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Editorial

Potential danger of isolated platelet transfusion in patients with dengue infection

The explosive release of pro-inflammatory cytokines in patients with dengue virus infection has cascading effects on endothelial cells lining blood vessels so that the endothelial lining resembles a 'war zone'[1]. The activated endothelium is sticky; dysfunctional endothelium may be leaky. These transient endothelial phenomena (battle scars) are more pronounced in patients with dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) compared to those with uncomplicated dengue fever. The sticky activated endothelium causes platelets to adhere to it, thus decreasing the number of platelets free-floating in circulation and possibly is a major mechanism of thrombocytopenia in dengue infection. Reduced organ perfusion as platelets sticking onto the endothelium occlude its microvasculature may contribute to organ (system) failure and death. Capillary leak seen in dengue virus infection is likely to be a consequence of endothelial dysfunction, as the integrity of the vessel wall barrier is affected.

Thrombocytopenia is a defining characteristic of dengue infection. The spectrum of illness caused by dengue infection includes asymptomatic infection, acute febrile illness and severe forms such as DHF or DSS, which can even lead to death. Atypical presentations of dengue, wherein an isolated organ is affected or an isolated organ system fails, are now increasingly reported from India and other parts of the world[2].

Thrombocytopenia due to platelets adhering to sticky endothelium (and occluding the microcirculation), is classically described in primary thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome[3]. von Willebrand factor (vWF) is a protein stored within Weibel Palade bodies in the endothelium. Activation of endothelium leads to exocytosis of vWF onto endothelial surface. ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin repeats) is a vWF cleaving protease. ADAMTS13 deficiency is now recognized as the cause of TTP (inherited deficiency) and haemolytic uremic syndrome (acquired deficiency caused by ADAMTS13 antibodies). Ultra-large (uncleaved) vWF multimers, secondary to ADAMTS13 deficiency, are extremely adhesive and trap platelets forming platelet microthrombi, which in turn can lead to microcirculatory occlusion of vital organs, organ failure and death. Infusions of fresh frozen plasma/ cryosupernatant provide ADAMTS13 supplementation and have been shown to dramatically improve survival in TTP[3].

(High) vWF-(low) ADAMTS13 imbalance predisposing to platelet microthrombi in microvasculature, is now documented in a variety of acute thrombocytopenic conditions (such as dengue[4,5], malaria[6], unselected critical illness with multi-organ failure[7]) and chronic thrombocytopenic conditions (like hypersplenism in portal hypertension)[8].

In a study of children with multi-organ failure associated with thrombocytopenia admitted to Intensive Care Unit, low plasma ADAMTS13 and high vWF levels were seen[7]. In children who died, autopsies revealed vWF rich microthrombi. Children treated with intensive plasmapheresis (which corrects the vWF–ADAMTS13 imbalance, by removing vWF multimers and providing ADAMTS13 by fresh frozen plasma infusions) had increase in plasma ADAMTS13 activity and reversal of organ failure[7]. Thus, the sequence in critically ill patients who die of multi-organ system failure and thrombocytopenia appears to be systemic inflammatory response syndrome, leading to endothelial activation, platelet sequestration onto endothelium occluding microvasculature, organ system failure and death.

In patients with dengue infection, studies document thrombocytopenia, high vWF level, evidence of

endothelial activation (proteins contained within Weibel Palade bodies are increased in circulation suggesting exocytosis of the contents of Weibel Palade bodies), low ADAMTS13 level and ultra-large vWF multimers[4,5]. Plasma levels of vWF antigen were the best predictor of progression to DHF. These studies clearly document that inflammatory cytokinemia, endothelial activation and propensity for microvascular occlusion by platelets are more marked in patients with DHF and DSS.

Dengue infection occurring during pregnancy can become life-threatening. Intensive plasma exchange has been used to treat TTP-like illness in a pregnant woman infected with dengue[9]. Increased platelet adherence to the endothelium in dengue is likely to be of profound clinical significance. It appears dangerous to transfuse platelets to a patient with dengue, in whom the activated sticky endothelium traps platelets in microcirculation, and can lead to (or cause progression of) organ system failure.

Compared to other blood products, blood banks use added precautions when platelets are isolated and stored. Storage of platelet concentrates is associated with loss of viability as well as activation of platelets. Keeping the stored platelets in continuous motion (using platelet agitators) is one of the measures used in blood bank to try and reduce these damages to stored platelet concentrates. Transfusion of activated platelet concentrates may have pro-thrombotic side effects[10]. Thus, there is a potential for harm when isolated platelet transfusions (which may contain activated platelets) are given to a patient with dengue and thrombocytopenia (who probably has activated endothelium, onto which platelets stick). While isolated platelet transfusions are the most common blood product transfused in dengue patients, most prophylactic platelet transfusions given in patients with dengue infection are deemed unnecessary[11,12].

Have platelet transfusions been shown to be harmful in patients who have thrombocytopenia, secondary to endothelial sequestration of platelets? Platelet transfusion, given to manage thrombocytopenia, during surgery and in immediate perioperative period independently predicts death after liver transplantation[13]. Transient vWF/ADAMTS13 imbalance occurs during and immediately after liver transplantation[14]. In another scenario, in a thrombocytopenic patient with severe ADAMTS13 deficiency, raised plasma vWF levels and portopulmonary hypertension, isolated platelet transfusions led to an acute rise in pulmonary hypertension; subsequently, with long-term fresh frozen plasma infusions (providing ADAMTS13 supplementation) the pulmonary hypertension decreased. The authors felt that in this patient, the transfused platelets got deposited in pulmonary microvasculature, leading to a sudden increase in pulmonary artery pressure[15]. It was clear that in both these clinical scenarios, isolated platelet transfusions were harmful.

Do we currently have definitive data that isolated platelet transfusions are harmful in dengue patients? This information is not available now. However, the theoretical basis for the potential for harm is quite strong, based on accruing data, as presented above. Prophylactic platelet transfusions in stable patients with dengue fever may delay normalization of platelet counts and may actually increase the duration of hospitalization[12,16]. However, the potential for harm by isolated platelet transfusions will be markedly higher when the endothelium is more activated. Marked endothelial activation is seen in DHF and DSS. It is also possible that isolated organ system involvement termed ‘atypical presentation’ of dengue may reflect more pronounced endothelial activation in the microvasculature in that organ. The increasing reports of ‘atypical presentation’ of dengue may be a harmful consequence of the currently popular practice of using isolated platelet transfusions[17]. Activated endothelium of microvasculature expresses more vWF (the platelet adhesive protein), acting as traps for platelets. This platelet trapping in microvasculature leads to reduced perfusion, ischaemia and failure of the affected organ. Thus, the potential for harm by isolated platelet transfusions are higher in patients with DHF, DSS and possibly, in atypical presentation of dengue, compared to patients with stable uncomplicated dengue fever.

The current guidelines on the use of blood products in dengue virus infection do not specify against the use of isolated platelet transfusions[18]. The following two suggestions may be useful for the use of platelet transfusions in patients with dengue. First, avoid isolated platelet transfusions if possible (however, the need for platelet transfusion needs to be decided by the treating clinician in each patient, on a case by case basis). Second, if platelet transfusions are required for a patient, first infuse fresh frozen plasma/cryosupernatant (providing ADAMTS13 supplementation), then infuse platelets.

The need of the hour is systematic studies to assess if these suggestions for transfusion practices translate into a reduction in multi-organ system failure and mortality as well as decrease in the incidence of isolated organ system failure (atypical presentations) in patients with dengue virus infection.

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