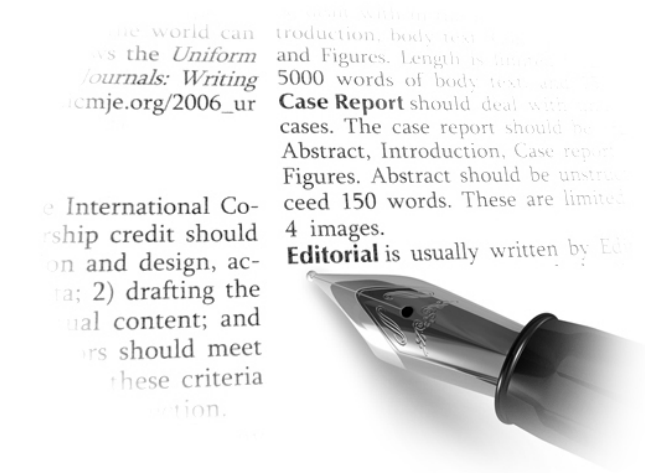

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Editorial

Venous thromboembolism in children and adolescents

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There have been growing concerns about venous thromboembolism (VTE), especially in Western counties where the incidence is greater than Asian counties. In Korea, the annual incidence of VTE per 100,000 population in all age group, age group of 0–9 years and 10–19 years were 8.83, 0.19 and 0.71 in 2004, and increased to 13.8, 0.30 and 0.64 in 2008, respectively, showing significantly lower incidence of VTE in children and adolescents in comparison to adults [1]. Although the incidence of VTE is remarkably lower in children compared to adults, pediatric VTE is also gaining increased awareness because severe VTE may lead to serious morbidity and even death in pediatric patients as well. It has been demonstrated that pediatric VTE is an increasingly common complication among hospitalized children, now occurring in 42–58/10,000 pediatric admissions [2, 3]; representing roughly a 10-fold increase over the original Canadian estimates from the early 1990s [4]. Of note, the majority of pediatric VTE occur in the tertiary care hospitals, where more intensive medical interventions with increased awareness and recognition can be provided [5].

Regarding the lower incidence of pediatric VTE, researchers have suggested that children have protective mechanisms: e.g. physiologic deficiency of coagulation factors leading to reduced capacity to generate thrombin; increased capacity of α2-macroglobulin to inhibit thrombin; enhanced antithrombotic potential of the vessel wall, and not yet being exposed to acquired thrombotic predictors such as smoking or antiphospholipid antibodies [6].

VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE) usually develops as a secondary complication of underlying clinical conditions such as venous catheterization, malignancy, infection/sepsis, congenital heart disease, trauma/surgery, and inherited or acquired thrombophilia, all of which act as risk factors for VTE in children and adolescents. Among these, the most common risk factor for VTE in pediatric patients is the venous catheterization [5, 6]. During intensive or supportive care of pediatric patients who require total parenteral nutrition, chemotherapy, or antibiotic administration, more than half of the DVTs in children and more than 80% of neonates occur in the upper extremity veins secondary to venous catheterization [6].

The impact of inherited thrombophilia on the pediatric VTE remains inconclusive mainly due to lack of statistical power [7]. However, VTE is a multifactorial disease, in which multiple heritable and environmental risk factors affect the overall disease risk, we may have to consider the involvement of inherited thrombophilia that includes deficiencies of antithrombin, protein C and protein S, and mutations of factor V Leiden (G1691A) and prothrombin (factor II G20210A), as 'additional' risk factors for VTE in children and adolescents, especially in patients with idiopathic VTE [6, 7]. The combination of the thrombophilia traits produced the highest odds ratio (OR) and showed a significant association with the first onset of pediatric VTE, as well as recurrence [6].

The common locations of pediatric VTEs are renal vein thrombosis, vena cava occlusion, and thromboembolic stroke of venous origin in neonates, and cerebral venous thrombosis, portal or mesenteric thrombosis, rarely purpura

fulminans in children [7]. The pediatric PE patients with emboli that obstruct more than half of pulmonary circulation present symptoms of cyanosis (hypoxia), tachypnea, dyspnea, cough, pleuritic chest pain, and hemoptysis. Pleuritic chest pain is the most common presenting symptom in adolescents, and unexplained persistent tachypnea should arouse suspicion of PE in all age group of children.

For the diagnosis of VTE, Doppler ultrasonography, venography, computed tomography (CT) and magnetic resonance (MR) imaging can be used. As venography is invasive, painful, and difficult to access in infants and children, noninvasive Doppler ultrasonography should be the first modality to diagnose DVT in children, especially for the DVT in lower extremities. Unlike adult patients, Doppler ultrasonography may not detect DVT in upper extremities or pelvis in children. If VTE is highly suspected and Doppler ultrasonography finding is negative, CT or MR should be performed to confirm the result. MR imaging and MR angiography are recommended to confirm the diagnosis of cerebrovascular occlusion. Ventilation/perfusion radionuclide scan and helical or spiral CT or MR angiography are suitable for the diagnosis of pediatric PE.

For the treatment of pediatric VTE patients, recommendations for antithrombotic treatment are based on small-scale studies in children and most of the guidelines are adapted from adult VTE protocols [6]. Acute-phase anticoagulation therapy may be provided with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) with anti-Xa activity or activated partial thromboplastin time (aPTT) monitoring. Heparins act by enhancing the activity of antithrombin, and LMWH is generally preferred in pediatric VTE patients as LMWH can be administered subcutaneously and has lower risk of heparin-induced thrombocytopenia. But UFH with a shorter half-life than LMWH is preferred in pediatric VTE patients with elevated risk of bleeding and compromised renal function. For the monitoring of the heparinization, the therapeutic range of UFH is 0.3–0.7 anti-Xa activity units/mL and LMWH is 0.5–1.0 anti-Xa activity units/mL, and the goal of APTT is 60–85 sec or approximately 1.5–2 times the upper limit of age appropriate normal value [8].

The recommended duration of heparinization during acute-phase treatment is 5–10 days according to adult protocol [8]. Anticoagulation therapy can be extended in the subacute phase with LMWH or warfarin. For the monitoring of warfarin therapy, the international normalized ratio (INR) should be 2.0–3.0 [8]. Anticoagulation therapy is recommended for 3–6 months for the first attack of VTE, and 6–12 months for idiopathic VTE [8]. Thrombolytic agents such as recombinant tissue plasminogen activator can be used in combination with anticoagulants in acute-phase, especially for the hemodynamically significant PE or potential clinical sequelae of VTE in children. A new antithrombotic agent such as argatroban, surgical treatment such as thrombectomy and inferior vena cava filter have been used to treat pediatric VTE patients in a pediatric tertiary care center in United States [9].

Recurrence rate of VTE is approximately 3% of neonates, 8% in older children and 21% of children with idiopathic VTE, and the mortality rate of pediatric PE is 2.2% [7]. A study from a pediatric tertiary care center in United States reported outcome of pediatric VTE as resolution in 77%, persistence or recurrence in 14%, and death in 9% [9]. Mortality in pediatric PE is more influenced by the underlying disease rather than emboli itself, and recurrent VTE may complicate recovery. Most important short-term complication is major hemorrhage either due to the thrombosis or secondary to anticoagulation. Postthrombotic syndrome (PTS), another well-known complication of pediatric DVT, is defined as edema, pain, skin pigmentation, and ulceration of the affected limb secondary to venous valvular damage initiated by DVT. PTS occurs in 20–50% of adults with DVT and up to 65% of children with DVT, causing disability in pediatric patients [6].

In this issue of **Blood Research**, Choi *et al.* [10] retrospectively analyzed the incidence, risk factors, diagnosis method, treatment and outcome of pediatric VTE patients admitted to a single tertiary hospital in Korea from 2003 to 2016. A total of 25 pediatric VTE patients were diagnosed during 13 years. The total incidence was 3.27/10,000 hospital admissions, that is remarkably lower than Caucasians. Age distribution showed bimodal peaks in neonates (32%) and adolescents (40%). Out of 25 pediatric patients, 80% had underlying primary diseases or risk factors such as venous catheterization (24%), malignancy (20%), and systemic disease (12%), showing relatively high incidence of malignancy. Interestingly, the deficiencies of protein C, protein S, and antithrombin were detected in 2 of 13, 4 of 13, and 1 of 14 examined patients, respectively. For treatment, 10 patients received acute-phase anticoagulation therapy usually with LMWH, 7 patients received long-term anticoagulation therapy with warfarin, and 4 patients received surgical treatment including thrombectomy and inferior vena cava filter and/or thrombolysis. Two of 25 patients (8%) died due to PE, and 2 of 5 patients (40%) with lower extremity DVT developed PTS. Although this study has limitations of retrospective study performed by a single institution with a relatively small number of patients, I believe, as the first comprehensive study of pediatric VTE in Korea, this research will provide a solid basis for future collaborative prospective study in Korea.

Pediatric VTE still has many difficult characteristics, e.g. lower but increasing incidence, many asymptomatic patients, various underlying primary diseases or risk factors, difficulties in diagnosis, high incidence of PTS with possible outcome of lifelong disability, and absence of standardized guidelines for treatment and prophylaxis, when compared to adult VTE. Prospective multi-center studies are needed to develop validated guidelines for diagnosis, antithrombotic therapy, prophylaxis and follow up monitoring for VTE

in children and adolescents. And more researches are needed to identify role of thrombophilia in pediatric VTE, to develop prothrombotic laboratory markers that predispose children to thrombosis, and to evaluate newly developed antithrombotic agents.

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