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Thrombo-hemorrhagic liability in children with congenital heart diseases

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Abstract

Background: The precise mechanisms of the increased incidence of hemostatic abnormalities in congenital heart disease (CHD) have not been determined. The aim of the study was to evaluate some indicators of activation of platelets and vascular endothelial cells in patients with CHD, evaluation of bleeding liability of these patients, and correlation with the clinical presentation of these patients.

Methods: This work was carried out on 20 patients with cyanotic congenital heart disease (CCHD), 20 patients with cyanotic congenital heart disease (ACHD), and 20 healthy children who served as the control group, aged between 1 and 10 years. All were subjected to full clinical examination, complete blood count, oxygen saturation, echocardiography, bleeding and coagulation times, PT, PTT, FDPs, plasma soluble P-selectin, E-selectin, and platelet factor 4 (PF4).

Results: There was significant prolongation of PT and PTT, and there was a significant lowering of platelet counts. These results were obtained in CCHD and ACHD, but were more significant in CCHD patients. There was a significant elevation in PF4 (55.0 ± 25.5 ng/mL), P-selectin (128.9

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± 42.44 ng/dL), and E-selectin (9461.5 ± 1701.24 pg/mL) levels in children with CCHD as compared to those with ACHD (PF4, 21 ± 7.94 ng/mL; P-selectin, 80.1 ± 13.2 ng/mL; E-selectin, 7969.6 ± 2127.5 pg/mL), and significant increase in both groups when compared to the control group (PF4, 8.1 ± 4.7 ng/mL; P-selectin, 27.83 ± 9.73 ng/mL; E-selectin, 6750.00 ± 3204.00 pg/mL). There was a significant negative correlation between oxygen saturation, plasma P-selectin ($r = -0.865$), E-selectin ($r = -0.401$), and PF4 ($r = -0.792$) in patients with CCHD.

Conclusion: Patients with CHD–both cyanotic and acyanotic–have variable degrees of increased liability for both thrombosis and hemorrhage that represents some sort of adaptation to preserve hemostasis and to protect these patients against the clinical presentation of both thrombosis and bleeding. This is to say that CHD patients have their own point of balance between thrombogenicity and bleeding liability. Wide-scale studies are needed to detect the normal levels of different thrombohemorrhagic parameters of these patients.

Introduction

The incidence of congenital heart disease (CHD) is approximately 6–8 in 1000 live births [1]. In patients with cyanotic congenital heart disease (CCHD) with hypoxemia, secondary erythrocytosis, high shear stress of the vessel wall, and platelet surface in association with blood hyperviscosity cause chronic endothelial dysfunction as well as platelet activation, that favors thrombogenesis in the microcirculation and increase the risk of thromboembolism [2,3]. The precise mechanisms of the increased incidence of thromboembolism in patients with CCHD have not yet been determined, but endothelial dysfunction, hemostatic abnormalities, and platelet activation may be the underlying factors causing hypercoagulability and thromboembolism [4].

Platelet factor 4 (PF4), a 70-amino acid protein released from the alpha-granules of activated platelets, binds with high affinity to heparin. Its major physiologic role appears to be neutralization of heparin-like molecules on the endothelial surface of blood vessels, thereby inhibiting local antithrombin III activity and promoting coagulation. As a strong chemoattractant for neutrophils and fibroblasts, PF4 probably has a role in inflammation and wound repair [5].

P-selectin is an adhesion molecule found in the secretory granules of platelets and Weibel–Palade bodies of endothelial cells, and is mobilized to the plasma membrane on activation [6]. Activated platelets expressing P-selectin on the surface release their granule contents, facilitating the adhesion of platelets and neutrophils to the endothelium and causing platelet aggregation and enlargement of thrombi through recruitment of leukocytes and platelets. Thus, P-selectin expressed on platelets is likely to play an important role in thrombus formation [7].

In humans, E-selectin is encoded by the *SELE* gene. Its C-type lectin domain, EGF-like, SCR repeats, and transmembrane domains are each encoded by separate exons, whereas the E-selectin cytosolic domain derives from two exons. The E-selectin locus flanks the L-selectin locus on chromosome 1 [8]. Different from P-selectin, which is stored in vesicles called Weibel–Palade bodies, E-selectin is not stored in the cell and has to be transcribed, translated, and transported to the cell surface. The production of E-selectin is stimulated by the expression of P-selectin, which is stimulated by tumor necrosis factor α, and it can also be stimulated by interleukin-1 and lipopolysaccharide [9].

The aim of this work is to evaluate some indicators of activation of platelets and vascular endothelial cells in patients with CHD, evaluation of bleeding liability of these patients, and correlation with the clinical presentation of these patients.

Patients and methods

After obtaining approval from the institutional review board and the ethics committee of Tanta Faculty of Medicine, informed written consent was obtained from all participants in this research. This prospective, randomized controlled study was carried out on 40 children with CHD, consisting of 20 children with cyanotic CHD and 20 children with acyanotic CHD from the cardiology unit of the pediatric department in Tanta University. In addition, 20 healthy children matched for age and sex served as the control group.

Exclusion criteria

We have excluded children with CHD receiving any drug affecting hemostasis as antiplatelets or anticoagulants, children with CHD with other organ diseases such as hepatic or renal diseases that can affect hemostasis, as well as CHD complicated with heart failure or infection.

The children underwent complete history taking, clinical examination, and the following investigations: chest X-ray, electrocardioram, echocardiography, SaO_2, complete blood count, bleeding time and clotting time, PT and a PTT, and FDP.

Pulmonary vascular resistance (PVR) was estimated in patients with pulmonary hypertension using the following equation [10]:

$$PVR = [V_{(TR)max}/V_{TI(RVOT)} \times 10] + 0.16,$$

where $V_{(TR)}$ refers to the maximum velocity of the tricuspid regurge jet and $V_{TI\ (RVOT)}$ refers to the velocity time integral of right ventricular outflow tract.

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