Temporary central line related thrombosis in a pediatric intensive care unit in central Saudi Arabia

Two-year incidence and risk factors

Ruqaiah AlTassan, *MD,* ***Hala Al Alem,*** *MD,* ***Talal Al Harbi,*** *MD.*

ABSTRACT

الأهداف: الهدف من الدراسة هو تقدير نسبة حدوث تجلطات وريدية في حالة استخدام القسطرة الوريدية المركزية المؤقتة للأطفال المنومين في وحدة العناية المركزة للاطفال وتحديد المسببات الممكنة لها.

الطريقة: أجريت دراسة استعدادية على الأطفال الذين نقلوا إلى وحدة العناية المركزة للأطفال (PICU) أقل من 14 عاما في مدينة الملك عبدالعزيز الطبية، الرياض، المملكة العربية السعودية خلال الفترة من 2009م إلى 2011م. وتم تسجيل المرضى في قاعدة بيانات القبول (PICU) وقاعدة بيانات مكافحة العدوى.

النتائج: في فترة الدراسة 2009–2011م كان عدد المرضى المنومين في وحدة العناية المركزة 1,361 مريض، احتاج منهم 248 مريضاً إلى قسطرة وريدية مركزية. اصيب 21 مريض بجلطة وريدية (8.5%). وجد من الدراسة أن الأطفال الذين احتاجو الى قسطرة وريدية أكثر من مرة، أكثر عرضة للتجلطات الوريدية ب6.2 مرات مقارنة بمن احتاجها مرة واحدة فقط (95% فترة الثقة 2.339-16.667) p=0.0003.

الخاتمة: نستنتج أن عدد مرات استخدام القسطرة الوريدية المركزية كان مؤشراً هاماً لحدوث تجلط الدم. فالمرضى الذين احتاجو القسطرة الوريدية المركزية أكثر من مرة واحدة هم أكثر عرضة للتجلطات الوريدية ب 6.2 مقارنة بمن احتاجو للقسطرة الوريدية المركزية مرة واحدة فقط.

Objectives: To estimate the incidence of temporary central venous line (CVL) related thrombosis among the pediatric population of critical care units, and to determine the possible predictors for developing CVL thrombosis.

Methods: A retrospective cohort study of patients ≤14 years of age who were admitted to the pediatric intensive care unit (PICU) at King Abdulaziz Medical City, Riyadh, Saudi Arabia from 2009 to 2011 was performed. The patients were recruited using the PICU admission database, and the infection control unit database.

Results: In 2 years, there were 1,361 admissions to the PICU. Only 248 patients required a central line for acute management. Twenty-one (8.5%) patients developed a thrombosis. The risk of thrombosis increased with multiple insertions of the central line compared with a single central line insertion (95% confidence interval: 2.339-16.667; p=0.0003).

Conclusion: Among all predictors, the number of CVLs was the only significant predictor of CVL thrombosis. Patients with multiple CVLs are at 6.2 times higher risk of developing thrombosis compared with those with a single CVL.

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From the Department of Pediatrics and Pediatric Intensive Care Unit (AlTassan, AlAlem), and the Department of Hematology Oncology (AlHarbi), King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Hala Al Alem, Division Head, PICU, King Abdulaziz Medical City, PO Box 22490, Riyadh 11426, Kingdom of Saudi Arabia. Fax. + 966 (11) 8011111. Ext. 12887. E-mail: alemh@ngha.med.sa

The use of central venous lines (CVL) has been a topic of interest, specifically in the critically ill patient care setting. Central venous lines are very important in critical care units. They provide easy venous access for administration of fluids, blood products, medications, and for hemodialysis as temporary lines. However, their use can be associated with several complications such as pulmonary embolism, infection,

or thrombosis. Thrombosis could be subclinical or clinically manifested.[1,2] Several studies have reported on CVL thrombosis, and most of them covered the adult population. There is a lot of variation in the incidence rates between the studies, and this variation is due to the different sensitivities of diagnostic tools, and the different levels of indices of suspicion.[2-6] Risk factors for CVL thrombosis are either inherited, such as coagulation disorders, or acquired like co-morbidities associated with coagulopathy such as cardiac, and hematological diseases, and patients on long-term central lines. Age is a major risk, and it is found that the risk is higher with extreme ages. High platelet counts at the time of CVL insertion is considered another risk factor. In addition, the lower venous central lines were more likely to become thrombosed than the upper venous central lines. Furthermore, the duration of CVL catheter placement plays a major role; the longer the duration the higher the risk of obstruction. The median time for development of thrombosis in CVL was reported as 18 days. The number of attempts at CVL insertions is considered an independent risk factor for CVL thrombosis.[7-9] This study focused on short-term CVL-related thrombosis in the pediatric intensive care unit (PICU), and aimed to assess how common thrombosis is in temporary CVLs, especially in the lines used for emergency management, and the impact of such a diagnosis on patient outcomes.

Methods. A retrospective cohort study was conducted on all patients (0-14 years of age) who were admitted to the PICU from January 2009 to January 2011, and required a CVL. The exclusion criteria included all patients with permanent lines, umbilical catheters, cardiology, and oncology patients. The study was performed at King Abdulaziz Medical City (KAMC, a National Guard government hospital) in Riyadh, Saudi Arabia. This setting is a tertiary hospital that serves the National Guard employees, soldiers, officers, and dependents, and the hospital sees a variety of cases. Our study was conducted in the pediatric critical care unit, which serves medical and surgical critical care patients, and has a capacity of 18 beds. After approval to conduct the study from King Abdullah Research Center at KAMC, Riyadh, the medical record numbers of the patients who required CVL were obtained from the infection control service database, and the data were collected from the patients' medical records. The age at admission, gender, and diagnoses were recorded for all admissions. Age was classified into 3 groups: neonates (0-28 days), infants (1-12 months), and children (1-14 years). The admission diagnoses were classified into the following categories: medical, surgical, trauma, and others (burns). All categorical variables (namely, age; gender; diagnostic category; type, site and side of line; symptoms; time of line removal; status of line; time of symptoms; type of anticoagulant; days of anticoagulation treatment; diagnostic tool; number of thrombosis with repeated admissions) were summarized in terms of frequency distribution. The continuous variables (namely, hemoglobin, white blood cells [WBC], platelets, prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR], duration of the line, and duration of anticoagulation) were reported as means and standard deviations. The categorical variables age, gender, and clinical (diagnostic category) characteristics were compared between thrombosed versus non-thrombosed groups using chi-square. The results were summarized as proportions, percent, and *p*-values (**Table 1**). The laboratory characteristics (complete blood count [CBC], PT, PTT, INR, protein C and protein S) between thrombosed and non-thrombosed groups were compared using Wilcoxon Rank Sum test. The results were reported as means, standard errors, and *p*-values (**Table 1**). All the statistical analyses were conducted and reported using SAS V9.2 (SAS Institute, Cary, NC, USA). All statistical tests were declared significant at an α level of 0.05 or less.

Results. There were 1,361 total admissions to the PICU over 2 years, and 295 patients required temporary CVLs. Two hundred and forty-eight patients met our inclusion criteria, and the others were excluded. Of the 47 excluded patients, 30 were oncology patients, 11 were cardiology patients, 3 had deep venous thrombosis (DVT) related to peripherally inserted central catheter (PICC) line, one had anti-phospholipid syndrome and developed a thrombosis related to a long-term central line (port-catheter), one had a thrombosis related to the external jugular vein, and one was on heparin prophylaxis. The overall PICU population was composed of 142 (57.3%) males. More than half (163 [65.7%]) of the PICU patients with CVL insertion were children aged from 1-14 years and most (113 [45.5%]) were medical patients (**Table 1**). Most of the lines were inserted in the femoral vein (171 [68.9%]), and most lines were inserted on the right side (177

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Table 1 - Demographic, clinical, and laboratory characteristics of the studied PICU patients.

Variables	No thrombosis (N=227)	Thrombosis (N=21)	*P*-value
Gender, n (%)			
Male	130 (57.3)	12 (57.1)	0.991
Female	97 (42.7)	9 (42.9)	
Age, n (%)			
Neonate (0-30 days)	11 (4.85)	2 (9.5)	
Infant (1-12 months)	63 (27.75)	9 (42.9)	0.177
Children (1-14 years)	153 (67.6)	10 (47.6)	
Diagnostic category, n (%)			
Medical	98 (43.2)	15 (71.3)	
Surgical	70 (30.8)	6 (28.6)	0.022‡
Trauma	46 (20.3)	0	
Burn	13 (5.7)	0	
Laboratory results (mean ± SE)			
WBC	13.0±0.52	14.78±2.31	0.570‡
Hb	100.47±1.84	113.80±7.38	0.027‡
Platelets	316.66±12.16	317.33±36.66	0.796‡
Protein C*	-	95.0±13.54	-
Protein S*	-	64.0±15.62	-
AT III*	-	89.0±10.03	-
PT	12.04±0.36	11.03±0.56	0.778‡
PTT	40.05±1.93	39.94±3.36	0.501‡
INR	1.48±0.13	1.25±0.06	0.746‡
Fibrinogen	2.18±0.18	3.21±0.35	0.009‡

PICU - pediatric intensive care unit, WBC - white blood count, Hb - hemoglobin, AT - anti-thrombin, PT - prothrombin time, PTT - partial thromboplastin time, INR - international normalized ratio, *only 3 observations, missing data, †Fisher exact test, ‡ - Wilcoxon rank test, SE - standard error

[71.3%]). Most the lines had multiple lumens (237 [95.6%]). On average, the first CVL was retained for 11 days (SD=7.6). The second CVL was also usually a femoral line (35 [14.1%]) inserted on the right side (26 [53.1%]) that had multiple lumens (48 [97.9%]). On average, the second CVL was retained for 13 days (SD=9.1) (**Table 2**).

As for thrombosis related characteristics, out of 21 patients diagnosed with a CVL thrombosis, based on clinical symptoms and positive Doppler ultrasound results, almost all patients (19 [95.2%]) presented with thrombotic symptoms before removal of the CVL. Limb swelling was a major presenting symptom in 17 patients

Table 2 - Central venous line related characteristics in the studied PICU patients.

Variables	No thrombosis (N=227)	Thrombosis (N=21)	*P*-value
Site of line one, n (%)			0.184‡
Internal jugular	47 (20.7)	3 (14.3)	
Subclavian	27 (11.9)	0	
Femoral	153 (67.4)	18 (85.7)	
Side of the line one, n (%)			0.995§
Right	162 (71.4)	15 (71.4)	
Left	65 (28.6)	6 (28.6)	
Lumen of line one, n (%)			0.606‡
Single	11 (4.85)	0	
Multiple	216 (95.15)	21 (100)	
Duration of line one (in days), (mean±SE)	11.02±0.50	10.71±1.61	0.891
Site of line 2, n (%)*			0.039‡
Internal jugular	10 (27.0)	0	
Subclavian	4 (10.8)	0	
Femoral	23 (62.0)	12 (100)	
Side of line 2, n (%)			0.362§
Right	21 (56.8)	5 (41.7)	
Left	16 (43.2)	7 (58.3)	
Lumen of line 2, n (%)			1.000‡
Single	1 (2.7)	0	
Multiple	36 (97.3)	12 (100)	
Duration of line 2 (in days), (mean±SE)	13.16±1.61	12.66±1.95	1.000Ω
Site of line 3,† n (%)			1.000‡
Internal jugular	5 (62.5)	1 (100)	
Subclavian	1 (12.5)	0	
Femoral	2 (25.0)	0	
Side of line 3, n (%)			0.444‡
Right	3 (37.5)	1 (100)	
Left	5 (62.5)	0	
Lumen of line 3, n (%)			-
Single	0	0	
Multiple	8 (100)	1 (100)	
Duration of line 3 (in days), (mean ± SE)	10.12±3.46	5.0††	-

PICU - pediatric intensive care unit, *Only 49 patients had 2nd line insertion, ‡Fisher Exact Test, §Chi-square test, ΩWilcoxon rank sum test, †Only 9 patients had 3rd line insertion, ††only one patient had thrombosis from the third line insertion and the duration of this line was 5 days

Table 3 - Thrombosis related characteristics in the studied PICU patients.

Variables	N=248 n (%)
Number of thrombosis with repeated admissions	
Yes	21 (8.5)
No	227 (91.5)
Thrombosis related characteristics	**n=21**
Symptoms	
Limb swelling	17 (80.95)
Line occlusion	2 (9.5)
Asymptomatic	2 (9.5)
Thrombosis status	
Complete	12 (57.1)
Partial	9 (42.9)
Site of thrombosis	
Lower	20 (95.2)
Upper	1 (4.8)
Time of removal of line in relation to thrombosis	
First 24 hours	10 (47.6)
After 48 hours	4 (19.05)
First week	6 (28.6)
>One week	1 (4.8)
Status of line	
Functioning	9 (42.9)
Non-functioning	7 (33.3)
Unknown	5 (3.8)
Time of symptoms	
Pre-removal	20 (95.2)
Post-removal	1 (4.8)
Status of line at time of removal	
No culture done	11 (52.9)
Not infected	7 (33.3)
Infected	3 (14.3)
Anticoagulants	
LMWH	19 (90.5)
Not used	2 (9.5)
Day of starting anticoagulants	
First day	6 (28.6)
Second day	10 (47.6)
Third day	3 (14.3)
Not used	2 (9.5)
Diagnostic tool	
Doppler ultrasound	21 (100)
Duration of anticoagulants (days), mean ± SE	51.65±8.30

PICU - pediatric intensive care unit,
LMWH- low molecular weight heparin, SE - standard error

Table 4 - Outcome of thrombosed CVL in the studied PICU patients.

Variables	N=21 n (%)
Outcome of thrombosis at 1 month	
Resolved	3 (14.3)
Regress	6 (28.6)
No changes	3 (14.3)
No follow-up	9 (42.85)
Outcome of thrombosis at 3 months	
Resolved	5 (23.8)
Regress	1 (4.8)
Progress	2 (9.5)
No follow-up	13 (61.9)
Outcome of thrombosis at 6 months	
No follow-up	19 (90.5)
Thrombosis was resolved	2 (9.5)
Outcome of patient	
Alive	13 (61.9)
Dead	8 (38.1)
Cause of death	
Disease related	8 (100)
None	0

CVL - central venous line, PICU - pediatric intensive care unit

(80.95%). Thrombosis was noticed most commonly at the lower site, mainly the femoral vein (20 [95.2%]) with complete thrombosis in 12 lines (57.1%). Almost half (10 [47.6%]) of CVL were removed within 24 hours of diagnosing thrombosis, and 9 (42.8%) CVLs were functioning at the time of diagnosing thrombosis. Out of 21 patients diagnosed with CVL thrombosis, 19 (90.5%) received low molecular weight heparin (LMWH), which was started within the first 48 hours in 16 (76.2%) patients. On average, the duration of therapy was 51.65 days (SD= 37.13) (**Table 3**).

The patients diagnosed with a CVL thrombosis were followed up at different time intervals. Follow-up at one month showed a regression of the thrombosis in 6 (28.6%) of the cases, while the 3-month follow-up showed a resolved thrombus in 5 (23.8%) of the cases. Only 2 (4.8%) patients had long-term follow-up at 6 months, which showed complete resolution of the thrombus (**Table 4**)

The overall incidence of thrombosis among patients with CVL in the PICU over 2 years is 8.6% (21/248). There was no significant difference in the incidence of CVL thrombosis either across genders or across different age groups (8.45% males, 8.5% females). Despite the non-significant difference in CVL thrombosis incidence across different age groups; it is worth noting

Table 5 - Predictors of CVL thrombosis in PICU patients.

Variables	OR	95% CI Lower bound-upper bound	*P*-value
Age (infant/neonate versus child)	2.533	0.954-6.725	0.0621
Gender (female versus male)	0.949	0.354-2.539	0.9163
Diagnostic category (surgical versus medical)	0.576	0.196-1.700	0.3181
Number of lines (2 or more versus 1)	6.243	2.339-16.667	0.0003
Platelet	0.999	0.997-1.002	0.4880
INR	0.463	0.123-1.743	0.2549

CVL - central venous line, PICU - pediatric intensive care unit, OR - odds ratio, CI - confidence interval, INR - international normalized ratio

that a decreasing trend of CVL thrombosis incidence was observed as age increased. The CVL thrombosis accounted for 15.4% neonates, 12.5% infants, and only 6.1% children. Among all predictors of a CVL thrombosis, the number of subsequent CVLs was the only significant predictor. The results indicated that patients who needed a second or third line inserted for longer periods were at a 6.76-fold higher risk for thrombosis compared with patients who needed only one line (95% confidence interval [CI]: 2.339-16.667; p=0.0003) (**Table 5**).

Discussion. Literature review revealed that most of the studies regarding central lines were in the adult population. Pediatric studies were focused on long-term lines in both cardiac and oncology patients or combined the short- and long-term lines in critical care units. The only study that focused on short-term lines was from KIDCAT (The Kids with Catheter-Associated Thrombosis), but it was limited to cardiac patients and the upper venous system.[1,2] The incidence of temporary central line thrombosis is not accurately known. It varies among studies, and the variation is due to the different sensitivities of diagnostic tools and different levels of indices of suspicion. Subclinical CVL thrombosis is very common; yet under estimated, while the clinically-manifested CVL-related thrombosis is infrequent.[1-7] In the Kingdom of Saudi Arabia, following a search in the PubMed database, we found a lack of studies that discussed the incidence of temporary line related thrombosis in children. This study is an observational study that evaluated CVL with no major risk factors; for example, hematological or cardiovascular diseases in a PICU population. The coagulopathy risk was not evaluated because of the small sample size investigated for that risk. From this observational study, we found that the incidence of the thrombosis among temporary central line insertions over 2 years was 8.5% (84/1000).

Risk factors for CVL thrombosis are inherited or acquired coagulation disorders. Extreme age, high platelet counts, and the location, and duration of the line are also considered high risk factors for thrombosis.[7,8] With excluding co-morbidities like hematology and cardiology diseases, we observed that thrombosis was higher in neonates compared with children. There was significant difference between diagnostic categories (p=0.022), hemoglobin(p=0.027) and fibrinogen (p=0.009) among patients diagnosed with CVL thrombosis versus no thrombosis.(**Table 1**)

The diagnosis of CVL thrombosis is predominantly reached using radiological tests, which vary in their sensitivity. Ultrasonography has an important role as a non-invasive diagnostic tool for the detection of CVL thrombosis, and is widely used compared to the venogram, but it has a low sensitivity.[9] In this observational study, all patients with suspected thrombosis underwent Doppler ultrasonography, and no further studies were required.

Management of the thrombosed CVL is controversial. The recent guidelines from the American College of Chest Physicians (ACCP)[10] divided the management into 2 categories: either the line is needed or it is not needed. If the line is needed, anticoagulants should be used, and the line can be left in place unless there is a serious adverse effect. If the line is not needed, it should be removed after 3-5 days of anticoagulant therapy if the patient had a risk of embolization, but if the patient has no risk for embolization the line can be removed without premedication with anticoagulants. The duration of the therapy is also controversial. Most physicians use anticoagulants for a minimum of 6 weeks, depending on the clinical condition.[10]

In our sample, all patients with thrombosis were treated with LMWH, except for one infant who had an intracranial hemorrhage, and one neonate who developed thrombosis 3 days after the line was inserted and for whom the primary team preferred to remove the line without anticoagulant therapy.

The limitations of our study were as follows: although the number of venous punctures (attempts) at the time of CVL insertion is a risk factor for CVL thrombosis, there was no documentation in the patients charts regarding the number of attempts, so, it was not included. The statistical analysis did not include the variables (site of the line, side of the line, lumen, duration of line, protein C, protein S, anti-thrombin III, and platelets) due to small sample size. In addition, the analysis for

the predictors of the long-term outcome of thrombosis was not carried out due to the insufficient sample size required to execute the underlying statistical model. Out of 21 patients, only 7 patients were reported to have a resolved thrombus during the follow-up period, while the rest of the 14 patients had no follow-up. Based on the data in the patients' charts, 6 patients were lost to outpatient follow-up and 8 patients died within the follow-up period.

We conclude that although the incidence of thrombosis related to CVL is not high, it requires attention and a high index of suspicion from physicians, especially in patients requiring multiple line insertions. Standardization of follow-up after central line insertion is needed for the early detection of complications and for appropriate intervention.

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