embolism. They found that CRP is not a reliable parameter .

Similarly, Tsai et al. [14] conducted a prospective study on a total of 159 venous thromboembolism patients and measured FVIII and CRP levels, in blood samples. They found that there was no association between venous thromboembolism and C-reactive protein levels

The present study showed that there was no difference in central line type and size between the studied groups. This was in accordance with, Huibonhoa et al. [15] conducted a post hoc study on

236 children admitted to the PICU, who had a non-tunneled CVC. They observed that the size and duration of CVC were not different among the studied group. This was in contrast with, Li et al. [16] enrolled a retrospective study on patients aged from birth to 18 (months) who were admitted to PICU and underwent at least one CVC placement. The patient's catheter types and sizes were significantly associated with the occurrence of CADVT.

The present study showed that regarding the comparison of the US between studied groups. There was an increase in the incidence of IV echoic material in group III compared with groups I, and II. Consistent with these results, Faustino et al. [17] showed that DVT was significantly diagnosed on the day of discharge or within 24 hours. of its removal.

The present study showed that regarding the effect of Enoxaparin sodium®, there was a significant increase in CVC occlusion in group III compared with groups I, and II. This was in accordance with, Kearon C et al. [18] collected and analyzed retrospectively Group 1 of Enoxaparin sodium®, at a prophylactic dose of 50 anti-Xa IU/kg/dose every 12 hours. subcutaneously. This was in contrast with, Merli G.J et al. large randomized National Institute of Allergy and infectious diseases trial was bringing together three clinical trial platforms covering four continents and over 300 hospitals. Researchers suggest that therapeutic doses of anticoagulants are not only safe but also superior to preventive ones. [19]

The present study showed that regarding risk factors there was an increase in the incidence of risk factors (TPN or MV) in group III compared with groups I, and II. These may also predispose to thrombosis since they can induce endothelial cell damage with the release of pro-coagulant factors and platelet activation, leading to thrombus formation and deep vessel occlusion. [20]. This was in accordance with, Lasagni et al. [21] collected and analyzed retrospectively a total of 78 CVC-VTEs children (median age at onset was 19 and 17 months). They found that TPN was the most frequent reason for CVC insertion. This was in contrast with, Sandoya et al. [22] conducted an observational, cross-sectional study on 35 patients to identify factors that are associated with the

development of venous thrombosis in patients with CVC admitted to the intensive care unit. They found that adequate nutritional status or malnutrition was not associated with a higher prevalence of thrombosis.

The present study showed that was a significant decrease of D-dimer on the 7th day compared with the 1st day in groups I, and II compared with group III. This was in accordance with, Evensen et al., [23] who conducted a prospective cohort study to measure circulating levels of FVIII and D-dimer. They found that D-dimer and FVIII showed significant linear associations with VTE risk.

The present study showed that regarding Alteplase®, there was a significant increase in patients who received Alteplase® in group III compared with groups II, and I. The catheter function was regained in 80% and 73.33% respectively in group II and group III. This was in accordance with Shen et al. [24] who published a retrospective pediatric subgroup analysis. This study also indicated that shorter times from observation of occlusion to intervention improved catheter patency outcomes. [25]

The present study showed that comparison of FVIII activity between the studied groups. There was an increase in FVIII activity in group III compared with groups I, and II on the 1st day. Also, there was an increase in FVIII activity in group III compared with groups I, and II. This was in accordance with, Faustino et al. [26] who conducted a prospective cohort study on 85 children who were admitted to the PICU within 24 hours after the insertion of a central venous catheter. They found that FVIII activity is significantly associated with incident CVC-related DVT.

The present study showed that regarding the ROC curve; FVIII activity was a significant predictor for central venous line thrombosis with cut-off value>152, sensitivity100%, specificity of 80%, PPV of 93.7%, and NPV of 100%. This was in accordance with, Huibonhoa et al. [15] found that "the sensitivity and specificity of physical examination with CVC dysfunction included in detecting CADVT diagnosed with ultrasound were 29.2 % and 80.2 %, respectively".

Conclusion:

- F VIII activity was a significant predictor for central venous line thrombosis.

•Enoxaparin sodium® was effective as thromboprophylaxis with a dose (of 0.5 mg/kg subcutaneously every 12 hours) within the normal range of factor VIII (up to 150%).

•Alteplase® dosing for CVC occlusion based on patient weight category and the volume of the affected catheter lumen with an efficacy of 73.33%. Conflict of interest: none to declare.

List of abbreviations:

CADVT: Catheter-associated deep venous thrombosis CVC: central venous catheter, DVT: deep venous thrombosis, ESR: erythrocytic sedimentation rate, PICU: pediatric intensive care unit, TPN: total parenteral nutrition, US: ultrasound, VTE: venous thromboembolism

Declarations

Ethics approval and consent: Local ethics committee of the Faculty of Medicine, Tanta University approved the study. The study is in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from the parents of all subjects of the study before enrolment.

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Table (1): Comparison of Demographic Data between the Studied Groups

		Groups									ANOVA	
		Group I			**Group II**			**Group III**			**F**	**P**
Age	**Range**	2.5	-	90	3	-	100	2.5	-	108	0.28	0.757
(Months)	**Mean ±SD**	22.467	±	29.330	16.400	±	23.525	20.950	±	24.388		
Weight	**Range**	5	-	25	5	-	30	3	-	25	0.04	0.99
(kg)	**Mean ±SD**	10.1	±	6.50	9.55	±	5.66	9.875	±	5.08		
Chi-Square		N		%	N		%	N		%	X^2	p
Gender	**Male**	7		46.67	10		50.00	10		50.00	0.05	0.96
	Female	8		53.3	10		50.0	10		50.0		

$\chi 2$, p: $\chi 2$, and p values for the **Chi-square test** for comparing the three groups, F, p: F, and p values for the **ANOVA test.**

Table (2): Effect of Enoxaparin Sodium® with a dose (of 0.5 mg/kg subcutaneously every 12 hours). on the Studied Groups

Enoxaparin sodium®	**Groups**			**Chi-Square**
	Group I	**Group II**	**Group III**	

	N	%	N	%	N	%	X^2	p
CVC occlusion	0	0.00	5	25.00	15	75.00	22.589	<0.001*
No CVC occlusion	15	100.00	15	75.00	5	25.00		
Total	15	100.00	20	100.00	20	100.00		

CVC: central venous catheter

Table (3): correlation of FVIII with other parameters throughout the study

	FVIII activity (%) 1st day		FVIII activity (%) 7th day	
	R	**P**	**R**	**p**
Age (Months)	0.056	0.686	0.002	0.990
Weight (kg)	0.107	0.438	0.058	0.674
Hb (g/dL)	0.003	0.985	0.048	0.730
PLT (k/µL)	-0.224	0.100	-0.221	0.105
TLC (k/µL)	0.041	0.768	0.001	0.996
PT (second)	-0.271	0.045*	-0.279	0.039*
INR	-0.120	0.383	-0.159	0.246
PTT (second)	-0.344	0.010*	-0.316	0.019*
ESR 1ST HR (mm/hr.)	0.301	0.025*	0.249	0.066
S. Albumin (g/dl)	-0.221	0.104	-0.200	0.143
CRP	0.166	0.226	0.155	0.260
Central size	0.150	0.275	0.091	0.510
D-dimer <0.5ug/ml 1st day	0.237	0.082	0.221	0.105

PLT: platelets TLC: total leucocytic count PT: prothrombin time INR: international normalized ratio PTT: partial thromboplastin time ESR: erythrocytic sedimentation rate CRP: C-reactive protein

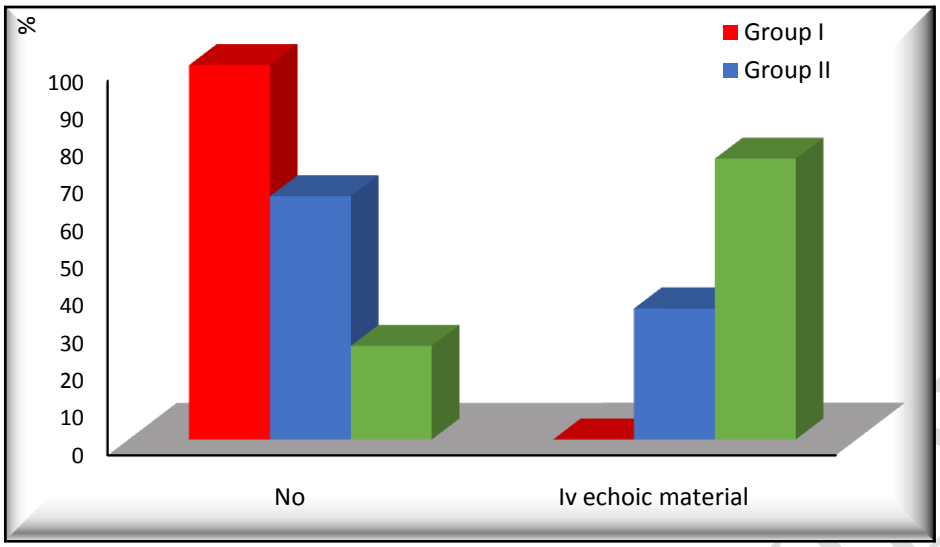

Figure (1): Comparison of Us between the Studied Groups.

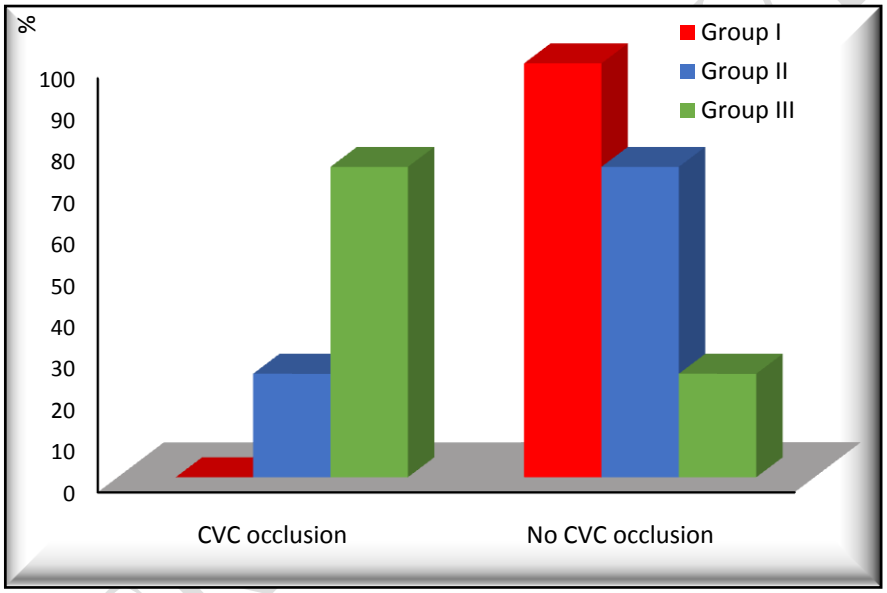

Figure (2): Effect of Enoxaparin sodium® between the Studied Groups.

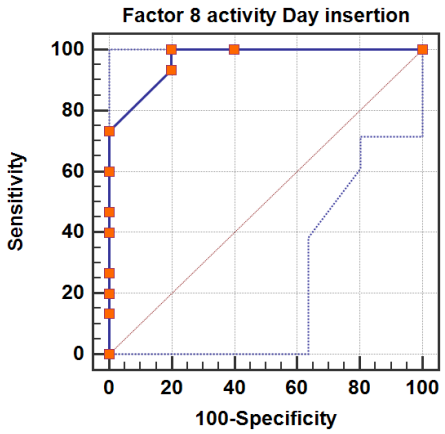

Figure (3): ROC curve for FVIII activity for predicting catheter-related thrombosis in critically ill children.