Dengue Hemorrhagic Fever in Trinidad and Tobago: A Case for a Conservative Approach to Platelet Transfusion

Anu Sharma,* Kenneth Charles, Dave Chadee, and Surujpaul Teelucksingh

Department of Clinical Medical Sciences, University of the West Indies, St. Augustine, Trinidad and Tobago;

Department of Life Sciences, University of the West Indies, St. Augustine, Trinidad and Tobago

Abstract. Dengue fever is endemic to Trinidad and Tobago. A retrospective analysis of all adult admissions at a tertiary hospital in Trinidad treated for dengue during January 1–December 31, 2008 was performed. A total of 186 patients were treated during this period: 98.9% (184) of the patients were thrombocytopenic; 45.2% were severely thrombocytopenic; 13 patients showed development of minor hemorrhage and only one case of major hemorrhage; platelet transfusion was given for 7% (13) of the cases; and 6 cases for which platelet transfusion was given did not show evidence of plasma leakage (12 of these cases did not show evidence of hemorrhage). There was a strong association between the lowest platelet value and hemoconcentration ($\chi^2 = 13.16$, $P < 0.025$). No association was found between giving a platelet transfusion and hemoconcentration or hemorrhage. Thrombocytopenia seen in dengue resolves spontaneously and independent of any transfusion used.

INTRODUCTION

Dengue fever is the most common arthropod-borne viral disease worldwide. It is endemic to 100 countries, 2.5 billion persons are at risk for infection, and an estimated 50 million infections occur each year.¹ The World Health Organization estimated that the incidence of dengue fever has increased by a factor of 30 over the past 50 years.² Dengue fever is caused by four closely related serotypes of the family *Flaviviridae*. They are enveloped, single-stranded, positive-sense RNA viruses. Infection with one serotype produces lifelong immunity to that serotype but only transient immunity (few months) to others.³ Dengue virus is transmitted by *Aedes aegypti* mosquitoes. This vector is highly susceptible to the dengue virus and feeds preferentially on human blood.⁴ These mosquitoes are daytime feeders and have crepuscular⁵ and nocturnal habits,⁶ which further enhance dengue transmission. These nocturnal components expand their feeding duration to periods when persons are at home at night. In addition, their almost imperceptible bite and multiple feeding strategy make them efficient disease vectors.^{4,6}

Dengue fever is a mild febrile illness. However, in a small percentage of cases, dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) can develop. This feared complication is characterized by bleeding diathesis and plasma leakage as a result of increased microvascular permeability.⁷ This disease is associated with re-infection, which is believed to be caused by cross-reactive antibodies from the primary dengue infection that facilitate virus entry into cells.⁸ With the immune system primed by the first infection, higher antibody titers are produced. The combination results in an amplified cascade of cytokine and complement activation. Immune-mediated thrombocytopenia⁹ and viral-mediated plasma leakage¹⁰ occur, which contribute to the development of DHF/DSS.

The first published report of DHF/DSS in Trinidad was in 1997,¹¹ but dengue virus has been endemic to Trinidad since 1991.¹² Recently, there was an alarming increase in the incidence rate from 3.62 cases per 100,000 persons¹³ in 2007 to 182 cases per 100,000 persons¹⁴ in 2008. With this re-emergence

came a dengue panic syndrome, as described by Ahluwalia and Sharma.¹⁵ Many medical practitioners rushed into administering platelet transfusions, despite previous studies demonstrating that this may be unnecessary.^{16,17} We sought to study and rationalize the necessity for platelet transfusions in dengue fever with a view to guiding national policy.

MATERIALS AND METHODS

The records of all adult admissions at the Medical Associates Hospital in St. Joseph, Trinidad, who were treated for dengue during January 1–December 31, 2008 were reviewed. An adult was defined as a person ≥ 12 years of age. Dengue fever was defined as fever with at least two of the following criteria: anorexia, rash, aches and pains, leukopenia, thrombocytopenia, and warning signs (abdominal pain or tenderness, vomiting, clinical plasma leakage, and/or increase in hematocrit). Medical consultants and clinical decision makers were not informed or influenced and data were gathered retrospectively.

Demographic data included age, month of admission, home address, and ethnicity. Laboratory values recorded were minimum platelet count, minimum leukocyte count, percentage hematocrit change from baseline during hospitalization, and the results of the dengue acute-phase serum IgM and IgG rapid tests (Dengue Duo Cassette; PanBio, Windsor, Queensland, Australia). Change in hematocrit was used to determine if hemoconcentration occurred, which was defined as an increase $\geq 20\%$ from baseline. Minor or major hemorrhage, platelet transfusions administered with pre-transfusion and post-transfusion platelet values, and whole/packed erythrocyte transfusions given were also recorded. Minor hemorrhage was defined as any bleeding manifestation without a decrease in hemoglobin/hematocrit values and hemodynamically stable vital signs (epistaxis, gum bleeding, and petechiae were included in this category). Major hemorrhage was defined as bleeding producing a decrease in hemoglobin/hematocrit and hemodynamic compromise (including hematemesis, melena, hematuria, massive vaginal bleeding, and disseminated intravascular coagulation).

Statistical analysis. Data were analyzed and subjected to chi-square analysis to detect seasonal trends in hospital admissions. Proportions were compared by using the Pearson

*Address correspondence to Anu Sharma, 5 Sundaree Drive, Longdenville Old Road, Chaguanas, Trinidad and Tobago. E-mail: anu.sharma@gmail.com

chi-square test. The calculated P values were Yates corrected. For continuous variables, data were subjected to Pearson's product moment correlation analysis. A P value less than 0.05 was considered significant. All data were analyzed by using the SPSS statistical package version 16.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

One hundred eighty-six patients were clinically give a diagnosis and treated for dengue fever over the study period. The two age groups with the highest frequencies were persons 46–60 years of age (28.5%, $n = 53$) and persons 18–25 years of age (21.5%, $n = 40$) groups. The male to female ratio was approximately 1:1.51.1% (95) males and 48.9% (91) females. A total of 72.6% (135) of the patients were IgM positive and 60.2% (112) were IgG positive. Dengue IgM testing was not conducted for 17.7% (33) of cases, and IgG testing was not conducted for 21% (39) cases. A total of 18.8% (35) of the patients had a negative rapid IgG test result, which suggested primary infection. Of these patients, 68.6% (24) had a hematocrit change $< 20\%$ from baseline. Most patients (75.7%, $n = 143$) were admitted in during August–November (Figure 1).

A total of 79% (147) of patients had a leukocyte count $< 5 \times 10^9/L$; 59.1% were neutropenic ($< 4 \times 10^9/L$), 98.9% (184) were thrombocytopenic (platelet count $< 150 \times 10^3/\mu L$), and 45.2% (84) were severely thrombocytopenic ($< 20 \times 10^3/\mu L$). A total of 25.3% (47) of patients had a hematocrit change $> 20\%$ (hemoconcentration) from baseline. Only 7.5% (14) of patients showed development of hemorrhage; one patient showed major hemorrhage (hematemesis secondary to concomitant alcoholic cirrhosis). A total of 3.8% (7) of all patients satisfied the World Health Organization criteria for DHF/DSS and none of the patients died.

Platelet transfusions with consent were given to 7% (13) of the patients. Eleven of these 13 patients had platelet counts $< 10 \times 10^3/\mu L$. There was no evidence of plasma leakage in six patients who were given platelet transfusions given, and there was no evidence of hemorrhage in 12 patients. The mean pre-transfusion platelet count was $8 \times 10^3/\mu L$ and the mean post-transfusion platelet count was $16 \times 10^3/\mu L$. Four patients were given transfusions of packed erythrocytes: one for major upper gastrointestinal hemorrhaging confirmed by endoscopy, one

for β -thalassemia, and two as a substitute for platelet transfusions when platelets were not available from the National Blood Transfusion Service.

There was a strong association between the lowest platelet value and hemoconcentration ($\chi^2 = 13.16$, $P < 0.025$), and 89.4% of the patients showed hemoconcentration and had a minimum platelet level $< 50 \times 10^3/\mu L$. There was also a weak but significant correlation between minimum platelet level and hemoconcentration (Pearson's $r = -0.282$, $P < 0.01$) (Figure 2). Additionally, a weak association was found between the age of the patient and hemoconcentration ($\chi^2 = 10.12$, $P < 0.1$), and 74.5% of patients who showed this change in hematocrit were 26–60 years of age (Figure 3).

No association was found for giving platelet transfusions and hemoconcentration or hemorrhage. There was also no association between ethnicity of the patient and severity of dengue (thrombocytopenia or hemoconcentration).

DISCUSSION

Trinidad and Tobago is one of the 100 countries to which dengue virus is endemic. It is commonly known that the dengue season in Trinidad coincides with the rainy season, which is during May–November when more than 60% of the rainfall occurs. Average temperatures also peak during May–June and September–October. It was found that the rate of dengue viral replication¹⁸ in *Ae. aegypti* mosquitoes and the risk of dengue infection¹⁹ increased directly with temperature. Consistent with the study of Chadee and others,¹² we found that the highest number of dengue cases was during the rainy season (75.7% during August–November).

Confirmatory tests for dengue have been rapidly evolving over time. The Panbio rapid dengue IgM/IgG test used in this study is the only commercially available and easily accessible laboratory test in Trinidad and Tobago. In an evaluation of commercially available IgM tests, the Panbio rapid dengue test was found to have a sensitivity of 77.8% and specificity of 90.6%.²⁰ Hunsperger and others²⁰ recommended not using IgM seropositivity as a confirmatory test in a dengue-endemic area because IgM titers can remain positive > 60 days. Because dengue has been endemic to Trinidad and Tobago for the past 19 years, results of the dengue IgM tests were not used as an inclusion criterion. In the 18 (9.7%) patients where IgM test

FIGURE 1. Frequency of admission by month, Trinidad and Tobago.

FIGURE 2. Scatter plot showing correlation between platelet minimum level and hemoconcentration, Trinidad and Tobago. HCT = hematocrit.

results were negative and the 31 (16.7%) patients for whom this testing was not conducted, disease course and clinical manifestations were consistent with a diagnosis of dengue, and other differential diagnoses were ruled out by blood culture, smear, and influenza rapid test results. A total of 68.6% (24) of patients with IgG-negative test results did not have any evidence of plasma leakage (measured as hemoconcentration). This finding is consistent with those of previous reports, which suggested that primary infections had a milder disease course.¹

Severe dengue is characterized by plasma leakage leading to shock, severe hemorrhage and/or severe organ impairment.²¹ Several authors have sought to identify clinical predictors for the development of severe dengue. Our study found a weak but significant correlation and a strong association between the minimum platelet level and hemoconcentration ($r = -0.282$, $\chi^2 = 13.16$, $P < 0.025$). A total of 89.4% of the patients who had an increased hematocrit $> 20\%$ also had a platelet count $< 50 \times 10^3/\mu\text{L}$. Thrombocytopenia can therefore be used as an indicator of increased risk of DHF/DSS. This finding is a well-established association,²² and the mechanism by which it occurs appears to be synergistic.

When dengue virus infects a previously infected host, cross-reactive but non-neutralizing (because a different serotype may be the infecting agent) antibodies are produced in larger numbers. These antibodies facilitate viral entry into cells and promote enhanced viral replication. Higher viral titers have been shown to be correlated with disease severity.²³ Virus and non-neutralizing antibodies activate cytokine release (interleukin-8 [IL-8] and IL-10) and the complement cascade, respectively. Interleukin-8 and RANTES (regulated upon activation, normal T-cell expressed, and secreted) chemokine cause local vascular leakage, which would be increased by endothelial cell apoptosis in response to viral infection.²⁴ Production of IL-10 has been correlated with thrombocytopenia.²⁵ As a result, the initiating event of the virus would cause thrombocytopenia initially and then plasma leakage and thus result in our finding of their correlation.

The feared complication of DHF/DSS motivates clinical practitioners in Trinidad to use prophylactic platelet transfusions in the management of dengue fever. Currently, patients with severe thrombocytopenia (platelet count $< 20 \times 10^3/\mu\text{L}$) receive prophylactic transfusions to prevent bleeding despite

FIGURE 3. Variation of hemoconcentration by age, Trinidad and Tobago.

a lack of evidence to support this practice. Many patients receive platelets following these guidelines, and it is common to have a shortage of these blood products during a dengue outbreak. However, this practice results in resources being wasted, elimination of platelet supplies, and putting patients at risk for alloimmunization to many HLA-specific and platelet-specific antigens from random donor platelets. It has been suggested to use single donor apheresis platelets for platelet transfusions to lower the risk of alloimmunization.²⁶ However, it is currently impossible to obtain these platelets in Trinidad and Tobago.

Our study showed that 45.2% (84) of patients were severely thrombocytopenic, and 84.5% (71) of these patients did not receive platelet transfusions, only fluid support. Of the 49 patients who had significant hemoconcentration, 85.7% (42) did not receive prophylactic platelets. Despite similar severities of thrombocytopenia and DSS in patients who did and did not receive platelets, those who were managed with fluid support only recovered and did not show development of severe bleeding, which is consistent with results of previous reports.^{16,17} Prophylactic platelet transfusions offer no benefit to patients and there is no associated increase in morbidity or mortality with a conservative approach to transfusion.

In our study, there were two patients in whom blood transfusions were used because platelets were not available. Hebert and others²⁷ recommended that blood transfusions be used in critically ill patients to maintain hemoglobin values at 7–9 g/dL. Blood transfusion for dengue is only indicated for patients with significant clinical bleeding.⁵ In our two patients, there was no evidence of hemorrhage or decrease in hemoglobin levels, and one of these patients showed an increase in hematocrit > 20% from baseline. These patients do not meet the criteria for blood transfusions and represent over-treatment by physicians.

In summary, because dengue is endemic to Trinidad and Tobago, its resurgence should be expected on a regular basis. To save resources and protect patients against alloimmunization, prophylactic platelet transfusion should be avoided. In cases of major hemorrhage, transfusion of packed erythrocytes would be more beneficial than platelet transfusion. With proper management of shock using intravenous fluids, thrombocytopenia seen in dengue resolves spontaneously and independent of any transfusion used.

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Authors' addresses: Anu Sharma, Longdenville Old Road, Chaguanas, Trinidad and Tobago, E-mail: anu.sharma@gmail.com. Kenneth Charles and Surujpaul Teelucksingh, Department of Clinical Medical Sciences, Faculty of Medical Sciences, University of the West Indies, St. Augustine, Trinidad and Tobago. Dave Chadee, Department of Life Sciences, University of the West Indies, St. Augustine, Trinidad and Tobago.

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