ORIGINAL ARTICLE

PAEDIATRIC THROMBOSIS: A FIVE-YEAR EXPERIENCE FROM A TERTIARY CARE CENTER OF PAKISTAN

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Background: Advances in imaging techniques and longer survival of chronic medical conditions contribute to the increase in paediatric thrombosis. We aim to determine the incidence, underlying risk factors, management and clinical outcome of paediatric thrombosis at a multidisciplinary facility of Pakistan. **Methods:** A retrospectively analysis of the medical records of patients in the paediatric age group admitted at the Aga Khan University hospital from January 2013-September 2018 was performed. Site of thrombosis, associated risks factors, management options and outcome of thrombotic event were evaluated. **Results:** Of the 22,320 paediatric hospitalization, 35 paediatric patients were diagnosed with thrombosis (15 cases per 10,000 admissions). The median age of the study group was 15 years and twenty patients (57%) were male. The commonest site of thrombosis was in lower limb venous 11 (31%), followed by upper limb venous thrombosis 6 (17%), abdominal vein thrombosis 7 (20%), cerebral venous thrombosis 5 (14%), pulmonary embolism and arterial thrombosis 3(9% each). Eighty three percent had underlying clinical condition including central venous catheter [CVC] (26%), malignancy and infection (14% each), antiphospholipid antibody syndrome (9%), inherited thrombophilia (9%), congenital heart disease (6%), while thrombotic thrombocytopenic purpura and autoimmune disorder (3% each). Twelve (34%) patients were treated with heparin only, 8 (23%) received heparin followed by warfarin while warfarin as a single agent was given in 2 (5.7%) patients. One patient died of pulmonary embolism while 9 (25%) had persistence or recurrence of thrombosis. **Conclusion:** Incidence of paediatric thrombosis was 0.15%. CVC placement was the most common associated risk factor. Warfarin and heparin both were found to be safe anticoagulation option. Recurrence rate was found to be high.

Keywords: Thrombosis; Children; Risk factors

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INTRODUCTION

Thrombosis was once reported to be rare occurrence in paediatric age group but with the improved and advanced imaging techniques the diagnosis and henceforth the incidence of thrombosis in the paediatric population is increasing.[1] The annual incidence of thrombosis as reported in 2001 by Dutch registry in paediatric population was 0.14 per 10,000 children.[2] A bimodal distribution has been observed in paediatric population with peaks in neonatal period and adolescence.

There is a high frequency of secondary risk factors associated with paediatric thrombosis as compared to adult thrombosis.[3] Approximately 90% of the paediatric thrombosis is related to some underlying medical or surgical risk factors. Central venous lines alone accounts for most of the childhood thrombosis.[4] Heritable prothrombotic disorders are also found to be associated with unprovoked paediatric thrombosis.[4]

The reported cumulative incidence of recurrence of thrombosis in children at 1 to 2 years is 6–11%.[5] A study from United States stated outcome of thromboembolism in paediatric population as complete resolution in majority of cases accounting up to 77%, persistence or recurrence in 14% while death was reported in 9% of sunjects.[6] However with the advent of advanced diagnostic modalities and knowledge of underlying prothrombotic states, the overall outcome of thrombosis in children has been improved.[7] Most of the incidence of thrombosis in childhood and related risk factors has been reported by western literature, whereas few studies have been conducted on Asian population.[8]

Difference in race and ethnicity appears to be a contributory factor to the geographic variations between different study populations.[9] Pakistan has the sixth largest population in the world with 45% population under the age of 18 years and a growth rate of more than 2% per year. The risk factor of thrombosis in paediatric

population in Pakistan remains unknown primarily due to dearth of published epidemiological data. It is therefore imperative to conduct an epidemiologic study to gauge the burden of paediatric thrombosis in our population. With this aim, we conducted a retrospective study was conducted to review the records of all paediatric patients diagnosed with venous thromboembolism (VTE) admitted at a tertiary care hospital.

MATERIAL AND METHODS

A retrospective five years analysis was performed at Aga Khan University Hospital, Pakistan from January 2013 and September 2018. The data for patients' demographics, site of thrombosis, associated risks factors, treatment and complications of thrombotic event like recurrence or death were evaluated through electronic medical record. Hospital admission rate for paediatric patients were extracted from the department of Health Information Management System. Patients from 0 to 18 years of age were taken as paediatric population and were included in the study if thrombus is identified via ultrasound Doppler, computed tomography (CT) scan or magnetic resonance imaging (MRI). Patients were categorized according to age as neonates, infants, children and adolescents (details in Table-1). Patient with more than one admission for thrombosis were considered as single incidence.

The data was descriptively presented, and analysis was performed among various age groups. Statistical package for social sciences 19 was used for analysis of data. Frequencies were calculated for quantitative variables like age, site of thrombosis and risk factors.

The study was approved by institutional ethical review committee (3872-Pat-ERC-15).

RESULTS

Of the 22,320 paediatric hospitalizations, VTE was diagnosed in 35 cases. The incidence of thrombosis was found to be 15 cases per 10,000 admissions (0.15%) with no difference in observed between male and female genders (1.2:1). The median age at the time of presentation was 15 years (2 days–18 years) with a peak incidence in adolescent group with 23 patients (Table-1). Figure-1 shows the distribution of the patients with thrombosis based on their age group.

The commonest site of thrombosis was lower limb veins (n=11, 31%), followed by abdominal vein thrombosis (n=7, 20%), upper limb venous thrombosis (n=6,17%), cerebral sinus venous thrombosis (n=5,14%), pulmonary embolism and arterial thrombosis (n=3, 9% each) as shown in table-1.

Out of 35, 29 (83%) patients had underlying clinical conditions and risk factors for thrombosis. 31% had more than one risk factors. Known risk factors identified in the study includes CVC placement in 9 (26%), malignancy in 5 (14%) [Hodgkin's lymphoma with CVC placement, acute lymphoblastic leukaemia with L-asparaginase treatment, acute myeloid leukaemia, Ewing's sarcoma and gliomata cerebri], infection in 5(14%) [Miliary tuberculosis, pneumonia, meningitis (2), cerebellar abscess], antiphospholipid antibody syndrome (APLA) and inherited thrombophilia in 3 (9%) each, congenital heart disease (CHD) 2(6%), thrombotic thrombocytopenic purpura and autoimmune disorder [dermatomyositis] in 1 (3%) each. Table-2 describes the risk factors associated along with the site involved.

Testing for inherited thrombophilia was performed in 16 patients of which two were diagnosed with underlying protein C deficiency and one with protein S deficiency. Prothrombin gene mutation or factor V Leiden mutation was not performed in any of our patients due to non-availability of these tests at our facility. Positive lupus anticoagulant was found in 3 out of 16 tested, while anticardiolipin IgG and IgM levels were elevated in 3 out of 13 tested. In six patients (17%) no apparent cause was identified for thrombosis.

Twenty-two (63%) patients received anticoagulation. Six patients were managed with unfractionated heparin (UF) and 2 received low molecular weight heparin (LMWH) followed by warfarin. LMWH and warfarin as a single agent were given in 12 and 2 cases respectively. Anticoagulation was continued for at least 3 months in all patients with definitive underlying aetiology while in cases where no apparent cause was identified, it was continued up to 6 months.

Among those who did not receive anticoagulation, thrombocytopenia and active bleeding were identified in 10 while 3 underwent CVC removal with follow-up observation without anticoagulation. None of the patients underwent thrombectomy, thrombolysis or placement of inferior vena cava filter. Post-thrombotic syndrome (PTS) and anticoagulation related bleeding were not reported in any patient. One patient (3%) died of pulmonary embolism on day 10 of diagnosis and 9 (25%) had recurrence at a median duration of 170 (±61) days from the time of diagnosis due to either non-compliance of anticoagulation (4 patients) or persistence of underlying risk factor (5 patients), while the rest (72%) showed complete resolution of thrombosis during a follow-up period of 1 year.

Table-1: Characteristics of paediatric patients with thrombosis

Total patients	**35**
Male/female	20/15
Age at diagnosis, median, year	15 (2 days – 18 years)
Neonates (0- 28 days)	2
Infants (1–12 month)	2
Children (1–12 year)	8
Adolescents (12–18 year**)**	23
Location of Thrombosis	
Lower venous	11 (31%)
Abdominal	7 (20%)
Hepatic vein	3
Portal vein	3
Renal vein	1
Upper venous	6 (17%)
Cerebral sinus venous	5 (14%)
Pulmonary embolism	3 (9%)
Arterial	3 (9%)

Table-2: Site of thrombosis and its associated risk factors

Site of Thrombosis (n)	Associated risk factors [11 (31%) Patients had more than one risk factor] n (%)
Lower limb venous thrombosis (11)	Central venous catheter 4 (36) Malignancy 2 (18) Infection 2 (18) Heritable thrombophilia [Protein S] 1 (9) Congenital heart disease 1 (9) Antiphospholipid antibody syndrome 1 (9)
Upper Limb venous thrombosis (6)	Central venous catheter 4 (66) Malignancy 1 (17) Antiphospholipid antibody syndrome 1 (17)
Abdominal thrombosis (6) **Hepatic vein 3** **Portal vein 3** **Renal vein 1**	 No cause 3 Antiphospholipid antibody syndrome 1, No cause 2 No cause
Cerebral venous sinus thrombosis (5)	Infection [Meningitis] 2 (40) Gliomata's cerebri 1 (20) Thrombotic thrombocytopenic purpura 1 (20) Congenital heart disease 1 (20)
Pulmonary Embolism (3)	Hodgkin's lymphoma 1 (33) Infection [miliary tuberculosis] 1 (33) Dermatomyositis 1 (33)
Arterial thrombosis (3)	Heritable thrombophilia [Protein C deficiency] 2 (67) Central venous catheter 1 (33)

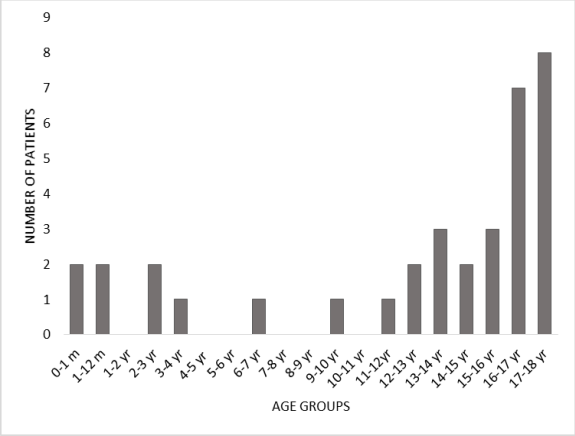

Figure-1: Age distribution of paediatric patients with thromboembolism (yr: years, m: months)

DISCUSSION

An increasing amount of thrombosis in children is being reported not only because of modern imaging techniques but also due to improved care of chronic illnesses. CVC placement is an important component of the management of critically sick children but unfortunately has contributed significantly to the increasing rate thrombotic events. Additionally, children with debilitating medical issues or life-threatening conditions have improved survival because of advancements of medical modalities however these modern and intensive therapies can be complicated can be complicated by thrombotic events.[10]

In Pakistan, so far thrombosis is a neglected research area with few published studies

that mostly included adult population, while for children it is only limited to cerebral venous sinus thrombosis. In Pakistan the reported incidence of venous thrombosis ranges from 2.6–12.82% which includes all age groups and mostly related to post-surgical thrombosis.[11,12] There is no published data on incidence of paediatric thrombosis or its associated risk factors in this specific age group from Pakistan.

In this single institution study, the paediatric thrombosis incidence was found to be 15 cases per 10,000 paediatric patients. The rate is considerably higher than the previously reported thrombosis incidence from Korea (3.27 cases per 10,000 admissions)[8] and Australia (8 cases per 10,000 admissions)[13]. On the contrary, our incidence was lower than that of United States (21.9 per 10,000 admissions) as reported by Wright JM *et al*.[6]

In the literature, the bi-modal age-stratified distribution of paediatric thrombosis is well defined.[10] However, in our study we observed an apparent bi-modal distribution with a significant peak incidence in the adolescent group which was less marked in the neonatal period (Figure-1). This might be due in part to the low number of neonates in our patient group. Similar finding was reported by Wright JM *et al*.[6]

Children who are admitted are at the highest risk of forming thrombosis because of various adjoining factors like immobility, CVC placement as well as inflammation, infection or surgery.[14] Therefore, paediatric thrombosis is a multifactorial disorder, and the acquired factors have a greater impact on thrombotic risk than heritable thrombophilic defects.[14] In paediatric population, CVC placement is the most significant risk factor for thrombosis.[15] Depending on the type of CVC, the patient population and the imaging modality, venous thrombosis rates varies widely from 2.6–34% in children.[15] Similarly in this study, most of the patients (83%) had an underlying risk factor, with CVC insertion being the most frequent.

Children with malignancies have reported rate of deep venous thrombosis of 3.6–10.4%.[16] This depends on various factors for instance cancer itself is a prothrombotic state and the risk is aggravated with the use of chemotherapeutic agents such as steroids and asparaginase, the frequent use of CVC and infection.[16] In our study we observed malignancy as the second most common risk factor.

Acute infection is an independent risk factor for thrombosis other than the underlying conditions linked with increased thrombosis and the risk of thrombosis is highest within first 2 weeks of infection.[17] All types of acute infections including viral and bacterial are associated with increased risk of thrombosis. In our study five children had underlying infections all of which were bacterial except for one child with cerebral abscess in which causative organism could not be identified.

Congenital heart disease is also often associated with increased risk of thrombosis due to multiple reasons including not only the type of cardiac defect but changes in the coagulation system due to their CHD, type of procedure to correct the cardiac defect and CVC placement during hospitalization. Hence escalating the incidence of venous thrombosis in these patients.[18] Two of our patients with CHD had CVST and lower limb venous thrombosis. However further correlation with type of cardiac defect and relation with corrective surgery could not be established. Moreover, both these patients did not have CVC placement when thrombotic event was identified.

There is a strong association between heritable prothrombotic disorders and thromboembolism in adults, but the impact of inherited thrombophilia on the occurrence of thrombosis without presence of other risk factors in children is low.[19] The identification of heritable thrombotic defect is crucial as it might affect the durations of anticoagulation therapy and genetic counselling. In our study heritable thrombophilia workup was performed inconsistently; about 16 (46%) patients were tested, of which 2 were found to be protein C and one was protein S deficient. However, these low levels were found during acute thrombotic event and anticoagulation which would lower these protein levels, thereby making the diagnosis highly questionable. None of the patients had repeat assay during follow-up period of one year. In order to establish definitive diagnosis, these assays should be repeated after completion of anticoagulation therapy and can be further confirmed on molecular studies. None of the patients were tested for prothrombin gene mutation or factor V Leiden mutation because of the non-availability of these test at our facility.

Similarly, altogether 46% were tested for presence of lupus anticoagulant or anticardiolipin antibodies. Of which 3 turned out to be positive for APLA. Autoimmune workup to determine whether the APLA was primary or secondary were not performed. Data for the incidence, thrombosis risk and effective treatment of paediatric APLA are limited and heterogeneous.[20] A study conducted by Jingran *et al* showed increased thrombotic events in patients with APLA.[20]

Treatment options for paediatric thrombosis are inferred from the studies performed in the adult population.[21] Direct oral anticoagulants remain in clinical trials in children and are still not recommended outside of clinical trials. However, there is dire need of guidelines for paediatric population because of age related variations in the aetiology of the disease and hence in the management decisions.[22] Anticoagulation used in our patients include unfractionated heparin, LMWH or vitamin K antagonist with a minimum duration of 3 months, while no anticoagulation associated bleeding was observed. We found both warfarin and heparin as safe anticoagulation option in our cohort of children.

None of the patients underwent thrombectomy or thrombolysis as none of them presented with life or limb threatening symptoms. Thrombocytopenia and active bleeding were identified as major limitation against anticoagulation in 13 patients; however, this population did not show extension of thrombus or recurrence. CVC removal was performed in three patients without anticoagulation and complete thrombus resolution was identified. In this study, thrombosis resolution (72%) was comparable, however the recurrence rate was high (25%) while mortality rate (3%) was low when compared to the study conducted by Wright JM et al and Audu CO *et al*.[5,6]

Our study has many limitations. Firstly, it was a retrospective review of record with follow-up for only one year therefore, incomplete data collection and analyses is a possibility. Secondly, it was a single center study hence the reported incidence might not be truly reflective of the true incidence. Finally, the frequency of inherited thrombophilia cannot be assessed as a limited number of patients were tested for these disorders. As the study was conducted in a single tertiary care hospital of Pakistan and the sample size was not large enough, it does not reflect the whole population but still its results highlight the importance of thrombosis in paediatric population.

CONCLUSION

In conclusion, the clinical characteristics of paediatric thrombosis patients with respect to risk factors and treatment pattern were comparable to studies from western countries, however the bimodal age distribution was less marked. Recurrence rate was found to be higher. A wide scale prospective study needs to be done to know the actual incidence of thrombosis in paediatric age group along with their long-term outcome in Pakistan.

Conflict of Interest: None

AUTHORS' CONTRIBUTION

AR: Write-up. HM: Data collection, analysis and interpretation. SAA: Proof reading, referencing. NN: Write-up.

REFERENCES

1. Chan AK, Monagle P. Updates in thrombosis in paediatrics: where are we after 20 years? Hematology Am Soc Hematol Educ Program 2012;2012:439–43.
2. van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr 2001;139(5):676–81.
3. Chalmers EA. Epidemiology of venous thromboembolism in neonates and children. Thromb Res 2006;118(1):3–12.
4. S Revel-Vilk , A Chan, M Bauman, P Massicotte. Prothrombotic conditions in an unselected cohort of chidren with venous thromboembolic disease. J Thromb Haemost 2003;1(5):915–21.
5. Audu CO, Wakefield TW, Coleman DM. Paediatric deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2019;7(3):452–62.
6. Wright JM, Watts RG. Venous thromboembolism in paediatric patients: epidemiologic data from a paediatric tertiary care center in Alabama. J Pediatr Hematol Oncol 2011;33(4):261–4.
7. Nowak-Göttl U, Janssen V, Manner D, Kenet G. Venous thromboembolism in neonates and children-update 2013. Thromb Res 2013;131(Suppl 1):S39–41.
8. Choi HS, Choi CW, Kim HM, Park HW. Venous thromboembolism in paediatric patients: a single institution experience in Korea. Blood Res 2016;51(3):164–70.
9. White RH, Keenan CR. Effects of Race and Ethnicity on the Incidence of Venous Thromboembolism. Thromb Res 2009;123(Suppl 4):S11–7.
10. Julie Jaffray, Guy Young. Deep Vein Thrombosis in Paediatric Patients. Pediatr Blood Cancer 2018;65(3).
11. Naheed F, Kammeruddin K, Tufail A, Baillie P, Hussain A. Evaluation of risk factors for venous thrombo-embolism and thrombo-prophylaxis with unfractionated heparin in post operative gynaecological patients. J Surg Pak 2008;13(3):95–8.
12. Rathore MF, Hanif S, New PW, Butt AW, Aasi MH. Khan SU (2008) The prevalence of deep vein thrombosis in a cohort of patients with spinal cord injury following the Pakistan earthquake of. Spinal Cord 2005;46(7):523–6.
13. Newall F, Wallace T, Crock C, Campbell J, Savoia H, Barnes C, *et al*. Venous thromboembolic disease: a single-centre case series study. J Paediatr Child Health 2006;42(12):803–7.
14. Setty BA, O'Brien SH, Kerlin BA. Paediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases. Pediatr Blood Cancer 2012;59(2):258–64.
15. Ullman AJ, Marsh N, Mihala G, Cooke M, Rickard CM. Complications of central venous access devices: a systematic review. Paediatrics 2015;136(5):e1331–44.
16. Klaassen ILM, van Els AL, van de Wetering MD, van Ommen CH. Increasing incidence and recurrence rate of venous thromboembolism in paediatric oncology patients in one single centre over 25 years. Thromb Haemost 2017;117(11):2156–62.
17. Schmidt M, Horvath-Puho E, Thomsen RW, Smeeth L, Sørensen HT. Acute infections and venous thromboembolism. J Intern Med 2012;271(6):608–18.
18. Silvey M, Brandão LR. Risk factors, prophylaxis, and treatment of venous thromboembolism in congenital heart disease atients. Front Pediatr 2017;5:146.

19. Tormene D, Fortuna S, Tognin G, Gavasso S, Pagnan A, Prandoni P, *et al*. The incidence of venous thromboembolism in carriers of antithrombin, protein C or protein S deficiency associated with the HR2 haplotype of factor V: a family cohort study. J Thromb Haemost 2005;3(7):1414–20.
20. Ma J, Song H, Wei M, He Y. Clinical Characteristics and Thrombosis Outcomes of Paediatric Antiphospholipid Syndrome: Analysis of 58 Patients. Clin Rheumatol 2018;37(5):1295–303.
21. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, *et al*. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e737–801.
22. Goldenberg NA, Takemoto CM, Yee DL, Kittelson JM, Massicotte MP. Improving evidence on anticoagulant therapies for venous thromboembolism in children: key challenges and opportunities. Blood 2015;126(24):2541–7.

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