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Original Research Article

Significance of APTT as early predictor of bleeding in comparison to thrombocytopenia in dengue virus infection

Hamsa B. T., Srinivasa S. V.*, Prabhakar K., Raveesha A., Manoj A. G.

Department of Medicine, Sri Devraj URS Medical College, Kolar, Karnataka, India

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***Correspondence:**
Dr. Srinivasa S. V.,
E-mail: hamsareddy12@gmail.com

ABSTRACT

Background: Dengue is a systemic viral infection transmitted by mosquitoes such as Aedes aegypti or Aedes albopictus. Dengue Fever (DF) is characterized by fever, headache, muscle or joint pain, and rash. The spectrum of dengue virus infection spreads from an undifferentiated fever and dengue fever (DF) to dengue haemorrhagic fever (DHF) with shock. Factors responsible for bleeding manifestations in dengue are vasculopathy, thrombocytopenia, coagulopathy, and disseminated intravascular coagulation (DIC). Coagulopathy results in derangement of activated partial thromboplastin time (APTT) which is an indicator of impending bleeding risk.
Methods: A prospective study was conducted from June to December in 2017 in R L Jalappa Hospital. Patients aged above 18 years with febrile thrombocytopenia who are positive for dengue virus serology (NS1Ag and/ or IgM) were included in the study. Serial daily monitoring of platelet count and analysis of APTT levels were done. APTT was considered abnormal if it was more than 33.8s. Patients were followed up for evidence of leaking and bleeding manifestations.
Results: Out of 170 patients 28.1% patients had bleeding manifestations. Bleeding signs were seen on clinical examination in 52.37% of patients. capillary leak was found in the form of Pleural effusion in 35.3%, Ascites in 41.2% and Periorbital edema in 31.2% of patients. Elevated APTT levels were seen in 110(64.7%) patients. Among patients with abnormal APTT platelet transfusion was done in 78.9% of patients, and among those with normal APTT levels platelet transfusion was done in 21.1% of patients.
Conclusions: Our study showed significant correlation between bleeding manifestations and prolonged APTT levels as well as thrombocytopenia with abnormal APTT levels. Study concluded that 21.1% of platelet transfusions could have been prevented considering prolonged APTT as a predictor of bleeding manifestation, thus saving the resources and reactions due to platelet concentrate transfusion.

Keywords: APTT in dengue, APTT vs Dengue, Early prediction of bleeding, Platelet transfusion in Dengue, Severity in Dengue, Thrombocytopenia

INTRODUCTION

Dengue is a systemic viral infection transmitted by mosquitoes. Dengue virus infection is a major health concern in India. It is one of the most prevalent severe infections among in patients in many hospital settings. Peak incidence occurred during the months of July and August when this study was carried out.

Dengue Fever (DF) is characterized by fever, headache, muscle or joint pain, and rash.[1] The spectrum of dengue virus infection spreads from an undifferentiated fever and dengue fever (DF) to dengue haemorrhagic fever (DHF)

with shock and expanded dengue syndrome. The hallmark of DHF is plasma leakage, this may lead to shock.[1] Dengue virus is a mosquito-borne Flavivirus that is transmitted by mosquitoes such as Aedes aegypti or Aedes albopictus.[2] Both DF and DHF could have bleeding manifestations. Many factors play a part in the pathogenesis of bleeding manifestations in dengue including coagulopathy which results in derangement of activated partial thromboplastin time (APTT) and the international normalised ratio (INR).[3]

Mechanisms of bleeding in dengue infection are vasculopathy, thrombocytopenia, coagulopathy, and disseminated intravascular coagulation (DIC).[4] objective of the study was to measure APTT levels in dengue virus infection and to identify the role of APTT in comparison with thrombocytopenia as an indicator of bleeding manifestation to assess the real need of platelet transfusions.

METHODS

A prospective study was conducted from June to December in 2017 in medicine ward, R L Jalappa Hospital. Patients aged above 18 years with febrile thrombocytopenia who are positive for dengue virus serology (NS1Ag and/or IgM) were included in the study. Patients with underlying cirrhosis, bleeding disorder, on anticoagulant therapy and febrile thrombocytopenia patients who are negative for dengue serology were excluded from the study. A written informed consent was obtained from each patient. Ethical clearance was obtained from the central ethical review committee of Sri Devraj URS Medical College.

Blood sampling was done on patients with febrile thrombocytopenia to analyse for Dengue serology (Ns1Ag and IgM). Serial daily monitoring of platelet count and analysis of APTT levels were done. For this study APTT was considered abnormal if it was more than 33.8s. Patients were followed up during their stay in the hospital for clinical progression and for evidence of leaking and bleeding manifestations.

Platelet concentrate transfusion were done in patients with bleeding manifestations and also among those with severe thrombocytopenia in view of impending bleeding risk. During the study none of the patients developed adverse reactions to platelet transfusion.

Data was entered into Microsoft excel and cleaning and coding the data was transferred into statistical program for social sciences software (SPSS). Categorical data was represented in the form of frequencies and proportions. Chi square was used as test of significance for categorical data. Continuous data was represented in the form of mean and SD. Student T test was used as test of significance for categorical data. A probability value (p value) <0.05 will be considered statistically significant.

RESULTS

During the study period 170 patients with thrombocytopenia who are positive for dengue virus serology by ELISA method were recruited of whom 103 (60.6%) were Male and 67 (39.4%) were female. Out of 170 patients 88 (51.8%) had headache, 51 (30%) had Myalgia, 8 (4.7%) rashes, and 22 (12.9%) joint pain as major clinical features (Table 1).

Table 1: Clinical features among study participants.

Clinical features	Present	Absent
Headache	88 (51.8%)	82 (48.2%)
Myalgia	51 (30%)	119 (70%)
Rashes	8(4.7%)	162 (95.3%)
Joint pain	22(12.9%)	148 (87.1%)

Daily assessment and history were elicited to look for evidence of bleeding manifestations. Out of 170 study participants, 28.1% patients had bleeding manifestations in the form of epistaxis in 3.5%, haematemesis in 2.4%, bleeding gums in 7.6%, hematuria in 0.6%, malena in 14.1% of patients (Table 2).

Table 2: Incidence of various bleeding manifestations among study participants.

Bleeding manifestations	Present	Absent
Epistaxis	6 (3.5%)	164 (96.5%)
Haematemesis	4 (2.4%)	166 (97.6%)
Haemoptysis	0(0%)	170 (100%)
Bleeding gums	13(7.6%)	157 (92.4%)
Hematuria	1(0.6%)	169(99.4%)
Malena	24(14.1%)	146(85.9%)

Bleeding signs were looked for everyday by thorough clinical examination. Bleeding signs were seen in 52.37% of patients. most common bleeding sign observed was palatal haemorrhages which were seen in 21.8% of study participants. Followed by conjunctival haemorrhage in 6.47% of patients. Petechae was observed in 5.9% of study participants (Table 3).

Table 3: Evidence of bleeding signs on clinical examination in study participants.

Bleeding signs	Present	Absent
Petechae	10 (5.9%)	160 (94.1%)
Palatal haemorrhage	37 (21.8%)	133 (78.2%)
Conjunctival haemorrhage	11(6.47%)	159 (93.53%)

Capillary leak, a common and severe manifestation in dengue virus infection was screened for among study participants on daily basis based on clinical examination

and investigations like abdominal ultrasonography and chest radiography. Most common manifestation of capillary leak leading to fluid collection in third space was Ascites, which was seen in 41.2% of study participants. Ascites was most commonly seen in mild to moderate grade. Next common manifestation of capillary leak was pleural effusion which was bilateral and transudative and was seen in 35.3% of study participants. Periorbital edema was noticed on daily clinical examination in 31.2 % of patients (Table 4).

Table 4: Evidence of capillary leak among study participants.

Capillary leak	Present	Absent
Pleural effusion	60 (35.3%)	110 (64.7%)
Ascites	70 (41.2%)	100 (58.8%)
Periorbital edema	53(31.2%)	117 (68.8%)

Daily platelet count estimation was done from the day of onset of fever among study participants and were followed up. The degree of thrombocytopenia was graded based on platelet count as shown in Table 5. Patients with severe Thrombocytopenia were closely monitored for evidence of any bleeding manifestations. Platelet transfusion was considered in patients with severe thrombocytopenia and among patients with severe bleeding manifestations regardless of platelet count.

APTT levels were measured among study participants to look for coagulation derangement, laboratory Reference control level was 33.8sec. Any APTT level which was above this control value was considered as prolonged APTT.

APTT level was prolonged in 64.7% of study participants and 35.3% patients had normal APTT levels within the laboratory control range (Table 6). Mean elevated APTT level among study participants was 38sec.

Table 5: Serial daily platelet count among study participants.

Thrombocytopenia	Day 1	Day 2	Day 3	Day 4	Day 5
Mild (<50.000-100000)	12 (7.1%)	10 (5.9%)	17 (10%)	26 (15.3%)	44 (25.9%)
Moderate (20.000-50.000)	53 (31.1%)	48 (28.2%)	61 (35.9%)	79 (46.5%)	79 (46.5%)
Severe (<20.000)	102 (60%)	109 (64.1%)	87 (51.2%)	54 (31.8%)	19 (11.2%)
Normal (>1.00000)	3 (1.8%)	3 (1.8%)	5 (2.9%)	11 (6.5%)	28 (16.5%)

Table 6: APTT levels among study participants.

APTT	Frequency	Percent
Abnormal(>33.8sec)	110	64.7
Normal	60	35.3
Total	170	100.0

Among patients with prolonged APTT levels platelet transfusion was done in 78.9% of patients, and among those with normal APTT levels platelet transfusion was done in 21.1% of patients without evidence of bleeding manifestation in view of severe thrombocytopenia and suspecting impending severe bleeding manifestations (Table 7). APTT levels were prolonged in 64.7% patients among which bleeding manifestation was seen in 57.27% patients, 51.8% of patients with prolonged APTT levels received platelet concentrate transfusion. 35.4% patients had APTT levels within the control range and among them 48.43% patients had bleeding manifestation. 44.53% patients with normal APTT levels received platelet transfusion (Table 8).

Table 7: APTT levels and platelet concentrate transfusion.

APTT	Platelet transfusion		Total
	Yes	No	
Abnormal	45	65	110
	78.9%	57.5%	64.7%
Normal	12	48	60
	21.1%	42.5%	35.3%
Total	57	113	170
	100.0%	100.0%	100.0%

Table 8: Correlation of APTT levels, thrombocytopenia with bleeding manifestations and platelet transfusion.

		Bleeding		Total	Platelet transfusion		Total
		Yes	No		Yes	No	
APTT (>33.8 sec)	Count	63	47	110	57	53	110
	%	57.27	42.72	100	51.81	48.18	100
Thromboytopenia (<50000)	Count	62	66	128	57	71	128
	%	48.43	51.56	100	44.53	55.46	100

Around 21.1% of patients with normal APTT levels without any evidence of bleeding manifestations received platelet transfusion in view of impending bleeding risk due to thrombocytopenia.

DISCUSSION

Bleeding manifestations are an important clinical feature in Dengue fever. Abnormal haemostasis and plasma leakage are the main pathophysiological hall marks in DHF.[5] All clinical presentations of dengue are manifested by capillary leakage, impairment of coagulation profile and organ involvement.[6] When the signs of coagulopathy and plasma leakage are developed it is considered as severe dengue which is a potentially deadly combination.[7] Most commonly bleeding manifestations are attributed to low platelet count. But a significant proportion of bleeding manifestations are due to the presence of coagulopathy associated with dengue fever. Coagulopathy is indicated by prolongation of activated partial thromboplastin time, which is altered during a limited time during course of the disease. Thrombocytopenia is universal in DHF and is one of the criteria considered by the World Health Organization (WHO) for clinical case definition of dengue fever.[8]

In dengue haemorrhagic fever and dengue shock syndrome, there is an increase in vascular permeability that leads to leakage of plasma mainly from capillary bed into the extra-vascular compartments, resulting in polyserositis and ultimately haemoconcentration and hypotension.

In our study including 170 patients, elevated APTT was seen in 64% of patients of which 57% had bleeding manifestation. Platelet transfusion was done in 51.8% of patients with elevated APTT levels. Normal APTT and without any evidence of bleeding manifestation was seen in 35.3% of patients, among which 21.1% of patients received platelet transfusion in view of low platelet count despite the absence of bleeding manifestation.

In addition to thrombocytopenia, coagulopathy as indicated by prolonged APTT levels is also one of the important indicators of bleeding manifestations in dengue fever patients.[9] Vascular alteration is the principal factor involved in dengue severity.[10] This study showed a significant correlation between prolonged APTT levels and bleeding manifestations.

CONCLUSION

Our study showed significant correlation between bleeding manifestations and prolonged APTT levels as well as thrombocytopenia with abnormal APTT levels in dengue fever patients. Our study concluded that 21.1% of platelet transfusions could have been prevented considering prolonged APTT as a predictor of bleeding manifestation, thus saving the resources and reactions due to platelet concentrate transfusion.

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