

Research Article,

Determination of Prevalence of Thrombosis and Predisposing Factors in Patients Followed Up With a Central Venous Catheter in Pediatric Intensive Care Unit.

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Abstract:

Objective: Objective of this study is determination of prevalence of thrombosis and predisposing factors in critically ill patients with central venous catheter (CVC) placement in Pediatric Intensive Care Unit.

Material and method: Of 76 cases with CVC placement aged between 1 month to 18 years; venous structures at the extremity where the CVC was placed and their symmetrical equivalents were prospectively examined by using Doppler ultrasonography (DUSG) at days 0, 3, 7, 14 and 28.

Results: Median age of the cases included in the study was 19 (2-201) months. Of the cases; 49 (64.5%) was male and 27 (35.5%) was female, with a male/female ratio of 1.81:1. 55 (72.3%) of the cases had an underlying disease. Most common accompanying diseases were neurological and neuromuscular diseases (35.5%), followed by inborn errors of metabolism (14.4%). More than one catheters were placed for 26 (34.2%) of the cases. A total of 107 catheters were placed. Median catheter dwelling time was 12 (2-46) days. Most commonly placed catheters were of Seldinger type (90%). As an early complication, arterial embolism was observed in one (0.9%) case and pneumothorax in one (0.9%) case. As a late complication during the period with a catheter placed, six (7.8%) cases developed catheter infections and 11 (14.4%) cases developed catheter-induced thrombosis. Four (36.3%) of the cases which developed thrombosis were symptomatic. In six (54.4%) of the cases, thrombosis was determined to occur within first three days. When the cases were evaluated in regard to risk factors for thrombosis other than CVC placement, a significant association of CPR application ($p=0.004$) and multiple catheter placement ($p<0.001$) with thrombosis was determined in uni- and multivariate analyses. 72.7% of the cases with thrombosis were examined for hereditary risk factors and no significant evidence was determined.

Conclusion: Our study reveals that multiple catheter placement and CPR application significantly increases risk of thrombosis. Even in absence of any clinical finding, routine evaluation with DSUG within first seven days following catheter placement is useful. Our results suggest that screening for hereditary risk factors which may cause predisposition to thrombosis in all patients with thrombosis in presence of acquired risk factors is unnecessary.

Key words: catheter, central vein, children, intensive care unit

Introduction:

Establishment of a permanent and safe vascular access in critically ill children is one of the most

important factors in treatment success and patient's comfort¹. In pediatric intensive care units (picu), central venous catheters (cvc) are placed due to

several indications including intravenous fluid resuscitation and drug administrations, parenteral nutrition, transfusion of blood and blood components, invasive monitorization of hemodynamic parameters, renal replacement therapies and therapeutic apheresis procedures². The most important complications related to central venous catheters are bleeding and vascular injury in the early period and infections and thrombosis in the late period. Catheter-related thrombosis may be symptomatic or asymptomatic. Symptomatic thrombosis usually present with pain, skin tenderness, increased heat, circulatory failure, edema and changed skin color. However, most of the cvc-related thrombosis in children are asymptomatic thrombosis which are detected only radiologically in the absence of any evidence or presents with severe complications like pulmonary embolism³. Therefore, all patients with cvc placement should be monitored for thrombosis. In the literature, there is no consensus on follow-up protocols for pediatric patients with central venous catheter; in what patients, in what frequency and by which methods thrombosis should be screened and which path to follow for identifying the etiology in patients with thrombosis. Objective of this study is investigation of prevalence and time of thrombosis in patients with cvc placement hospitalized in picu, as well as thrombosis-related clinical and laboratory findings and the facilitating risk factors for thrombosis in patients with thrombosis.

Material and method:

Study population and design:

This study was conducted with 76 pediatric patients who were hospitalized in Samsun Ondokuz Mayıs University Medical Faculty Hospital PICU and placed a cvc during follow-up. Patients' demographic and clinical data, as well as catheter features and catheter-related complications were prospectively examined after obtaining an approval from local ethics committee. CVCs were placed to the patients due to need for parenteral nutrition, need for a long-term treatment where use of peripheral veins were impossible, hemodynamic monitorization, continuous analgesia, need for sedation or inotropic agents, chemotherapeutic procedures, transfusion of blood and blood components or need for frequent blood sampling, renal replacement therapy (hemodialysis, hemofiltration, hemodiafiltration etc) and therapeutic apheresis procedures. A platelet count $>50000/\text{mm}^3$ and prothrombin and partial

thromboplastin time values in normal range were stipulated for catheters placed under elective conditions. Necessary blood components were infused where these conditions could not be provided. Central venous catheters were placed in the setting of operating theatre or at bedside. They were placed in the setting of operating theatre by an experienced faculty member in anesthesiology under the guidance of Doppler ultrasonography (DUSG), whereas they were placed at bedside by the faculty member in charge of PICU with blind method. For all patients, systemic sedation together with local and systemic analgesia was applied prior to the procedure. When needed, a neuromuscular blocking agent was used. During the procedure, the patients were monitored for heart rate and rhythm, respiratory rate and oxygen saturation. Prior to the procedure, appropriate hand cleaning and aseptic conditions were ensured. Sterilization of the catheter placement site was performed using a 10% povidone iodine solution. After the procedure, correct and venous localization of the catheter was observed using blood gas analysis and plain x-ray. To avoid catheter obstruction, patients received continuous fluid infusion. Routine anticoagulant treatment was not given. All patients with catheter placement were monitored during their follow-up for mobilization status, age and congenital heart diseases, as well as acquired factors that may pose a risk for thrombosis including malignancies, burns, surgery and thrombocytosis.

The vessel in which a catheter was placed and the vessel symmetrical to it were examined for presence of thrombosis by using DUSG (Siemens Acuson X300 portable USG device p9-4 probe) at the day of catheter placement and days 3, 7, 14 and 28. DUSG imaging procedure was performed at bedside and by a senior research assistant of radiology. It was considered asymptomatic thrombosis when thrombosis was viewed within lumen of the vein in which the catheter was placed in a patient with no sign or symptom, when vein could not be completely compressed, when there was no spontaneous flow within the vein and when the flow did not comply with breathing. It was considered symptomatic thrombosis when there were clinical signs indicating impaired blood flow such as edema, redness and circulatory failure distal to the catheter together with an appearance radiologically consistent with thrombosis within the vein in which the catheter was placed. Patients with detected thrombosis were consulted to department of hematology and an anticoagulant

treatment was initiated. These patients were investigated for hereditary and acquired causes of thrombosis (protein c, protein s, antithrombin iii, factors viii and ix, vwf, homocysteine, prothrombin 20210a and presence of factor v Leiden mutation).

Statistical analysis:

Characteristic data are presented as n (%) for categorical variables, and as mean ± sd or median (lower-upper limit) for continuous variables, where appropriate. For comparing frequency of qualitative variables, chi-square test or fisher’s exact t-test was used. Mann-whitney u test was used for two-group comparisons and kruskal-wallis test was used for multi-group comparisons. A logistic regression analysis was created to examine effect of predisposing factors on thrombosis. Results of uni- and multivariate analyses were represented after calculation of odds ratios with a confidence interval of 95%. Statistical analyses were performed by using spss version 21 software (spss inc., Chicago, IL, usa). For all tests, p<0.05 values were considered statistically significant.

Results:

In this study, a total of 107 cvcs (1 for 50 patients, more than 1 for 26 patients) were placed in a total of 76 patients, 27 (35.5%) of which were female and 49 (64.5%) were male. The median age was 19 (2-201) months and of the patients; 22 (28.9%) were under 1 year of age and 6 (7.9%) were over 14 years of age. Fifty five (72.3%) patients had a comorbid disease during their hospitalization in the intensive care unit. The most common comorbid diseases were chronic neurological and neuromuscular diseases (31.5%), followed by malignancies (14.4%) and inborn errors of metabolism (11.8%). Cvc’s placed to the patients were classified into three major groups: seldinger, hickmann and dialysis catheters. 91.5% of the catheters were placed blindly at bedside. the most common catheter type was seldinger and the most commonly preferred anatomical region was right femoral vein. Median catheter dwelling time was determined to be 12 (2-46) days. Patients’ demographic, clinical and catheter properties are represented in table 1.

Table 1: Demographic, clinical and catheter properties of the patients included in the study

Demographic and clinical properties	
Age (month) (median [lower-upper limit])	19 (2-201)
Gender (n [%])	
• Male	49 (64.5)
• Female	27 (35.5)
Underlying disease (n [%])	
• Chronic neurological and neuromuscular diseases	27 (35.5)
• Inborn errors of metabolism	11 (14.4)
• Malignancy	9 (11.8)
• Congenital surgery-requiring conditions	4 (5.2)
• Joubert syndrome	1 (1.3)
• Congenital nephrotic syndrome	1 (1.3)
Diagnosis at hospitalization in intensive care unit (n [%])	
• Sepsis	36 (47.3)
• Respiratory failure	14 (18.4)
• Central nervous system infection	8 (10.5)
• Post-operative follow-up	6 (7.9)
• Trauma	6 (7.9)
• Status epilepticus	4 (5.3)
• Near-drowning	2 (2.6)
Catheter properties:	
Site of placement (n [%])	

• Femoral	63 (58.6)
• Subclavian	31 (28.9)
• Internal jugular	13 (12.5)
• Right extremity	74 (69.1)
• Left extremity	33 (30.9)
Method of placement (n [%])	
• Blind	98 (91.5)
• Under the guidance of Doppler ultrasonography	9 (8.5)
Status of placement (n [%])	
• Emergent	47 (43.9)
• Elective	60 (56.1)
Catheter diameter (n [%])	
• <5F	40 (37.3)
• ≥5F	67 (62.7)
Catheter length (n [%])	
• <12 cm	59 (55.1)
• ≥12 cm	48 (44.9)

In our study, due to catheter placement, two patients (1.8%) developed acute severe complications, with one (0.9%) patient having arterial embolism and one (0.9%) having pneumothorax. The most common catheter-related late-term complications were determined to be catheter-related thrombosis in 11 (14.5%) patients and catheter infection in six (7.8%) patients. Of 11 (14.4%) patients with thrombosis; nine (81.8%) were male and two (18.1%) were female, and the median age was determined to be 18 (3-201) months. Of the patients; two (18.2%) were under one year of age and one (9.1%) was over 14 years of age. None of the patients had a hereditary or acquired risk factor for thrombophilia. Six (54.5%) out of 11 patients with thrombosis, the catheter Seven (63.6%) of our patients had no symptom associated with thrombosis. In these patients, thrombosis was detected during routine examination with DSUG. Thrombosis was symptomatic in four (36.3%) patients.

When the patients with thrombosis were examined for hereditary risk factors which may cause predisposition to thrombosis, none of the patients was determined to have such a condition that may cause predisposition to thrombosis. Patients with and without thrombosis were compared in regard to acquired risk factors. No statistically significant differences were determined in regard to age,

localization was right femoral vein. Catheter placement was performed under emergent conditions in seven (63.6%) patients. Catheters were placed blindly for patients with thrombosis. No thrombosis was detected in none of the catheters placed under the guidance of ultrasonography. Median catheter dwelling time in patients with thrombosis was 7 (2-46) days. Only one (9%) patient died due to sepsis and multi-organ insufficiency within first week (day 6) after catheter placement. Throughout the study, there was no patient died due to thrombosis and its complications. Detailed demographic data and catheter properties of the patients with thrombosis are shown in Table 2.

gender, administration of TPN (total parenteral nutrition), need for inotropic agents, need for mechanical ventilation, surgical intervention, catheter infection, sedation, duration of hospital stay before catheter placement and catheter dwelling time, whereas a statistically significant difference was determined when compared in regard to multiple catheter placement and performance of CPR (cardiopulmonary resuscitation) (Table 3).

Table 2: Detailed demographic data and catheter properties of the patients with thrombosis

Patient	Age (Month)	Gender	Diagnosis at hospitalization	Diagnosis at hospitalization in PICU	Catheter type	Catheter dwelling time (day)	Catheter diameter and length	Catheter localization	Method/type of catheter placement	Duration of hospitalization in ICU before catheter placement
No. 4	7	M	HIE	SIRS	Seldinger	7	4F 8 cm	Right femoral	Blind/emergent	-
No. 6	16	M	Demyelinating disease	Respiratory failure	Dialysis	2	7F 10 cm	Right femoral	Blind/elective	2 days
No. 9	18	M	Acute abdomen	Sepsis	Seldinger	4	4F 8 cm	Right femoral	Blind/emergent	2 days
No. 38	18	M	Near-drowning	SIRS	Seldinger	16	5F 8 cm	Right femoral	Blind/emergent	-
No. 54	41	F	Congenital respiratory tract disease	Postop follow-up	Seldinger	4	5F 8 cm	Right femoral	Blind/emergent	-
No. 10	44	M	Metabolic disease	Sepsis	Seldinger	2	5F 13 cm	Right femoral	Blind/emergent	-
No. 11	201	M	Malignancy	Sepsis	Seldinger	25	7F 15 cm	Right femoral	Blind/elective	4 days
No. 14	8	F	Immunodeficiency	Respiratory failure	Seldinger	12	4F 8 cm	Right subclavian	Blind/elective	1 day
No. 26	162	M	VP shunt dysfunction	CNS infection	Seldinger	46	7F 13 cm	Right femoral	Blind/elective	5 days
No. 49	81	M	Joubert Syndrome	Sepsis+CRF	Dialysis	7	7F 13 cm	Right subclavian	Blind/emergent	-
No. 57	3	M	Cystic fibrosis	Sepsis	Seldinger	20	4F 8 cm	Left femoral	Blind/emergent	-

Abbreviations: PICU: Pediatric intensive care unit, HIE: Hypoxic-ischemic encephalopathy, SIRS: Systemic inflammatory response syndrome, CNS: Central nervous system, VP: ventriculoperitoneal, CRF: Chronic renal failure.

Table 3: Comparison of the patients with and without thrombosis in regard to risk factors causing predisposition to thrombosis

Risk Factors	Thrombosis (+) n=11	Thrombosis (-) n=65	P value
Age (month) *			
<1y	2 (18.1%)	20 (30.7%)	0.398
>14y	1 (9%)	6 (6.2%)	0.998
Gender *	M: 9 (81.2%) F: 2 (18.2%)	M: 40 (61.5%) F: 25 (38.5%)	0.197
TPN *	10 (90%)	59 (90%)	0.895
Inotropic agents *	6 (54.5%)	28 (43.1%)	0.482

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Mechanical ventilation *	11(100%)	56 (86.1%)	0.192
Surgical intervention *	1 (10%)	18 (27.6%)	0.852
Multiple catheter placement *	9 (81.2%)	17 (26.1%)	<0.001
Catheter infection *	2 (18.1%)	4 (6.1%)	0.174
CPR *	5(45.4%)	7(10.7%)	0.004
Sedation *	11 (100%)	50 (65.7%)	0.077
Duration of hospital stay before catheter placement **	1,2 (0-5)	1,5 (0-12)	0.798
Catheter dwelling time **	7 (2-46)	13 (2-36)	0.223

Abbreviations: TPN: Total parenteral nutrition, CPR: Cardiopulmonary resuscitation.
*: n (%), **: median (lower-upper limit)

In our study age; catheter type; catheter’s internal diameter, length and number of lumens; catheter localization; method of catheter placement (emergent/elective or blind/under the guidance of USG); administration of TPN; need for inotropic agents; surgical intervention; multiple catheter placement; catheter infection; use of sedative-analgesic-neuromuscular blocking agents; performance of CPR; catheter dwelling time; duration of stay in intensive care unit; presence of congenital heart disease; malignancies and transfusion of blood components were determined as risk factors which may cause predisposition to thrombosis. Administration of TPN, need for transfusion of blood components, use of inotropic

agents and catheter properties other than catheter lumen were similar in majority of patients included in the study. None of the patients included in the study underwent thoracic or orthopedic surgeries which may cause predisposition to thrombosis. Therefore, a multivariate analysis was performed with the parameters of age, catheter internal diameter, multiple catheter placement, catheter infection, performance of CPR, catheter dwelling time, use of sedative-analgesic-neuromuscular blocking agents and underlying congenital heart disease. The age was group as <1y, 1-14y and >14y. Multiple catheter placement and performance of CPR were determined to be independent risk factors (Table 4).

Table 4: Evaluation of the risk factors for thrombosis using multivariate regression analysis

Risk Factor	OR (%95 CI)	P value
Age groups (years)		0.759
• <1	Reference	
• 1-14	2.1 (0.13-34.15)	0.579
• >14	9.1 (0.02-4039.72)	0.476
Performance of CPR	15.1 (1.54-147.54)	0.020
Multiple catheter placement	8.9 (1.19-67.45)	0.033

Sedation	252809501.2 (0.000-)	0.998
Catheter dwelling time	0.9 (0.81-1.63)	0.296
Congenital heart disease	--	--
Catheter diameter		0.185
• 4F	Reference	
• 5F	0.4 (0.02-7.82)	0.596
• 7F	14.5 (0.51-410.97)	0.117
• 9F	--	--

Abbreviations: OR: odds ratio, CI: confidence interval, CPR: Cardiopulmonary resuscitation.
Dependent variable: thrombosis

Discussion:

Central venous catheter placement is one of the most common practices in PICU⁴⁻⁶. Major determinants for selection of type and localization of a catheter to be placed in intensive care units include treatment to be given, duration of treatment and experience and habits of the team. Thusly, it is observed that most commonly femoral vein and secondly subclavian vein were preferred in studies^{3,7}. Consistently with the literature, in our study, the most commonly preferred anatomical region was femoral vein, followed by subclavian vein. There are several studies on methods of central venous catheter placement and catheter placement under the guidance of imaging has been shown to reduce development of catheter-related complications⁸⁻¹¹. In our study, catheters were placed to the majority of the patients blindly at bedside by a PICU specialist. Number of lumens and internal diameter of catheters were determined by age, body weight and anatomic features. Catheters with less lumen were preferred as much as possible and most commonly preferred ones were 4F and 5F catheters.

As thrombosis related to central venous catheter placement is a severe problem in critically ill patients, there are several studies on formation, prevalence and prevention of thrombosis in the literature. In these studies, prevalence of thrombosis in children with CVC placement has been reported as ranging between 0 to 81%^{3,4}. In our study, prevalence of thrombosis was determined to be 14.4%. When association between thrombosis and age in patients with central venous catheter placement is reviewed, in the literature age groups of <1 years and >14 years have been reported to be at more risk compared to other age groups¹²⁻¹⁴. Of the patients in our study; 22 (28.9%) were <1 year of age and 7 (9.2%) were

>14 years of age, and ratio of patients in the at-risk group for thrombosis was 38.1%. Four (36.3%) of 11 patients with thrombosis were in the at-risk age group. However, contrary to the literature, no significant difference was determined between the patients with and without thrombosis in regard to age groups in our study. In previous studies, gender has also been thought to be a risk factor for thrombosis and evaluated from this point of view. It has also been found that, in the adolescent age group, female gender may be predominant due to hormonal reasons but gender may not be a risk factor for different age groups¹³. Similarly, in our study, gender was determined not to be any risk factor element for thrombosis.

Patients' comorbid diseases and medical interventions made during follow-up also may increase predisposition to thrombosis. In a study by Reiter et al.¹² they also aimed to determine risk factors for thrombosis in patients hospitalized in PICU and to develop an effective scoring system. In that study, they determined presence of CVC, infection, being <1y and >14y of age, immobilization, trauma, obesity, malignancy, orthopedic surgery, thrombophilia, burns and use of exogenous estrogen as risk factors. At the end of the study, they observed a 2.1-fold increase in risk of thrombosis for each risk factor. In our study, in addition to these risk factors, performance of CPR, mechanical ventilation, sedation, presence of an underlying congenital heart disease and multiple catheter placement each were considered a risk factor. As our patients did not have burns, thrombophilia, obesity, use of exogenous estrogen and orthopedic surgery, these factors were not taken into consideration. Among other risk factors, consistently with the literature, performance of CPR and multiple catheter placements were determined to be significant in multivariate

analyses. In the literature, there is limited number of studies investigating the association between cpr and thrombosis. In a study by Takemoto ET al.¹⁵, they reported that cvc placement was the most indispensable risk factor for venous thrombosis in hospitalized patients and that, following cvc placement, accompanying malignancies and presence of a heart disease causing hemodynamic instability were the most important risk factors for thrombosis. Another study addressing importance of hemodynamic instability for thrombosis is the study by Schroeder et al.¹⁶ which they conducted with patients underwent cardiac surgery. In that study, patients' status of having post-operation catheter-related thrombosis, risk factors and their responses to prophylaxis were evaluated, it was concluded that the most important risk factor for thrombosis was found to be cvc placement and that there were hemodynamic instability and circulatory failure, which developed due to heart failure during follow up. In our study, a significant association was determined between performance of CPR just before catheter placement or during catheter dwelling time and thrombosis. As duration of stay in intensive care unit lengthens out, patients' need for catheter placement increases. Therefore, critically ill patients may have to be placed more than one catheter. In our study, we concluded that multiple catheter placement was a risk factor for thrombosis. However, it should also be taken into consideration that these patients had longer duration of stay in picu, were connected to mechanical ventilator and remained immobilized for a long period of time. While thrombosis is asymptomatic in majority of the patients, it presents with symptoms including edema, circulatory failure and erythema in some patients. In a study of 101 patients conducted by Edward ET al.¹⁷ prevalence of asymptomatic thrombosis was determined to be 16%. In our study, however, rate of asymptomatic thrombosis was determined to be 9.2%. Prevalence of symptomatic thrombosis was, however, determined to be 5.2%. In a study by Rohrer et al.¹⁸ which they conducted with 59 hospitalized cases with at least 2 risk factors for thrombosis, they evaluated extremities of the patients for thrombosis by using dsug twice a week and determined prevalence of thrombosis as 5 in 10,000. In a Canadian study by Massicotte ET al.³, they examined hospitalized patients for a mean of 24 months; they determined cvc-related thrombosis in 244 patients and found prevalence of thrombosis as 3.5 in 10,000. Recommendations concerning

widely accepted and routine imaging method which are recommended for follow-up of thrombosis in patients with central venous catheter placement are not included in the literature. Because catheter-related thrombosis occurs more commonly within first 7 days after catheter placement in the studies on thrombosis, performing an usg twice within first 7 days is recommended^{19,20}. In a study by Beck ET al.²¹, they evaluated thrombosis in 93 patients hospitalized for more than 48 hours in picu through once-a-week dsug examination at days 2, 4, 6 or 7 after cvc placement or until removal of the catheter. As a result of the study, they found that thrombosis occurred most commonly within first 4 days. In a study by Dubois ET al.²², they evaluated thrombosis in 214 cases with catheter placement through dsug examination at days 2, 4, 7, 14, 21 and 28. Patients with thrombosis were confirmed by a venous angiography. They reported that the time of detection of thrombosis was mostly within first 7 days. In our study, time of detection of thrombosis of 63.6% of the patients with thrombosis was within first 7 days after catheter placement and only 18.1% of the patients were symptomatic. Consistently with the literature, our study indicates that use of ultrasonography, which is easy-to-perform and cost-effective for follow-up of all patients with central venous catheter in picu, is important in reducing morbidity and mortality which may occur due to potential late complications of thrombosis. Limitations of our study are small number of patients and the fact that almost all of the patients were immobilized due to underlying diseases. We are in thought of that this may influence independent risk factors. Another limitation is that we evaluated thrombosis in the patients only with dsug examination. In previous studies, dsug examination is known to be a more inefficient method particularly for imaging of subclavian vein in upper extremity compared to venous angiography^{23, 24}. In conclusion, venous thromboembolism is an important problem in critically ill patients who are hospitalized in picu and had a cvc. Patients with risk factors should be particularly monitored for thrombosis. Results of our study indicate that multiple catheter placement and performance of cpr significantly increase risk of thrombosis. Because prevalence of asymptomatic thrombosis is high, routine examination with dsug within first 7 days after catheter placement is useful, even in the absence of clinical evidence.

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