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Thrombocytopenia in Dengue Fever and The Role of Platelet Transfusion

KEYWORDS: Dengue Fever, Platelet transfusion, Thrombocytopenia

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ABSTRACT *Background: Dengue fever (DF) is an upcoming public health issue. Prophylactic blood product transfusions are commonly practiced though not recommended. This study reviews the clinical profile of patients with DF, details of resuscitation and blood product transfusion in our hospital.* **Methods***: A prospective observational study enrolling patients presenting with clinical suspicion of DF. Detailed history, physical findings, laboratory investigations and treatment modalities were documented.* **Results:** *Thrombocytopenia was observed in 86 % of patients. Severe thrombocytopenia at admission was seen in 22 % of patients. Only 7.2% of the patients required platelet transfusions. Severe thrombocytopenia had higher mean hemoglobin and total WBC counts, higher rate of overt bleeding, DHF as well as and mortality. No significant association was noticed with age, duration of failure and occurrence of DSS.* **Conclusion:** *Early recognition of dengue and prognosticating severity of illness, rather than prophylactic transfusion will ensure good clinical outcomes.*

INTRODUCTION

Dengue fever (DF) is a commonly seen mosquito vector borne viral infection and one of the most prevalent diseases of the tropical and sub-tropical regions. Nearly half the global burden of dengue is borne by the south-east Asian countries of India, Indonesia, Myanmar and Thailand (1). Plasma leakage, haemo-concentration and abnormalities in homeostasis characterize severe dengue. Prophylactic platelet transfusion in the absence of major bleeding is commonly used in DF with thrombocytopenia with the intention of preventing hemorrhagic complications (2). Though the medical fraternity throughout the world recognizes the role of platelet transfusion while dealing with hospitalized dengue patients, the exact indication and situation in which they are to be transfused vary. Prophylactic platelet transfusion in DF is neither standardized nor supported by clinical evidence (3). In many places platelets are transfused not based on medical rationale, but due to intense social pressure on the treating physicians by the patients or their relatives. Therefore, this study reviews the clinical profile of patients with DF, details of resuscitation and blood product transfusion in our hospital.

Materials and Methods:

This prospective observational study was conducted in Christian Medical College, Vellore, a 2700-bed tertiary care hospital in Tamil Nadu, South India between October 2012 and September 2013. All adolescent and adult patients more than 15 years of age presenting with clinical suspicion of DF (fever, headache, myalgia, arthralgia, retro orbital pain and rash) were screened. All patients who tested positive for Dengue IgM enzyme-linked immunosorbent assay (ELISA) (Panbio®; Dengue Duo cassette) with all other serological tests and blood culture negative were considered as having confirmed DF and were included in the analysis. Serological tests were performed on all patients for pathogens believed to be endemic to our region. These included scrub typhus IgM ELISA (InBios International, Inc., Seattle, WA, USA), leptospira IgM ELISA (Panbio®) and a Widal test. These tests were performed on the seventh day of onset of fever or later.

Details of history and results of a thorough physical examination were entered on a standard data collection sheet after obtaining a written informed consent. The routine baseline investigations included complete blood count (CBC) analysis, serum electrolytes, test for malarial parasites, liver and renal function tests. Details of treatment including blood product transfusion were documented. All in-patients were followed up till discharge from the hospital.

Statistical methods

Statistical analysis was performed using SPSS software (SPSS Inc. Released 2007. SPSS for Windows, version 16.0. Chicago). Mean (SD) were calculated for the continuous variables and t-test or Mann–Whitney test was used to test the significance. Categorical variables were expressed in proportion and chi-square test or Fisher exact test was used to compare dichotomous variables. The clinically significant associations of severe thrombocytopenia were analyzed by univariate analysis and their 95% confidence intervals (CI) were calculated. For all tests, a two sided p value of 0.05 or less was considered statistically significant.

This study was approved by the Institutional Review Board and patient confidentiality was maintained using unique identifiers and by password protected data entry software with restricted users.

Results:

During the study period, 386 patients were confirmed to have DF. There was a slight male predominance (56.9

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%). The mean age of patients was 30.9 ± 12.5. The overwhelming majority (90.1 %) of patients were in the age group 15-50 years. Most of the patients were from Tamil Nadu (78.4%) and the neighboring state of Andhra Pradesh (18.1%), the remainder were from Kerala and Karnataka. Most of the patients presented between the months of June-January which coincides with the North West monsoon in Tamil Nadu.

In the emergency department, most of the patients were triaged as priority 2 or 3 (93 %) while 7 % of the patients were triaged as priority 1 and required immediate resuscitation. Sequential Organ Failure Assessment (SOFA) score, which provides valuable prognostic information regarding organ dysfunction and hypoperfusion state was calculated and analyzed. The mean SOFA score was 3.0 (SD: 2.2). 65 % of the patients had a SOFA score of 3 or less, while higher scores of >6 and > 8 were seen in 6.2 % and 2 % of patients respectively. The baseline characteristics are shown in Table 1.

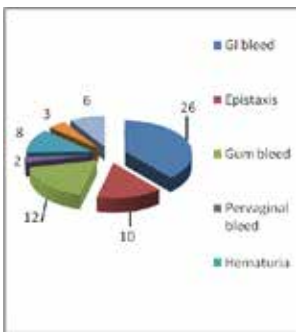
Table 1: Demographic characteristics and investigations

Variable		N (%)
Age (years)		30.9 + 12.5
Sex	Male	220 (57 %)
	Female	166 (43 %)
Duration of fever (days)		5.8± 2.4
State	Tamil Nadu	303 (78.4 %)
	Andhra	70 (18.1 %)
	Others	13 (3.3 %)
Total WBC count (cells/ cumm)		
<4000		180 (46.6 %)
4000-10,000		168 (43.5 %)
>10,000		38 (9.9 %)
Platelet count (cells/ cumm)		
> 150000		54 (14 %)
< 150000		332 (86 %)
< 20000		85 (22 %)
< 10000		17 (4.4 %)
Haemoglobin (g%) mean; (SD)		14.8 (2.1)
Haematocrit (%) (N=251)		42.20 (6.6)
Serum creatinine > 1.4 mg/dl		95 (19.6 %)
DHF		42/ 386 (11 %)
DSS		14/ 386 (3.6 %)

WBC: White blood cell; DHF: Dengue Hemorrhagic fever; DSS: Dengue Shock Syndrome.

Clinical features and laboratory investigations:
The mean duration of fever was 5.8± 2.4 days. Common associated symptoms included myalgia (86.5%), headache (64%), vomiting (45.8%), arthralgia (12%), abdominal pain (20%), dry cough (13%), loose stools (7%) breathing difficulty (7%) and altered sensorium (1.2 %). Overt bleeding manifestations were seen in 14 % of patients with some patients having bleeding manifestations from more than 1 site. The common sites of bleeding are shown in Figure 1.

Figure 1: Bleeding sites among patients with Dengue Fever (N=59)



The mean hemoglobin was 14.8 (SD: 2.1) g % and the mean hematocrit was 42.2 (SD: 6.6). Most patients had normal or low total White blood cell (WBC) count. The WBC count was <4000 cells/ cumm in 46.6 % of patients while it ranged from 4000-10,000 cells/ cumm in 43.5 % of patients. Leucocytosis (WBC count>10,000 cells/ cumm) was seen in only 9.9 % of patients with DF. Thrombocytopenia (platelet count < 150000 cells/ cumm) was observed in 86 % of patients while severe thrombocytopenia (platelet count < 20000 cells/ cumm) at admission was seen in 22 % of patients. Renal failure (serum creatinine >1.4 mg %) at admission was observed in 19.5 % of patients. Dengue hemorrhagic fever (DHF) was seen in 11% and Dengue shock syndrome (DSS) in 3.6% of patients.

Blood product transfusion and outcome:
Only 7.2% (28/386) of the patients required platelet transfusions. Only 8 (2 %) patients required packed red cell transfusion for severe bleeding while 7 (1.8 %) patients required fresh frozen plasma or cryoprecipitate for treating severe coagulopathy. Three patients who expired did not require platelet transfusion while 3 patients required packed red cells for anemia due to bleeding but did not require platelet transfusion as they did not have significant thrombocytopenia. Most patients were followed up and treated on an outpatient basis. Only 28.2 % of patients required admission. The mean duration of hospital stay was 4.4 (SD: 6.3) days. Four percent of patients required admission to the medical intensive care unit. The mortality rate was 2.3 %.

Significant parameters associated with severe thrombocytopenia at presentation were studied using univariate analysis. (Table 2) Compared to patients with platelet count >20,000 cells/ cu mm, patients with severe thrombocytopenia (platelet count < 20000 cells/ cu mm) had a higher mean hemoglobin (15.8; SD: 1.9 vs 14.2; SD: 2.1; p value= 0.029), higher mean total WBC counts (6737; SD: 5651 vs 4890; SD: 285; p value=0.0097), higher rate of overt bleeding (30.5 % vs 9.3 %; OR: 4.32. 95% CI: 25-8.2), higher incidence of DHF (29.4 % vs 6.9 %; OR: 4.66; 95% CI:2.3-9.45) and higher mortality (5.8 % vs 1.3 %; OR: 4.64; 95% CI:1.05-21.13). No significant association was noticed with age, duration of failure and occurrence of DSS.

Discussion
Dengue virus infection (DI) has become a serious public health problem. Several outbreaks of DI have been reported from India. Of particular significance is the 2005 World Health Assembly resolution (WHA) on the revision of the International Health Regulations (IHR) which includes dengue as an example of a disease that may constitute a public health emergency causing international concern with implications for health security due to disruption of health support systems and

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Table 3: Significant parameters associated with severe thrombocytopenia (< 20000 cells/ cumm) at presentation.

Variable	Patients with platelet count < 20000 cells/ cu mm) N=85	Patients with platelet count > 20000 cells/ cu mm) N=301	Un adjusted OR (95% CI)	P value
Age in years (SD)	31.91(12)	30.60(13)		0.394
Female sex; n (%)	27 (32 %)	139 (46 %)	0.58(.34-1)	0.038
Duration of fever (days)(SD)	5.77(2)	5.8(2.5)		0.55
Total WBC count (cells/ cu mm) (SD)	6737(5651)	4890(2857)		0.009
Haemoglobin (g %)(SD)	15.8(1.9)	14.2(2.1)		0.029
Creatinine (mg %)	1.31(0.63)	1.14(.31)		0.075
Platelet transfusion; n (%)	19 (22 %)	9 (2.9 %)	9.34(3.8-23.48)	<0.001
Overt bleeding; n (%)	26 (30.5 %)	28 (9.3 %)	4.3(2.25-8.2)	<0.001
DHF; n (%)	22 (29.4 %)	21 (6.9 %)	4.66(2.3-9.45)	<0.001
DSS; n (%)	6 (7 %)	8 (2.6 %)	2.78(.83-9.16)	0.055
Secondary dengue; n (%)	80 (94 %)	251 (84 %)	3.19(1.17-9.42)	0.009
Mortality; n (%)	5 (5.8 %)	4 (1.3 %)	4.64(1.05-21.13)	0.029

rapid epidemic spread beyond national borders.

Dengue is a self limiting acute mosquito transmitted disease characterized by fever, headache, musculoskeletal pains, rash, nausea and vomiting. It is caused by a single stranded RNA virus DEN belonging to Flaviviridae family. Aedes agypti is common in water filled habitats and is the vector involved in disease transmission. Some infections result in Dengue Haemorrhagic Fever (DHF) and in its severe form, Dengue Shock Syndrome (DSS) can be life-threatening. Bleeding manifestations are highly variable and do not always correlate with the laboratory abnormalities in the coagulation, profile. One of the primary problems in management of dengue is the misinterpretation and resultant uncertainty of the term Haemorrhagic Fever, implying a significant haemorrhagic component to the patho-physiology and overshadowing the increased permeability causing depletion of the intravascular component. The pathophysiology of plasma leakage is due to increased vascular permeability during the acute febrile stage and becomes more prominent in the toxic stages. Plasma leakage is evidenced by haemo-concentration, hypo-albuminemia, pleural effusion, ascites and shock syndrome. The bleeding tendency is caused by vasculopathy, thrombocytopenia, platelet dysfunction and coagulopathy(4, 5).

In our study, majority of dengue cases involved adult population in the age group of 21-30 years. Thrombocytopenia was observed in 86% of our patients, which is comparable to other studies. Pervin et al reported that thrombocytopenia was found in 90.93% of their confirmed cases on admission (6). This prevalence was slightly higher than the findings of Chairulfatah et al. who found an incidence of 83% and Makroo et al. with 84.8% in hospitalized dengue patients (7,8).

In a study done by Kulkharni et al, transfusion rate was 78.4% but he also implied that 51% of transfusions were inappropriate (9). Makroo et al, recorded 84.88% incidence of thrombocytopenia with 9.7% bleeding manifestations, such as petechiae, gum-bleeding, epistaxis, etc., which necessitated the use of platelet transfusion, although 31of these were noted to have had received inappropriate platelet transfusion(8). Our study witnessed a low transfusion rate. In our study, 18.6% had platelet counts less than 20000/cumm., with 13.9% heamorrhagic manifestations and transfusion was done only in 5.9% patients. It was also observed that transfusions could be withheld till the bleeding features manifest. This is in accordance with the recent guidelines on management of dengue (10, 11).

Lye, et al, reported no clinical benefit from prophylactic platelet transfusion in adult dengue patients (12). Infact, emphasizes the possible risk factors involved in prophylactic platelets transfusion, such as alloimmunisation and platelet refractoriness leading to allergic reactions, febrile non-hemolytic reactions, and bacterial sepsis. Rarely, it can also lead to acute lung injury, viral and parasitic infections. Pulmonary edema from volume overload during platelet transfusion has also been reported in DF (13).

Based on the findings of Kaur et al, absence of significant effect on the duration of bleeding due to higher platelet counts suggests that bleeding in DHF/DSS cannot be attributed to thrombocytopenia alone (14). From our study, conducted among 386 patients only 23 of them were transfused based on clinical signs of bleeding manifestations.

Conclusion:

Attempting to increase the platelet counts by transfusing blood products in the absence of major bleeding has not conferred any protective benefits from bleeding in dengue. Rather, early recognition of dengue, and prognosticating severity of illness, and aggressive hemodynamic resuscitation, will ensure good clinical outcomes.

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