Review Article

Transfusion support in patients with dengue fever

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Abstract

Dengue fever has emerged as a global public health problem in the recent decades. The clinical spectrum of the disease ranges from dengue fever to dengue hemorrhagic fever and dengue shock syndrome. The disease is characterized by increased capillary permeability, thrombocytopenia and coagulopathy. Thrombocytopenia with hemorrhagic manifestations warrants platelet transfusions. There is lack of evidence-based guidelines for transfusion support in patients with dengue fever. This contributes to inappropriate use of blood components and blood centers constantly face the challenge of inventory management during dengue outbreaks. The current review is aimed to highlight the role of platelets and other blood components in the management of dengue. The review was performed after searching relevant published literature in PubMed, Science Direct, Google scholar and various text books and journal articles.

Key words: Dengue fever, platelets, transfusion

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Introduction

Dengue fever has emerged as a major public health problem in tropical and subtropical regions across the world. With an increase in the global burden of this arboviral infection, health care services are continuously striving to improve patient management and searching for innovative approaches to control vector transmission. Various grades of bleeding manifestations have been defined by World Health Organization (WHO);[1] but, there are few guidelines as to the transfusion management of patients with dengue.

Prophylactic platelet transfusions are given in dengue fever with thrombocytopenia to prevent hemorrhagic complications. Although the use of prophylactic platelet transfusions is increasing in countries where dengue is endemic, it is associated with risks and has financial implications.[2] The decision to transfuse platelets is based on several factors including estimation of platelet count and function, cause of thrombocytopenia, the status of coagulation system, the presence or likelihood of bleeding and the risks of transfusion.[3] Other transfusion strategies include blood transfusion for severe bleeding manifestations, fresh frozen plasma (FFP) and cryoprecipitate for patients with deranged coagulation profile.

The review was carried out after searching the literature in PubMed, Science Direct and Google scholar using keywords combinations: Dengue fever, platelets, transfusion, prophylactic transfusions, and thrombocytopenia.

Epidemiology

World Health Organization has classified dengue as the most important mosquito borne viral disease in the world in its 2012 report.[4] Dengue is now endemic in >125 countries. Almost 75% of the world's population exposed to dengue lives in the Asia Pacific region of the world.[4,5] The incidence of dengue has increased 30-fold between 1960 and 2010.[6] Dramatic expansion of dengue in the recent past has been attributed to urbanization, population explosion, ineffective vector control measures, weather changes, and increase in travel.[7,8] Emerging strains of virus with higher virulence are causing more severe epidemics.[9]

Global estimates of dengue show dengue infections to the tune of 50 million to 200 million annually with over 20,000

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dengue related deaths each year.[10,11] However, due to poor disease surveillance, inadequate reporting, difficulties in diagnosis, and lack of consistent analysis, the true global burden of disease and associated impact is not known.[4,7,8,11-13]

Like most arboviruses, dengue virus is maintained in nature in cycles that involve preferred blood-sucking vectors and vertebrate hosts. The virus is transmitted to humans by *Aedes aegypti* and in some cases by *Aedes albopictus*. The expansion of villages, towns, and cities in endemic areas, and the increased mobility of people have increased the number of epidemics. Dengue fever, which was once confined to Southeast Asia, has now spread its tentacles to Southern China, countries in the Pacific Ocean and America.[14]

Pathophysiology

The dengue virus is an RNA virus of the flaviviridae family with four major serotypes. Various genotypes within each serotype have varying epidemic potential. Once inside the skin, dengue virus binds to Langerhans cells and enters through binding between viral proteins and membrane proteins on the Langerhans cell. The dendritic cell moves to the nearest lymph node. Meanwhile, the virus genome is translated in membrane-bound vesicles on the cell's endoplasmic reticulum, where new viral proteins are produced that replicate the viral RNA and begin to form viral particles. Immature virus particles are transported to the Golgi apparatus and the mature new viruses bud on the surface of the infected cell and are released by exocytosis. They are then able to enter other white blood cells, such as monocytes and macrophages.[15]

Various antibodies are generated; some bind closely to the viral proteins and target them for phagocytosis, but some bind the virus less well and deliver the virus into a part of the phagocytes where it is not destroyed but is able to replicate further.[15] The pathogenesis of dengue is a complex interplay of host immunity and genetic predisposition combined with certain viral virulence factors. The dengue virus genome encodes three structural proteins mainly capsid (C), precursor membrane (prM) and envelope protein (E). The seven nonstructural proteins include NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. Recent evidence suggests that antibody binds to an epitope based on the affinity and accessibility of that epitope in the intact virion. Demonstration of neutralizing antibodies and their target epitopes on the dengue virion has implications for vaccine design.[16,17]

Dengue hemorrhagic fever is associated with an abnormal immune response with production of cytokines or chemokines, activation of T-lymphocytes and disturbance of hemostatic system. Release of cytokines causes systemic effects of plasma leakage and circulatory insufficiency. Moreover, there is increase in apoptosis and endothelial cell dysfunction.[18]

Halstead described the antibody dependent enhancement theory. Upon second infection with a heterotypic dengue virus, antibody dependent enhancement occurs, which increases risk of developing dengue hemorrhagic fever in individuals recovered from a primary dengue infection.[19] There is enhanced T-cell activation in secondary infection. This phenomenon is known as original antigenic sin.[20] Severe dengue is associated with predominance of high cytokine producing cells with excessive release of inflammatory cytokines. This causes vascular leak and tissue damage.[16]

The bleeding manifestations in dengue are caused by vasculopathy, thrombocytopenia, platelet dysfunction and coagulopathy.[18] Thrombocytopenia in dengue is multifactorial. In the early stage, bone marrow hypo-cellularity followed later by immune mediated destruction of platelets are proposed as the mechanisms for thrombocytopenia.[18] Platelet dysfunction (the absence of adenosine diphosphate release) was initially demonstrated in patients with dengue hemorrhagic fever during convalescence.[21] The platelet dysfunction could be due to exhaustion from platelet activation triggered by immune complexes.[22]

During the acute febrile stage, mild prolongation of the prothrombin time and partial thromboplastin time, as well as reduced fibrinogen levels, have been demonstrated by various authors.[21,23] However, the coagulation abnormality is well-compensated for in the majority of patients.

Viral virulence factors have been identified with specific viral mutations linked to disease severity. Host factors such as extremes of age, female sex, ethnicity, and comorbidities such as diabetes and hypertension are associated with severe disease.[24-26] Human genetic susceptibility to severe dengue has been better defined with certain *human leukocyte antigen* polymorphisms in genome wide association studies.[27,28]

Platelet Transfusions

Thrombocytopenia is a common cause of concern in dengue to both patients and attending clinicians. There are no clear guidelines for management of thrombocytopenia and platelets are ordered as a routine in most hospitals. Prophylactic platelet transfusions are defined as platelet transfusions given in the absence of clinical bleeding, in contrast to therapeutic platelet transfusions given to patients with clinical bleeding.[29] There is controversy as to the efficacy of prophylactic platelet transfusions and the exact trigger for platelet transfusion in dengue. Although some recommend a trigger of <20,000/μl

in the absence of bleeding, lowering the transfusion trigger to <10,000/μl as has been shown in a study on patients with acute myeloid leukemia does not increase the risk of bleeding. However, it reduces the number of patients who receive platelet transfusions.[29,30] The British Committee for standardization in hematology guidelines on platelet transfusion recommend a trigger of 10,000/μl for stable thrombocytopenic patients without additional risk factors for bleeding.[31] Similar guidelines have been issued by the Directorate of national vector borne diseases control program, Government of India [Table 1].[32] Besides recommending a trigger of 10,000/μl, these guidelines also state that prophylactic platelet transfusions are not required in stable patients with platelet count below 20,000/μl.

Studies in pediatric patients of dengue shock syndrome have shown no benefits of prophylactic platelets and FFP transfusion. Instead, such transfusions are the cause of fluid overload and prolonged hospital stay.[33] In a study on adults with acute dengue, the authors found prophylactic platelet transfusions to be ineffective in preventing bleeding.[29] Lack of efficacy of prophylactic platelet transfusions has been reported in literature by various authors.[29,30,33] In a comparative study between patients with dengue shock syndrome who received platelet transfusions and those who did not receive transfusions, the authors observed significant difference in the development of pulmonary edema and the length of hospitalization but no difference was observed in the incidence of bleeding manifestations. Preventive transfusions also did not produce improvement in coagulation status.[33] The Trial of Platelet Prohylaxis study of United Kingdom examined the safety of a therapeutic only platelet transfusion strategy with no prophylactic platelet transfusions in thrombocytopenic patients. In dengue shock syndrome patients who received prophylactic platelet transfusion, it was observed that the increment in platelet count was transient and returned to pre transfusion values within 5 h of transfusion.[34]

Table 1: Guidelines for transfusion in dengue fever

Blood component	Indication
Packed red cells	Loss of blood (overt blood) - 10% or more of total blood volume
	Refractory shock despite adequate fluid administration and declining hematocrit
	Replacement volume should be 10 ml/kg body weight at a time and coagulogram should be done
	If fluid overload is present packed red cells are to be given
Platelets	In general there is no need to give prophylactic platelets even at <20,000/cumm
	Prophylactic platelet transfusion may be given at level of <10,000/cumm in absence of bleeding manifestations
	Prolonged shock; with coagulopathy and abnormal coagulogram
	In case of systemic massive bleeding, platelet transfusion may be needed in addition to red cell transfusion
Fresh frozen plasma/ cryoprecipitate	Coagulopathy with bleeding
	Patient's clinical condition may be considered or as per the advise of the physician

In patients with dengue hemorrhagic fever or dengue shock syndrome, duration of shock is the main risk factor for severe bleeding.[35,36] Hence, early recognition and prevention of shock is the key to treatment. Serial monitoring of hematocrit along with judicious intravenous therapy reduces the use of blood products and shortens hospital stay.[33]

In a study on transfusion requirement of patients with dengue infection, the authors observed no correlation between clinical bleed and platelet count. About 37% of patients with dengue hemorrhagic fever or dengue shock syndrome had coagulopathy. About 21.5% of platelet transfusions were considered inappropriate.[37] Inappropriate platelet transfusions in absence of bleeding have been reported from 13% to as high as 56.2% by various authors.[38-40] A study conducted in four tertiary level hospitals of Delhi observed that 73.5% of patients with dengue hemorrhagic fever and 48.7% of dengue fever classified as per WHO guidelines were given platelet transfusions.[41] Sugianto *et al*. observed no significant difference in the frequency of bleeding in patients who received single unit platelet transfusion and those who did not receive any transfusion.[42]

Transfusion of other Components

Patients with severe bleeding that compromises cardiovascular function can be given blood transfusion as a life saving measure. However, there is risk of fluid overload due to decompensated cardiac status. In such patients with massive bleeding, packed red cells may be transfused. Guidelines issued by Government of India recommend red cell transfusions for patients with overt blood loss 10% or more of blood volume and in refractory shock with declining hematocrit.[32]

Thrombocytopenia is not the only predictor of severe bleeding as has been reported in literature.[35] Due to multifactorial etiology of bleeding in patients with dengue, it is wise to conduct a coagulation profile in addition to platelet count before giving platelet transfusions. In a study from Taiwan, 53.8% of patients showed coagulopathy.[43] Coagulopathy can be managed by FFP transfusions but preventive FFP transfusion is not indicated in dengue hemorrhagic fever.[44] Use of FFP or cryoprecipitate is indicated in coagulopathy with bleeding as per the advice of the physician and after taking into account the clinical condition of the patient.[32] Recombinant factor VIIa may be given in severe uncontrolled bleeding. It enhances

thrombin generation. It also increases the activity and function of patients' and transfused platelets by direct activation of factor X on platelet surface.[18]

Challenges

Blood transfusion services constantly face challenges year after year during dengue outbreaks due to lack of evidence based guidelines for clinical use of blood and blood components. The demand for platelets and FFP is increasing due to more number of cases with dengue hemorrhagic fever and dengue shock syndrome. Transfusion of blood components is associated with many adverse effects. The major risks associated with transfusion of platelets include febrile non hemolytic transfusion reactions, allergic reactions, bacterial sepsis, transfusion related acute lung injury, alloimmunization, and platelet refractoriness, pulmonary edema and transfusion transmitted infections.[45-48] Hence, it is prudent to consider transfusion only if the benefits outweigh the accompanying risks of transfusion.

Conclusion

Inappropriate use of blood and blood components during dengue fever outbreaks essentially depletes the inventory of blood centers. Further, lack of knowledge, absence of evidence based guidelines and panic like situation leads to flooding of transfusion services with blood and component requests. A centralized system of management with donor registries, guidelines and regular awareness programs can go a long way in better management of dengue outbreaks.

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