

## To Investigate the Relationship Between Common Bleeding Symptoms in Dengue and Platelet Levels

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### Abstract

**Background:** Dengue is an infectious disease caused by dengue virus (DENV). In general, dengue is a self-limiting acute febrile illness followed by a phase of critical defervescence, in which patients may improve or progress to a severe form. Severe illness is characterized by hemodynamic disturbances, increased vascular permeability, hypovolemia, hypotension, and shock. Thrombocytopenia and platelet dysfunction are common in both cases and are related to the clinical outcome. **Objective:** To study the common bleeding manifestations in dengue and see whether there is a correlation between them and platelet counts. **Method:** A prospective observational study was conducted in Upgraded Department of Pediatrics, Patna Medical College and Hospital, Patna, Bihar from Jan 2020 to January 2021. Children below the age of 14 years with dengue seropositivity were included in the study. Relevant blood investigations were done, and patients were managed according to World Health Organisation guidelines. **Results:** A total of 200 serologically positive dengue cases, with mean age of  $8.5 \pm 4.1$  years, were included in the study. Males were 53% and females 47%. Other than fever, which was present in all cases, the most common presenting complaints were vomiting (26%), headache (10%), black coloured stool (6%) and bleeding (5%). During the course of the illness, bleeding occurred in 60% of the children. Whilst 26% had melaena, 20% had petechiae, 8% had hematemesis, 4% had epistaxis and 2% had gum bleeding. All (100%) the patients who had platelet counts between 50,001-100,000/cu.mm developed haemorrhage and 89.8% of patients with platelet range between 20,001-50,000/cu.mm of blood had developed haemorrhage. However, of patients who had platelet counts less than 20,000/cu.mm, 35.1% developed haemorrhage and 52.6% did not have haemorrhagic manifestations. **Conclusions:** No correlation was found between platelet counts <100,000/cu mm and increase in incidence of bleeding manifestations in DHF.

**Keywords:** Dengue, Platelet, Bleeding.

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## Introduction

Dengue viruses (DENVs) are the most important human arboviruses worldwide and are transmitted by mosquitoes of the genus *Aedes* in the form of four distinct serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). Dengue causes serious infection in humans, resulting in morbidity and mortality in most tropical and subtropical areas of the world. It is estimated that there are currently 50–100 million cases of dengue every year worldwide, including more than 500,000 reported cases of dengue hemorrhagic fever and dengue shock syndrome (DHF/DSS)[1].

All dengue serotypes are capable of causing disease with a wide spectrum of clinical manifestations, ranging from an undifferentiated fever in a mild clinical form classically known as dengue fever (DF) to the severe clinical and potentially fatal DHF/DSS [2]. Initial symptoms are common to all patients, but the clinical manifestations of the severe forms rapidly evolve with symptoms including high fever, liver enlargement, circulatory failure (hypotension and shock), edema cavity (pleural, abdominal, and cardiac) and internal bleeding phenomena. The severe forms are primarily characterized by plasma leakage and thrombocytopenia with or without hemorrhage. The World Health Organization (WHO) classified the clinical presentations of DHF into four severity grades based on laboratory data: Grade I: fever with positive tourniquet test; Grade II: plus mild spontaneous bleeding; Grade III: presence of weak and rapid pulse; and Grade IV: profound shock with undetectable pulse. The last two are considered DSS [3].

Many dengue fever cases are self-limiting, but the complications, such as haemorrhage and shock can be life threatening [4]. Dengue haemorrhagic fever (DHF) ranks high among the newly emerging infectious diseases of public health significance and is the most important of the arthropod borne

viral diseases [5]. Approximately 2.5 billion people live in dengue-risk regions with about 100 million new cases each year worldwide [6].

### Methodology:

A prospective observational study was conducted in Upgraded Department of Pediatrics, Patna Medical College and Hospital, Patna, Bihar from January 2020 to January 2021 on children less than 14 years of age who were seropositive for dengue.

### The inclusion criteria were as follows:

- Seropositivity for any one or all of NS1Ag, IgM and IgG antibodies for dengue.
- An acute febrile illness lasting for 2-7 days.

### The exclusion criteria were as follows:

- All subjects seronegative for NS1Ag, IgM and IgG antibodies for dengue.
- Subjects with a history of bleeding disorders of other aetiology such as immune thrombocytopenic purpura, haemophilia etc.

The first 200 seropositive children who fulfilled the inclusion criteria were included in the study. Detailed demographic data, clinical history, physical examination findings and relevant baseline investigations (haemoglobin level, total leucocyte and differential count, platelet count, packed cell volume) were recorded as per pre-designed proforma. The children were managed as per World Health Organisation (WHO) guidelines [6]. The cases were followed up daily for the clinical and laboratory parameters till they were discharged. Haemoglobin level, platelet count and packed cell volume were done at least once per day and at more frequent intervals in children admitted to the paediatric intensive care unit (PICU). Prothrombin time (PT) activated partial thromboplastin time (APTT), international normalised ratio (INR), aspartate aminotransferase (AST), alanine

aminotransferase (ALT) and serum albumin were done as and when needed. Chest x-ray and ultrasonogram (USG) of abdomen were done to see capillary leak whenever needed. Widal test, test for malaria parasite, blood urea, serum creatinine, etc. were done when the clinical history and symptoms prompted us to do the same for diagnosis and management.

### Results:

A total of 200 serologically positive dengue cases, with mean age of  $8.5 \pm 4.1$  years,

were included in the study. Males were 53% and females 47%. Other than fever, which was present in all cases, the most common presenting complaints were vomiting (26%), headache (10%), black coloured stool (6%) and bleeding (5%). During the course of the illness, bleeding occurred in 60% of the children. Whilst 26% had melaena, 20% had petechiae, 8% had hematemesis, 4% had epistaxis and 2% had gum bleeding. None of the children with bleeding had received non-steroidal anti-inflammatory drugs (NSAIDS)

**Table 1: Comparison of mean haemoglobin, PCV and platelet counts on admission and during bleeding**

| Parameter                  | On admission | During bleeding |
|----------------------------|--------------|-----------------|
| Haemoglobin (g/dl)         | 12.43        | 6.98            |
| PCV                        | 41.5         | 26.51           |
| Platelet count (per cu mm) | 40865        | 15982           |

**Table 2: Relationship between shock and platelet counts**

| Shock | Platelet count per cu mm |                            |                            | Total Number (%) |
|-------|--------------------------|----------------------------|----------------------------|------------------|
|       | <20,000 Number (%)       | 20,000 – 50,000 Number (%) | 50,001- 100,000 Number (%) |                  |
| Yes   | 04 (08.0)                | 08 (09.3)                  | 10 (15.6)                  | 22 (11.0)        |
| No    | 46 (92.0)                | 78 (90.7)                  | 54 (84.4)                  | 178 (89.0)       |
| Total | 50 (100.0)               | 86 (100.0)                 | 64 (100.0)                 | 100 (100.0)      |

Among the bleeding children, mean AST was 124.2 IU/L (normal 1-55 IU/L), mean ALT 37.6 IU/L (normal 5-45 IU/L), mean PT  $23.597 \pm 15.654$  seconds (normal range 13.5 to 100 seconds), mean APTT  $45 \pm 16.2$  seconds (normal range 30.8 to 100 seconds) and the mean INR was 3.01. Signs of capillary leak were observed in 69% of

children and 11% had experienced shock. Whilst 20% and 18% of patients respectively developed signs of capillary leak on day 4 and day 5 of illness, 13% developed signs of capillary leak on day 6 of illness.

Range of onset of capillary leak was between 2nd and 8th day (Mean=4.7).

**Table 3: Relationship between haemorrhage and platelet counts during course of illness**

| Haemorrhage | Platelet count per cu mm |                          |                           | Total Number (%) |
|-------------|--------------------------|--------------------------|---------------------------|------------------|
|             | <20,000 Number (%)       | 20,000–50,000 Number (%) | 50,001-100,000 Number (%) |                  |
| Yes         | 56 (41.8)                | 64 (95.8)                | 18 (100.0)                | 120 (60.0)       |
| No          | 78 (58.2)                | 02 (04.2)                | 00                        | 48 (40.0)        |
| Total       | 134 (100.0)              | 48 (100.0)               | 18 (100.0)                | 200 (100.0)      |

**Table 4: Relationship between the bleeding pattern and platelet counts during course of illness**

| Bleeding     | Platelet count per cu mm |                          |                           | Total Number (%) |
|--------------|--------------------------|--------------------------|---------------------------|------------------|
|              | <20,000 Number (%)       | 20,000–50,000 Number (%) | 50,001-100,000 Number (%) |                  |
| No bleeding  | 78 (58.2)                | 02 (04.2)                | 00                        | 80 (40.0)        |
| Melaena      | 26 (19.4)                | 16 (33.3)                | 10 (55.6)                 | 52 (26.0)        |
| Haematemesis | 06 (04.5)                | 08 (16.7)                | 02 (11.1)                 | 16 (08.0)        |
| Petechiae    | 18 (13.4)                | 16 (33.3)                | 06 (33.3)                 | 40 (20.0)        |
| Epistaxis    | 02 (01.5)                | 06 (12.5)                | 00                        | 08 (04.0)        |
| Gum bleeding | 04 (03.0)                | 00                       | 00                        | 04 (02.0)        |
| Total        | 134 (100.0)              | 48 (100.0)               | 18 (100.0)                | 200 (100.0)      |

**Discussion:**

Thrombocytopenia has always been one of the criteria used by WHO guidelines as a potential indicator of clinical severity [7]. In the most recent 2009 WHO guidelines, the definitions generally describe a rapid decline in platelet count, or a platelet count less than 150,000 per microliter of blood [8]. Most clinical guidelines recommend that platelet transfusions be given to patients who develop serious hemorrhagic manifestations or have very low platelet counts, platelet counts falling below  $10-20 \times 10^9 L^{-1}$  without hemorrhage or  $50 \times 10^9 L^{-1}$  with bleeding or hemorrhage. The efficacy of platelet transfusions is controversial. In a study of 106 pediatric patients with DSS with thrombocytopenia and coagulopathy, there was no significant difference in hemorrhage between patients who received preventive transfusions compared to those who did not. Patients who received transfusion had a higher frequency of pulmonary edema and increased length of hospitalization [9]. Platelet transfusion did not prevent the development of severe bleeding or shorten the time to bleeding cessation and was associated with significant side effects. Thus, according to the authors, platelet transfusions should not be routinely performed in the management of dengue [10, 11].

In our study bleeding occurred in 58% of patients, 34% having gastrointestinal (GI)

bleeding (26% melaena, 8% haematemesis), 20% having petechiae, 4% having epistaxis and 2% having gum bleeding. Our study is similar to that of Ahmed MM [12], who found haematemesis in 19%, gum bleeds in 16%, epistaxis in 12%, melaena in 8% and sub conjunctival haemorrhage in 4%. It is also similar to a study by Ratageri et al. [13] where GI bleeds were seen in 22% and petechiae in 18%. However, a study done by Kishore et al., [14] showed haemorrhage into skin (purpura, petechiae or ecchymoses) as the commonest manifestation of bleeding (17%).

In our study platelet counts less than 100,000 per cu mm were present in all dengue patients. A study by Kulkarni et al. [5], revealed thrombocytopenia in 84% of children with dengue and a study by Ahmed MM [12] revealed thrombocytopenia was seen in 68.5% dengue patients. However, in a study by Banerjee et al [15], thrombocytopenia was seen in only 19% dengue patients. In our study, 9% of patients had platelet counts between 50,000-100,000 /cu. mm, 24% had platelet counts between 20,000-50,000/cu.mm and 67% had platelet counts less than 20,000/cu.mm. In a study by Malavige et al [17], 24.2% had platelet counts between 50,000-100,000/cu mm, 46% had platelet counts between 20,000-50,000/cu mm and 30% had platelet counts less than 20,000/cu.mm. In a study by Kamath et al. [16],

62.3% had platelet counts less than 50,000/cu.mm.

Our observations were similar those of Joshi et al. [18], Sunil Gomber et al [20], and Dhooria et al [21] who also found poor correlation between thrombocytopenia and bleeding manifestations. No correlation was found between reducing trend of platelet count and increase in incidence of bleeding manifestations indicating that abnormal platelet aggregation or disseminated intravascular coagulation may have a role in bleeding in DHF cases rather than reduction in absolute numbers as the cause of bleeding manifestations. However, a study by Narayanan et al [19], showed that bleeding has a correlation to platelet count only when it is less than 50,000/cu.mm of blood.

#### Conclusion:

Thrombocytopenia, coagulopathy, and vasculopathy are hematological abnormalities related to platelet and endothelial dysfunction generally observed in severe dengue. Among the causes and consequences, previous data have suggested an imbalance between clotting versus fibrinolysis systems as DIC. In a minority of patients with severe or prolonged shock, the abnormalities may be profound and, in combination with severe thrombocytopenia and the secondary effects of hypoxia and acidosis, may result in true DIC and major hemorrhage.

In 58.5% of children with primary dengue; petechiae, epistaxis, gingival bleeding were the common bleeding manifestations, whereas in 61% children with secondary dengue melaena and haematemeses were the common bleeding manifestations.

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