Childhood Venous Thromboembolism in Yeungnam Region in Korea: Multicenter Study

Soram Lee, M.D. 1, Jong Hyuk Youn, M.D. 1, Jae Young Lim, M.D. 1, Hee Won Chueh, M.D. 2, Jae Min Lee, M.D. 3, Jin Kyung Suh, M.D. 4, Ji Yoon Kim, M.D. 5, Eu Jeen Yang, M.D. 5, Kyung Mi Park, M.D. 5, Young Tak Lim, M.D. 5, Jikyoung Park, M.D. 5, Eun Mi Choi, M.D. 5, Ye Jee Shim, M.D. 5, Heung Sik Kim, M.D. 5, Sang Kyu Park, M.D. 5, Seom Gim Kong, M.D. 4, Eun Jin Choi, M.D. 10, and Eun Sil Park, M.D. 11

1Department of Pediatrics, Gyeongsang National University College of Medicine, Jinju, 2Department of Pediatrics, Dong-A University College of Medicine, Busan, 3Department of Pediatrics, Yeungnam University College of Medicine, Daeegu, 4Department of Pediatrics, School of Medicine, Kyungpook National University, Daegu, 5Department of Pediatrics, Pusan National University Children’s Hospital, Yangsan, 6Department of Pediatrics, Inje University Busan Paik Hospital, Busan, 7Department of Pediatrics, Keimyung University School of Medicine, Daeug, 8Department of Pediatrics, Ulsan University College of Medicine, Ulsan, 9Department of Pediatrics, Kosin University College of Medicine, Busan, 10Department of Pediatrics, College of Medicine, Daegu Catholic University, Daeug, 11Health Science Institute, Gyeongsang National University College of Medicine, Jinju, Korea

Background: Venous thromboembolism (VTE) is rare in pediatric patients compared to adults, but its incidence is gradually increasing. The purpose of this study was to analyze the incidence, risk factors, and prognosis of pediatric patients with VTE in Korea.

Methods: Between January 2000 and July 2017, 249,312 medical records of the patients older than 1 year who were hospitalized in the department of pediatrics of 10 university hospitals in Yeungnam region were retrospectively reviewed.

Results: The overall incidence of VTE was 4.9 per 10,000 admissions. Of the total 123 patients, 80 (65.0%) were male and the median age was 10.8 years (range, 1.0-23.5 years). Magnetic resonance imaging was performed most frequently to confirm the diagnosis of VTE (43.1%). Thrombosis occurred in the cerebral vessels (46.3%), lower extremities (25.8%), pulmonary (19.5%), abdomen (9.8%), and upper extremities (4.1%). One hundred and six patients had underlying causes such as cancer (27.6%), infection (26.8%), intravenous catheter insertion (17.9%), and surgery (14.6%). Protein C was evaluated in 39 patients (31.7%), protein S in 40 (32.5%), antithrombin (AT) III in 52 (42.3%), and homocysteine in 21 (17.1%). Among them, one patient with a family history of AT III deficiency had SERPINC gene mutation. Seventy-seven patients (62.6%) started anticoagulation treatment. Most (52.0%) were treated for more than 90 days.

Conclusion: Healthcare providers must be aware of the potential for VTE development in childhood. In the near future, a nationwide survey should be investigated to determine the incidence rate and the trends in VTE among Korean children.

Key Words: Venous thromboembolism, Pediatric patients, Epidemiology

pISSN 2233-5260 / eISSN 2233-4580
https://doi.org/10.15264/cpho.2018.25.1.43
Clin Pediatr Hematol Oncol 2018;25:43〜49

Received on March 26, 2018
Revised on April 3, 2018
Accepted on April 9, 2018

Corresponding Author: Eun Sil Park
Department of Pediatrics, Gyeongsang National University College of Medicine, Jinju-daero 816 beon-gil, Jinju 52727, Korea
Tel: +82-55-750-8829
Fax: +82-55-752-9339
E-mail: espark@gnu.ac.kr
ORCID ID: orcid.org/0000-0001-9344-7191
Introduction

The incidence of venous thromboembolism (VTE) is known to be relatively low in childhood; the reported incidence rate ranges from 0.7 to 4.9 per 100,000 person-years [1,2], while total incidence of Korea population is 13.8 per 100,000 person [3]. However, an increasing incidence of VTE in childhood was reported in the United States and Canada, especially in the tertiary care setting [1,4]. General population data from Denmark revealed that the population incidence is relatively stable (2.09 per 100,000 person-years) but with an upward trend showing an annual increase of 9.6% from 2001-2006 [5]. Pediatric VTE has a significant impact on both acute and chronic health outcomes, including increased risk of mortality, recurrence of VTE, and post-thrombotic syndrome [1,6-8]. According to a Canadian study, the mortality rate directly attributable to VTE was 2.2% and morbidity including recurrent thrombosis (8.1%) and postphlebitic syndrome (12.4%) was substantial. The increasing incidence of childhood VTE is postulated by experts to be a result of advanced tertiary healthcare resulting in improved survival of critically ill children at the cost of VTE. The evolution of diagnostic techniques and image modality also contributed to the increased incidence rate.

In 2016, Choi et al. [9] reported that the incidence rate of childhood VTE at a single center was 3.27 per 10,000 admissions; the authors also reported risk factors, diagnosis, and treatment data, but there is still lack of a nationwide epidemiologic survey on VTE in children. To the best of our knowledge, this is the first multicenter study investigating childhood VTE in Korea. The primary aim of this study was to evaluate the incidence rate and outcome of childhood VTE on a large scale, including risk factors and treatment.

Materials and Methods

Medical records of the patients hospitalized in the department of pediatrics of 10 university hospitals in the Yeungnam region were retrospectively reviewed by pediatricians from January 2000 to July 2017. Patients were selected by diagnostic codes (based on the International Classification of Diseases, ICD, Tenth Edition) and radiologic findings, ICD-10 codes were 180.2 and 180.3 for deep vein thrombosis (DVT); I26, I26.0, and I26.9 for pulmonary embolism (PE); D73, I81.1, I82.0, I82.2, I82.3, and K55.0 for intraabdominal thrombosis; G08.0 and I67.6 for cerebral vein thrombosis; and I82.8 and I82.9 for upper extremity DVT. Patients were also included in the study if there was any mention of thrombosis in the radiological reports. Patients younger than 1 year old were excluded because it was mostly catheter-related thrombosis in the neonatal intensive care unit. Demographic characteristics including sex and age at diagnosis, underlying disease, and clinical risk factors were collected. Results of thrombophilic testings and adjusted treatment data at the time of diagnosis were also collected.

Results

Of the total 249,312 hospitalizations during the study period, 142 medical records were reviewed retrospectively based on coding and radiologic data, among which with moyamoya disease or hemorrhagic cerebral infarction were excluded. Finally, 123 admissions were included and no patients were duplicated. The total incidence of VTE was 4.9 per 10,000 admissions (0.049%).

1) Characteristics of patients

Of the 123 patients, 80 (65.0%) were male and 43 (35.0%) were female. The median age at diagnosis was 10.8 years (range, 1.0-23.5 years), while that of the male was 11.7 years and the female was 9.2 years. Fig. 1 shows age distribution of the patients with 1-year interval. In previous studies, a bimodal peak incidence at under 1 year of age and during adolescence was reported. Because the current study excluded patients under 1 year old, the age distribution showed a relatively higher frequency among teenagers. VTE in cerebral vessels was the most common diagnosis (46.3%), followed by the lower extremities and pulmonary vessels (Table 1).
Childhood Venous Thromboembolism

Table 2. Investigations performed to confirm the diagnosis of VTE

| Investigation                  | N  = 123 (%) |
|--------------------------------|--------------|
| MRI                           | 53 (43.1)    |
| CT                            | 41 (33.3)    |
| Ultrasonography               | 17 (13.8)    |
| Venography or angiography      | 13 (10.6)    |
| Echocardiography              | 5 (4.1)      |
| V/Q scan                      | 1 (0.8)      |
| Othera)                       | 1 (0.8)      |

MRI, magnetic resonance imaging; CT, computed tomography; V/Q, ventilation/perfusion.

*a) Other: A 15.4-year-old male with mental change had underlying risk of acute myeloid leukemia and systemic lupus erythematosus. At the time of visiting emergency room, cardiopulmonary resuscitation was performed but he was expired. Cerebral and pulmonary embolism were diagnosed by clinical and neurologic exam.

Table 1. Characteristics of the patients

|                         | N = 123 |
|-------------------------|---------|
| Total VTE patients      | 123     |
| Male/Female             | 80/43   |
| Age at diagnosis, median (range), year | 10.8 (1.0-23.5) |
| Location of VTE (%)     |         |
| Pulmonary               | 24 (19.5) |
| Abdominal               | 14 (11.4) |
| Cerebral                | 57 (46.3) |
| Upper extremities       | 5 (4.1)  |
| Lower extremities       | 29 (23.6) |
| Others                  | 8 (6.5)  |

VTE, venous thromboembolism.

2) Diagnosis

Magnetic resonance imaging (MRI) was performed most frequently to confirm the diagnosis (43.1%), followed by computed tomography (CT) (33.3%) and ultrasonography (13.8%) (Table 2). Cerebral VTE was diagnosed mainly by MRI (80.7%); PE, CT (75.0%); VTE of lower limb, ultrasonography (48.3%).

3) Underlying clinical conditions (risk factors)

One hundred six patients (86.2%) had risk factors such as cancer (34 patients, 27.6%), infection (33, 26.8%), intravenous catheter insertion (22, 17.9%), surgery (18, 14.6%), and congenital heart disease or prosthetic valve (16, 13.0%) (Table 3). Other diagnoses included vascular disease, hematologic disease, and systemic diseases such as systemic lupus erythematosus, nephrotic syndrome, and others. Of the 34 patients, diagnosed with cancer, acute lymphoblastic lymphoma was present in 18 (52.9%) and solid tumor in 9 (26.5%) (Fig. 2). Fifty-seven patients (46.3%) had two or more risk factors.

4) Congenital thrombophilia

Protein C level was evaluated in 39 patients (31.7%), protein S in 40 (32.5%), antithrombin (AT) III in 52 (42.3%), and homocysteine in 21 (17.1%) (Table 4). Among them, 11 out of 39 (28.2%), 11 out of 40 (27.5%), 12 out of 52 (23.1%), and 3 out of 21 (14.3%) showed values below or above the reference range. However, only 2 patients underwent mutational analysis of related genes.
Among all patients, one patient with a family history of AT III deficiency had SERPINC gene mutation and one was diagnosed with MTHFR heterozygous variant. Factor V Leiden and prothrombin mutations were evaluated in 8 (15.4%) and 5 (4.1%) patients, respectively, and none of the patients had mutation.

When we analyzed the 17 patients without risk factors for VTE, the frequency of evaluation for congenital thrombophilia was higher than that of all patients (Table 5). Only the patient with MTHFR mutation underwent mutational analysis.

5) Treatment and outcomes

Seventy-seven patients (62.6%) started anticoagulation treatment. Twenty-six patients (33.8%) were treated with low molecular weight heparin and 19 (15.4%) were treated with conventional heparin (Table 6). The percentage of patients who did not receive any treatment was high (37.4%). Most patients (N=40, 52.0%) were treated for more than 90 days, and of the 49 patients who continued treatment, 16 (32.7%) were treated with warfarin.

Twenty-one patients (17.1%) had complications during follow-up, and 14 of them died due to septic shock (5 patients); cancer related complication (4); pulmonary embolism (2); heart failure (1); gastrointestinal bleeding (1); and unknown cause (1).

Discussion

In prospective pediatric registries in North America and

---

**Table 4. Congenital thrombophilia**

|                          | Evaluated pt, N (%) | Out of ref value a, N (%) | Mutational study, N | Diagnosed pt, N |
|--------------------------|---------------------|--------------------------|---------------------|-----------------|
| Protein C deficiency     | 39 (31.7)           | 11 (28.2)                | 1                   | 0               |
| Protein S deficiency     | 40 (32.5)           | 11 (27.5)                | 2                   | 0               |
| Antithrombin deficiency  | 52 (42.3)           | 12 (23.1)                | 1                   | 1*              |
| Homocysteine elevation   | 21 (17.1)           | 3 (14.3)                 | 1                   | 1*              |
| Factor V Leiden (G1691A) |                     |                          |                     |                 |
| Prothrombin (G20210A)    |                     |                          |                     |                 |

aReference value of Protein C defined as 70-120%, Protein S 60-150%, Antithrombin III 80-120%, Homocysteine 4.2-15.3 μmol/L.

bSERPINC1 gene mutation.

cMTHFR (C677T) heterozygous variant.

---

**Table 5. Congenital thrombophilia without any risk factor (N=17)**

|                          | Evaluated pt, N (%) | Out of ref value a, N (%) | Mutational study, N | Diagnosed pt, N |
|--------------------------|---------------------|--------------------------|---------------------|-----------------|
| Protein C deficiency     | 11 (64.7)           | 0                        | 0                   | 0               |
| Protein S deficiency     | 11 (64.7)           | 4 (36.4)                 | 0                   | 0               |
| Antithrombin deficiency  | 9 (52.9)            | 1 (11.1)                 | 0                   | 0               |
| Homocysteine elevation   | 8 (47.1)            | 1 (12.5)                 | 1                   | 1*              |
| Factor V Leiden (G1691A) |                     |                          |                     |                 |
| Prothrombin (G20210A)    |                     |                          |                     |                 |

aReference value of Protein C defined as 70-120%, Protein S 60-150%, Antithrombin III 80-120%, Homocysteine 4.2-15.3 μmol/L.

bMTHFR (C677T) heterozygous variant.
Table 6. Treatment

| Medication                          | N=123 (%) |
|-------------------------------------|-----------|
| Conventional heparin                | 19 (15.4) |
| LMWH                               | 26 (21.1) |
| Warfarin                           | 13 (10.6) |
| Aspirin                            | 14 (11.4) |
| Clopidogrel                         | 7 (5.7)   |
| Rivaroxaban                         | 1 (0.8)   |
| Urokinase                           | 2 (1.6)   |
| IVC filter                          | 1 (0.8)   |
| Surgery (thrombectomy)              | 2 (1.6)   |
| Unknown                            | 6 (4.9)   |
| No treatment                        | 46 (37.4) |

LMWH, low molecular weight heparin; IVC, inferior vena cava.

Europe, the annual incidence of VTE was estimated to be 0.7 to 1.4 per 100,000 children, 5.3 per 10,000 hospital admission among children, and 24 per 10,000 admissions of neonates to neonatal intensive care units [2,10,11]. Moreover, a dramatic increase in the US hospital-based pediatric VTE incidence rate (188 per 100,000 discharges) was reported in the 2000s [4,7]. Our retrospective multi-center cohort study revealed that the incidence was 4.9 per 10,000 admissions, a rate similar to previous reports. However, our data have several limitations. First, this study included data from multiple centers during extended time period, thus various diagnostic techniques and laboratory methods that differ in accuracy and consistency were included. Second, selection bias by researchers was inevitable in our retrospective analysis as many asymptomatic patients with VTE might be omitted.

One difference between adults and children with VTE was that the majority of cases (over 70%) in children were associated with clinical risk factors including Inherited thrombophilia (IT), whereas in adults, aging is the dominant risk factor for VTE (population attributable risk >90%) [12]. There are many acquired and transient conditions that lead to a prothrombotic state including sepsis, cancer, congenital heart disease, central venous catheter placement, surgery, strict immobilization, pregnancy, oral contraceptives, and persistent antiphospholipid antibody. Activated protein C resistance (designated as factor V Leiden) in the most common hereditary abnormalities predisposing to VTE [13,14]. The factor II variant G20210A is another common gene mutation; other inherited risk factors are disorders of AT III, protein C, protein S, and dysfibrinogenemia. The relative risk of IT leading to VTE in children was evaluated in a previous meta-analysis, which showed the odds ratio (OR) of AT III deficiency to be 9.4 (95% confidence interval [CI] 3.4-26.66), protein C deficiency 7.7 (95% CI 4.4-13.4), protein S deficiency 5.8 (95% CI 3.0-11.0), factor V variant G1691A 3.6 (95% CI 3.8-4.8), and factor II variant G20210A 2.6 (95% CI 1.6-4.4), which is similar to data in adults [12,13,15]. Although genetic variants in factor II (G20210A) and factor V (G1691A) show different patterns between ethnic groups, there is limited data concerning IT in childhood.

The rate of recurrent VTE was suggested to be 3% among neonates and 21% among children without idiopathic VTE based on follow-up reports [2,15,16]. The most important determinant of recurrence is the presence of transient clinical risk factors during the time of the first episode [17]. After an unprovoked first episode of VTE, the risk of recurrence was 10% during the first year after cessation of anticoagulant and 5% per year thereafter. In terms of IT, the risk of recurrent VTE is controversial. Some studies reported that children with AT deficiency had a 6.5-fold higher risk of recurrence compared with patients with non-thrombophilic VTE [18]. Numerous case control studies of patients with VTE due to a specific thrombophilia and patients with nonthrombophilic VTE as controls showed relative risks of 1.5 to 2.0 for most IT [12,13,19-21]. Because there is a lack of evidence that positive thrombophilia test results have an effect on patient management, thrombophilia screening in children with VTE and among thrombosis-prone families is still debated [22]. Although knowledge of IT may be useful to promote awareness of the potential need for prophylaxis in high risk situations, the potential harm of identifying a non-contributory problem leading to inappropriate management also exists [23]. To date, thrombophilia testing has been recommended in a limited number of patients with VTE, particularly if they are young (<50 years old), especially in association with weak provoking factors (minor surgery, immobility, unprovoked VTE, or combination oral anticoagulants), a positive family
history for disease, recurrent VTE events, or thrombosis in unusual sites such as the splanchnic or cerebral veins [24].

The existence of triggering factors for VTE is an important determinant of the duration of therapy; usually, 3 months of anticoagulant treatment is sufficient for patients with a first episode of VTE secondary to a reversible risk factor [25]. For those with an unprovoked (idiopathic) event and those with recurrent events, indefinite anticoagulation therapy should be considered [26]. Determining which patients will be recurrent remains difficult, and the role of the presence or absence of IT in guiding decision making about the duration of therapy remains controversial and incompletely proven.

The dramatic rise in the incidence of pediatric VTE in tertiary care pediatric centers was previously recognized and is attributed to intensive medical intervention at tertiary care centers and improved survival of critically ill patients. Also, the development of diagnostic technology contributed to the increased incidence by early detection of VTE. Due to recurrent VTE and post-thrombotic syndrome (PTS), the risk of major morbidities requires careful follow-up after completion of planned anticoagulant therapy. At follow-up visits, detailed evaluation of the patient’s history and physical examination can focus on the detection of recurrent VTE, and the clinical scoring system for the diagnosis of PTS should be adjusted.

In conclusion, close attention should be paid to the development of VTE in childhood, along with the development of improved medical care and a deliberate and individualized approach for the detection of IT and proper follow up. In the near future, a nationwide survey should be investigated to identify the incidence rate and trends in the VTE incidence among Korean children.

References

1. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE, Blood 1994;83:1251-7.
2. van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in the Netherlands, J Pediatr 2001;139:676-81.
3. Jang MJ, Bang SM, Oh D. Incidence of venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service Database, J Thromb Haemost 2011;9: 85-91.
4. Raffini L, Huang YS, Wittmer C, Feudtner C. Dramatic increase in venous thromboembolism in children’s hospitals in the United States from 2001 to 2007, Pediatrics 2009;124:1001-8.
5. Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen SR. Pediatric venous and arterial noncerebral thromboembolism in Denmark: a nationwide population-based study, J Pediatr 2011;159:663-9.
6. Creany S, Heiny M, Croop J, et al. Clinical course of post-thrombotic syndrome in children with history of venous thromboembolism, Blood Coagul Fibrinolysis 2012;23:39-44.
7. Setty BA, O’Brien SH, Kerlin BA, Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases, Pediatr Blood Cancer 2012;59:258-64.
8. Gokce M, Altan I, Ural S, et al. Recurrent pediatric thrombosis: the effect of underlying and/or coexisting factors, Blood Coagul Fibrinolysis 2012;23:434-9.
9. Choi HS, Choi CW, Kim HM, Park HW. Venous thromboembolism in pediatric patients: a single institution experience in Korea, Blood Res 2016;51:164-70.
10. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry, Pediatrics 1995;96:939-43.
11. Monagle P, Adams M, Mahoney M, et al. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry, Pediatr Res 2000;47:763-6.
12. Young G, Alhisetti M, Bonduel M, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. Circulation 2008;118:1373-82.
13. Kearon C, Julian JA, Kovacs MJ, et al. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial, Blood 2008;112: 4432-6.
14. Choi HS. Venous thromboembolism in children, Clin Pediatr Hematol Oncol 2017;24;1-10.
15. Nowak-Göttl U, Jünker R, Kreuz W, et al. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors, Blood 2001;97:858-62.
16. Goldenberg NA, Knapp-Clevenger R, Manco-Johnson MJ; Mountain States Regional Thrombophilia Group. Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children, N Engl J Med 2004;351:1081-8.
17. de Jong PG, Coppens M, Middeledorp S. Duration of anticoagulant therapy for venous thromboembolism: balancing benefits and harms on the long term, Br J Haematol 2012;158:433-41.
18. Limperger V, Kenet G, Goldenberg NA, et al. Impact of
high-risk thrombophilia status on recurrence among children with a first non-central-venous-catheter-associated VTE: an observational multicentre cohort study. Br J Haematol 2016;175:133-40.

19. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study, Lancet 2003;362:523-6.

20. Marchiori A, Mosena L, Prins MH, Prandoni P. The risk of recurrent venous thromboembolism among heterozygous carriers of factor V Leiden or prothrombin G20210A mutation, A systematic review of prospective studies, Haematologica 2007;92:1107-14.

21. Maraglione M, D’Andrea G, Colaizzo D, et al. Coexistence of factor V leiden and factor II A20210 mutations and recurrent venous thromboembolism, Thromb Haemost 1999;82:1583-7.

22. Klaassen ILM, van Els AL, van de Wetering MD, van Ommen CH. Increasing incidence and recurrence rate of venous thromboembolism in pediatric oncology patients in one single centre over 25 years, Thromb Haemost 2017;117:2156-62.

23. Kenet G, Limperger V, Shneyder M, Nowak-Göttl U. Risk factors for symptomatic venous and arterial thromboembolism in newborns, children and adolescents-What did we learn within the last 20 years? Blood Cells Mol Dis 2017;67:18-22.

24. Connors JM. Thrombophilia testing and venous thrombosis, N Engl J Med 2017;377:1177-87.

25. Kerlin BA. Current and future management of pediatric venous thromboembolism, Am J Hematol 2012;87:S68-74.

26. Monagle P, Chan AKC, Goldenberg NA, 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:e73S-801S.