VENOUS THROMBOEMBOLISM AND ITS OUTCOME IN PEDIATRIC PATIENTS AT A TERTIARY CARE HOSPITAL OF KARACHI

Rimsha Shahid Salim, Misbah Anjum, Safia Bibi, Shazia Soomro, Hifza Aiman, Shahzadi Dilawar
National Institute of Child Health, Karachi, Pakistan

Correspondence:
Rimsha Shahid Salim, National Institute of Child Health, Karachi, Pakistan
Email: rimsha_246@hotmail.com

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ABSTRACT

Venous thromboembolism (VTE) was once considered a rare finding in pediatric population but it has been increasing with recent advances in medical care and technology to diagnose it. This study was conducted to determine the clinical presentation, associated factors and outcome of VTE in hospitalized children in a tertiary care children hospital of Karachi. This descriptive cross sectional study was conducted at National Institute of Child Health, Karachi from December 2020 to January 2022. All patients hospitalized with VTE or who were diagnosed to have DVT while at hospital were included in study. Demographic characteristics, clinical presentation, medical history and laboratory workup was recorded in a semi-structured proforma. Patients were managed by treating physicians as per hospital protocol. Treatment details were recorded along with outcome. A Total of 36 children were diagnosed with VTE. Nine (25%) patients were admitted with clinical features suggestive of DVT while remaining 27 (75%) developed DVT during hospital stay. Median hospital stay of those who developed DVT at hospital was 15 days (IQR 10-30days). Infectious etiology (n=21, 58.3%) was the most common admitting diagnosis followed by central nervous system disorders (n=4, 11.1%). Common clinical features among VTE children were fever, seizures and edema of limbs. Prolonged hospital stay with immobilization and central venous catheterization particularly due to infectious etiology are common factors among children who develop VTE and such patients need to be considered for VTE prophylaxis and treatment.

Key Words: Venous thromboembolism, cerebral sinus thrombosis, anticoagulation

INTRODUCTION

Venous thromboembolism (VTE) is an increasing source of concern in hospitalized children(1). The children's hospitals solutions for patients safety national children's network, comprised of more than 100 pediatric hospitals in united states has shown deep venous thrombosis (DVT) and pulmonary embolism (PE) as one of the eleven preventable hospital acquired conditions(2). Although it carries low risk of mortality but there is significant risk of long term sequelae associated with VTE(1). It is comprises of both DVT and PE. Its incidence varies from 0.07-0.14 per 10,000 children in general population, 5.3 per 10,000 hospitalized children, 0.24 per 10,000 neonates and 0.51 per 10,000 live births with peak incidence in neonates and infants(3). About two thirds patients present with DVT and one third patients present with PE with or without DVT or less frequently in other veins like cerebral veins, portal, mesenteric renal or veins of upper extremities.

The VTE can present with a wide range of clinical symptoms including fever, localized tenderness, pain, edema, headache, seizures, focal neurological deficits or altered level of consciousness(4). It is secondary to certain risk factors in 95% of children. Different studies have identified central venous catheter, infections, congenital heart diseases, trauma or prematurity to be associated with high risk of DVT in hospitalized children(5,6). Whereas prolonged duration of mechanical ventilation and ICU stay are also recognized risk factors for DVT(7). Congenital prothrombotic conditions like protein C and protein S deficiency are shown to be associated with VTE in almost 5% of pediatric patients(7).

In adult population extensive data on risk factors are available and hence recommendations based on randomized clinical trials are also available for prevention of the hospital acquired DVT (8). In children such data and recommendations are limited due to relatively less common occurrence of DVT in pediatric population(9). Hence, guidelines for prophylaxis and treatment of pediatric patients have not been established and are mainly drawn from the data driven from adult population

Thus this study was conducted to report clinical presentation, risk factors, treatment patterns and outcome in children presenting with VTE so that the disease pattern can be understood better and provide basis for guidelines to anticipate prophylactic anticoagulant treatment.

METHODS

This cross-sectional study was conducted at National Institute of Child Health (NICH), Karachi, Pakistan over a period of two years from December 2020 till January 2022. A sample size of 36 patients was calculated on the basis of previous study having only 9.7 per 10,000 hospital admissions (99 DVT in 102,502 admissions) with deep venous thrombosis (9). Sample size was calculated on 95% confidence interval with 4% precision using OpenEPI software (6). Non probability consecutive sampling technique was followed to include all patients diagnosed with DVT during the study period. A questionnaire was developed comprising of 26 questions including demographic characteristics of patients, their clinical presentation, laboratory workup, risk factors, management and outcome.

Patients from all medical units and ICU with age ranging from one month to twelve years diagnosed as having DVT. Venous thromboembolism was defined on either duplex ultrasonography, computed tomography, magnetic resonance imaging or computed tomography angiogram showing thrombus in any of the deep veins. Demographic characteristics, clinical presentation, laboratory workup, risk factors, treatment received in hospital and outcome after management was recorded in a predesigned proforma. Details regarding any prophylaxis (anticoagulants) used in admitted patients were also recorded.

Statistical analysis

Data was entered and analyzed using Statistical Package for Social Sciences (version 23.0). Frequency and percentages were calculated for categorical variables while Mean ± standard deviation (SD) or median and inter quartile range were calculated for continuous variables.

RESULTS

A total of 36 children with VTE were hospitalized during the study period including 34(94.4%) children with only DVT and 2(5.6%) with DVT and PE. There were 20 (55.6%) males and 16 (44.4%) females. Mean age of patients was 64.53, SD± 45.55 months (range 5-180months). A total of 9 (25%) patients were admitted with presenting clinical features suggesting DVT at admission while remaining 27 (75%) developed DVT during their hospital stay. Fever was the most common presenting feature in children followed by seizures, edema of limbs and loose stools. A summary of presenting features is given in Table 1. Mean hospital stay was 22.64 days (SD± 26.82, range 2-120 days). Intensive care unit (ICU) admission was given in 5 children with mean duration of stay 2.72 ± 7.592 days (±2.72, range 0-30 days). Regarding admitting diagnosis (Table 2) most patients 21 (58.3%) were admitted with infectious causes followed by central nervous system diseases 4 (11.11%), cardiovascular disease 4 (11.1%) and other less common causes. Table 2 presents further details regarding admitting diagnosis. Diagnosis of VTE was confirmed by ultrasound Doppler in 27 (75%) cases, Computed Tomography (CT) in 7 (19.44%) cases and magnetic Resonance Imaging (MRI) in 2 (5.6%) cases. Twenty three (63.8%) cases were found to have DVT of legs followed by cerebral sinus thrombosis case (n=11, 30.5%), internal jugular vein thrombosis secondary to empyema thoraces (n=1, 2.8%) and 1 (2.8%) patient had portal vein thrombosis secondary to recurrent pancreatitis.

Frequency of DVT with respect to site of thrombosis is presented in Table 3. None of our patients had received prophylaxis for venous thromboembolism. International normalized ratio (INR) was found normal in 33 (91.7%) cases and prolonged in 3 (8.3%) cases. Thirty two (88.9%) patients were given anticoagulant treatment at admission including LMWH (low molecular weight heparin), in 28(77.8%) cases and unfractionated heparin in 4 (11.1%);

Table 1. Presenting clinical features of children in hospital with venous thromboembolism

Clinical feature	Frequency n (%)
Fever	21 (58.3)
Seizure	15 (41.66)
limb swelling	7 (19.44)
Loose stools	5 (13.88)
Hemiplegia	4 (11.11)
Lower limb weakness	2 (5.55)

whereas 4 (11.1%) patients were not given any treatment at admission including 3 (8.3%) due to prolonged INR i.e. deranged coagulation profile and 1 (2.8%) patient with empyema thoraces in whom thrombus was resolved following resolution of infection. Of those who received treatment at admission; 27 (75%) patients were switched to rivaroxaban, 4(11.1%) to warfarin and 1 (2.8%) patient died before 2 weeks follow up. Regarding outcome of children under treatment; 14 (38.9%) children recovered at 2 weeks, 6 (16.7%) recovered at 3 months and 5 (13.9%) children recovered at 6 months. Mortality was 13.9% (n=5) children at 2 weeks of treatment and 2 (5.5%) children at 3 months. 2 (5.6%) had persistent DVT on 6 months' follow up. During the study 2 (5.6%) children were lost to follow up.

Table 2. Admitting diagnosis

Admitting diagnosis		Number n(%)
Infections	Sepsis	8 (22.2)
	Tuberculosis	4 (11.1)
	Tetanus	3 (8.3)
	Enteric fever	1 (2.8)
	Measles	1 (2.8)
	Septic arthritis	1 (2.8)
	Empyema thoraces	1 (2.8)
	Meningoencephalitis	2 (5.6)
Central nervous system disorders	Seizure disorder	1 (2.8)
	Stroke	3 (8.3)
Cardiovascular disorders	Tetrology of fallot	2 (5.6)
	Tricuspid atresia	1 (2.8)
	Rheumatic heart disease	1 (2.8)
Others	Lymphoma	2 (5.6)
	GBS	1 (2.8)
	Transverse myelitis	1 (2.8)
	Recurrent pancreatitis	1 (2.8)
	Gaucher disease	1 (2.8)
	Nephrotic syndrome	1 (2.8)

Table 3. Site of thrombosis in children

Site of thrombosis		Frequency N (%)
Lower limb thrombosis	Total cases	23 (63.8)
	Left femoro-popliteal system	10 (43.4)
	Right femoro-popliteal system	10 (43.4)
	Bilateral femoro-popliteal system	3 (13.04)
Cerebral sinus thrombosis		11 (30.5)
Internal jugular vein thrombosis		1 (2.8)
Portal vein thrombosis		1 (2.8)

Table 4. Risk factors associated with VTE

PARAMETERS		Frequency n (%)
Risk factors	Sepsis	11 (30.6)
	Congenital heart disease	4 (11.1)
	Dehydration	4 (11.1)
	Tuberculosis	4 (11.1)
	Tetanus	3 (8.3)
	Recent surgery	3 (8.3)
	Protein C deficiency	2 (5.6)
	Central venous catheter	2 (5.6)
	Malignancy	2 (5.6)
	Empyema thoraces	1 (2.8)
	Septic arthritis	1 (2.8)
	Nephrotic syndrome	1 (2.8)

DISCUSSION

Venous thromboembolism is rare in pediatric population but its incidence is increasing due to advancement of diagnostic approaches. Guidelines for prophylaxis and treatment have not been established and recommendations for treatment are mainly drawn from adult population(10). Prolonged hospital stay is an established risk factor for DVT as shown by literature and our study also confirmed that. Median duration of hospital stay in these patients was 15 days. In a study by Atchison et.al. it was identified that hospital stay for more than 4 days is most important risk factor for hospital acquired DVT and these patients must be considered for prophylaxis(11). Similarly, other studies by CM Witmer et. al and Takemoto et. al. also identified prolonged hospital stay as a risk factor for hospital acquired VTE(12,13). Most common site of DVT was observed to be femoro-popliteal venous system of legs. Similar findings have been reported by various studies where femoro-popliteal venous system was the most common site of DVT in pediatric population(9).

Regarding clinical symptoms most common presenting feature was fever reported in 18 (50%) patients, followed by seizure, edema of limbs, loose stools, hemiplegia, and lower limb weakness. It was consistent with previously reported studies(14). Study by Turpie et. al. showed that most of the patients with venous thromboembolism present in a hospital setting with complains of edema and tenderness of limbs(15). In a study by Blann et. al. edema and tenderness was the most common presenting clinical features(16). CVST was found to be most commonly related to sepsis followed by congenital heart disease. Vieira et al. have also reported infection as the most common cause of VTE (17), while Branchford et al. found that most common factor leading to VTE was mechanical ventilation followed by systemic infection and hospitalization for more than 5 days(18). A study by Ozcan et al. also showed that infection is the main cause of CVST(19). We had 4 (11.1%) children with limb VTE having tuberculosis which suggests that tuberculosis patients are also at risk of VTE and may be considered for prophylaxis(20). This is explained by the fact that infections result in activation of coagulation pathway and platelets which in turn lead to thrombosis(20). Contrary to this study by Wagner et al. who found traumatic head injury as most common cause for VTE(21). As we did not include surgical patients in our study so we could not find the relation of trauma and VTE.

We had 1 child with nephrotic syndrome with diffuse venous thrombosis involving inferior vena cava, iliac, femoral and popliteal veins. Nephrotic syndrome is well established cause of venous thromboembolism(22). In study by Carpenter et. al. VTE was found in 3% children with nephrotic syndrome(23). Regarding treatment none of our children received prophylaxis even in diseases with prolonged hospital stay like tetanus or GBS etc. All patients after documentation of VTE were started on anticoagulation with LMWH in 28(77.8%) cases and unfractionated heparin in 4 (11.1%). Regarding treatment duration we have given for 3-6 months in all children in which primary risk factor was treated and for lifelong in children with prothrombotic conditions. Similar has been reported previously(2).

Mostly our children received LMWH which has now become treatment of choice in pediatric population due to easy subcutaneous twice or once daily dosing whereas unfractionated heparin is given in infusion in a hospital setting. It was followed by oral anti-factor Xa like rivaroxaban in 27 (75%) patients and vitamin K antagonists i.e. warfarin in 4 (11.1%). Mostly in our children rivaroxaban was used instead of warfarin because of less need of frequent monitoring and minimal risk of bleeding(24).

No treatment complication such as bleeding was observed in children treated with rivaroxaban while one child expired due to bleeding secondary to deranged INR of 9.0 following treatment with warfarin. Study by Chan et. al reported increased incidence of bleeding complications secondary to warfarin and

emphasized on closed monitoring while using anticoagulation(25). Similarly study by Clarke-Pearson identified significant risk of bleeding following start of anticoagulation therapy(26).

Almost 70% of our patients recovered within 6-months of treatment while 14% died. Similar findings were noted in study by Wright, in which he stated that 70% of the children with venous thromboembolism recovered while 14% patients had persistent DVT and 9% died(27). Goldenberg in his study discussed that although recurrence of VTE in children is rare but it is associated with increased morbidity and mortality and it can severely affect the quality of life(28).

The study provides a short term follow-up data from a single centre with a good number of patients showing relatively rare disease presentation known. Though due to time constraints the patients were not followed up beyond 6 months with persistent VTE, thus it is considered as the limitation of the study. Further studies are needed for prolonged follow-up to show the long term outcome of patients with persistent VTE.

CONCLUSION

Longer hospital stay is established risk factor for VTE and such children should be considered for prophylaxis. The problem is not that rare, therefore large scale studies and clinical trials are recommended to establish prophylaxis guidelines in paediatric patients admitted in hospitals.

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