Haemostatic Disorder in Dengue Hemorrhagic Fever

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Dengue viral infection is one of world health problems in tropical countries. It incidence is predicted as 20 million cases per year, and 500,000 of them present severe clinical manifestation e.g. as dengue hemorrhagic fever. In Indonesia, there are 10-30 thousand cases of dengue hemorrhagic fever a year with 2 percent mortality rate.

Dengue viral infection may be asymptomatic or clinically manifested such as undifferentiated fever, dengue fever or dengue hemorrhagic fever (DHF). Dengue hemorrhagic fever is the severe manifestation of dengue viral infection that characterized by plasma leakage and haemostatic disorder so that it potentially develops into dengue shock syndrome (DSS). Haemostatic disorder of dengue hemorrhagic fever includes vasculopathy, thrombocytopenia, defect in platelet function, coagulopathy, disseminated intravascular coagulation (DIC).

The immunopathology process that occurs in dengue hemorrhagic fever involves humoral and cellular immunity system. Hypothesis of secondary heterologous infection by Halstead suggested that antibody reaction against virus of previous infection would enhance the viral infection against monocyte and macrophage (antibody dependent enhancement). Besides that hypothesis, we have known about the role of complement, T-lymphocyte and various mediator such as TNF-α, IL-2, IL-6, IFN-γ, PAF, C3a, C5a and histamine that cause endothelial dysfunction, plasma leakage, shock, coagulation defect and bleeding manifestation. The role of IL-18 against differentiation of T-cell become T-helper 1 has been regarded as important role in pathogenesis of dengue hemorrhagic fever.

Manifestations of vasculopathy are the positive tourniquet test and petechiae that occur in early fever preceding thrombocytopenia. Vascular defect occurs as infiltration of vascular wall by lymphocyte, mononuclear phagocyte, IgM deposits, complement and fibrinogen. Vasculopathy is the result of direct influence of virus at early infection or as the result of immunologic reaction at convalescence period.

Thrombocytopenia with platelet counts<100.000/mm³ occurs on 3rd – 7th day of fever and back to normal on the 8th – 9th day. In dengue shock syndrome (DSS), the platelet count usually is <50.000/mm³ with a mean value of 20.000/mm³. Usually there is no bleeding even as platelet count is <20.000/mm³ except in prolonged shock.

The mechanisms of thrombocytopenia in dengue infection are: (1). Bone marrow suppression and (2). Destruction and lengthen of platelet life cycle. In early infection (<5 days), bone marrow profile reveals hypocellular condition and suppression of megacaryocyte. After that the haematopoiesis process will increase including megakaryopoiesis. During thrombocytopenia, the thrombopoietin plasma level increases. This fact suggests thrombopoiesis stimulation as compensation mechanism against thrombocytopenia condition. Platelet destruction was occurred through C5g fragment bounding, VD antibody presence, and platelet consumption during coagulopathy process and peripheral sequestration. The defect of platelet function is occurred through mechanism of defect in ADP release, elevation of β-tromboglobulin and PF4 level as the marker of platelet degranulation.

Coagulopathy occurs in various bacterial and viral infections including dengue viral infection. Coagulopathy result from viral interaction with endothelial, which finally cause endothelial dysfunction. Various studies show the presence of consumptive coagulopathy in dengue hemorrhagic fever grade III and IV. There are prolonged prothrombin time (PT), partial activated thromboplastin time (APTT), decrease
of fibrinogen and elevation of D-Dimer or FDP, and decrease of various coagulation factors (II, V, VII, IX, X and XII). Coagulation activation in dengue hemorrhagic fever as in sepsis is assumed to be occurred through extrinsic pathway (tissue factor pathway). Intrinsic pathway also has role through activation of Xla factor but not by contact activation (kalikrein Cl-inhibitor complex). Activation of antithrombin III in dengue hemorrhagic fever was found reduced in DSS and it was correlated to PT, APTT, albumin and fibrinogen level. Coagulopathy process that occurs beyond compensation level has cause fibrin accumulation, DIC and multiple organ failure.

How does haemostatic / coagulation disorder affect the bleeding risk and mortality of DHF and DSS patients needs further study; even though in DHF grade I; it usually recovers well without any therapeutic intervention. We conclude that haemostatic disorder in dengue hemorrhagic fever is a complex process that involving the function of vascular, thrombocyte and coagulation and related the clinical condition and severity.

REFERENCES