THROMBOCYTOPENIA AND PLATELET TRANSFUSIONS
IN CLINICALLY SUSPECTED DENGUE HAEMORRHAGIC
FEVER AND DENGUE SHOCK SYNDROME

Alex Chairulfatah, MD¹
Djatnika Setiabudi, MD¹
Ridad Agoes, MD²
Marc van Sprundel, MD, PhD³
Robert Colebunders, MD, PhD⁴

1. The Department of Childhealth, Padjadjaran University Medical School, JL. Pasteur 38, Bandung 40161, Indonesia; Email : bikarshs@bdg.centrin.net.id
2. The Department of Parasitology, Padjadjaran University Medical School, JL. Pasteur 38, Bandung 40161, Indonesia; Email : bikarshs@bdg.centrin.net.id
3. The Department of Epidemiology and Community Medicine, University of Antwerp, Universiteitsplein 1, B - 2610 Antwerp, Belgium; + 32 3 820 25 22, Email : vsprund@uia.ua.ac.be
4. The Departement of Clinical Sciences, Institute of Tropical Medicine and University of Antwerp, Nationalestraat 155, B – 2000 Antwerp, Belgium; +32 3 247 64 26, +32 3 247 64 32, Email : bcoleb@itg.be

Keywords : Dengue Haemorrhagic Fever, Dengue Shock Syndrome, thrombocytopenia, platelet transfusions.

Correspondence : R. Colebunders
Institute of Tropical Medicine
Nationalestraat 155
B-2000 Antwerp, Belgium
☎ +32 3 2476426 - ☏ +32 3 2476432 - Email : bcoleb@itg.be
Abstract

The presence of thrombocytopenia was determined in 1300 patients with clinically suspected Dengue Haemorrhagic Fever (DHF) (1198; 92%) and Dengue Shock Syndrome (DSS) (102; 8%), admitted to 4 major hospitals in Bandung, Indonesia. A dengue serological test was performed on 1100 (85%) of the 1300 patients. In 763 (69%) of them evidence was found of a present or previous Dengue infection. Of all clinically diagnosed DHF/DSS patients, thromocyte counts of less than 100.000/µl were present in 445 of 1300 (34%) patients on admission and in 637 (49%) during hospitalization. Severe bleeding was recorded in 76 (6%) of all 1300 clinically suspected DHF/DSS cases and occurred more often in patients with severe thrombocytopenia. One hundred and fifty six (12%) of all clinically suspected DHF/DSS cases received a platelet transfusion, among them only 30 (19%) had a platelet count below 25.000/µl. No difference in the frequency of bleeding was observed comparing patients who received or did not receive a platelet transfusion (even in those with a platelet count < 25.000/µl).

In conclusion, a relatively large number of patients with clinically suspected DHF/DSS in Bandung Hospitals receive platelet transfusions, even if thromocyte counts are above 25.000/µl. This study suggests that in most DHF/DSS cases platelet transfusions do not influence the incidence of severe bleeding in DHF/DSS cases. Treatment costs for DHF/DSS cases could be reduced if these unnecessary platelet transfusions were not given.

Keywords: Dengue haemorrhagic fever, Dengue shock syndrome, Thrombocytopenia, Platelet transfusions, Indonesia
Introduction

The clinical diagnosis of Dengue Haemorrhagic Fever (DHF), especially in the early phase of illness is not easy. Laboratory findings suggesting DHF, such as thrombocytopenia and a rising haematocrit, are usually only observed by day 3 or 4 of the illness (WHO, 1997). The pathogenesis of haemorrhage in Dengue is only partly understood (Boonpucknavig, 1979; Natth, 1989; Halstead, 1992), but is related to a combination of factors: including thrombocytopenia, coagulopathy and vasculopathy of uncertain nature. Thrombocytopenia < 100.000/µl is considered as one of the criteria of the World Health Organization (WHO) case definition of DHF (WHO, 1997).

The use of platelet transfusions in DHF/DSS patients remains controversial. In a recent study in India platelet transfusions were only given in DHF patients with spontaneous bleeding and platelet counts < 50.000/µl; prophylactic platelet transfusions were used when platelet counts were < 25.000/µl (Wali, 1999). In general prophylactic platelet transfusions are considered to be indicated if thrombocyte counts drop < 10.000/µl (Heckman, 1997). However, physicians often do not follow these guidelines. In a study carried out in a pediatric institute in Malaysia it was found that in 18.5 % of the platelet transfusions, the indications for these transfusions were inappropriate (Jamal, 1998). One of the aims of our study was to evaluate whether this was also the case in Bandung, Indonesia.

Methods

This retrospective study is part of a DHF/DSS hospital based surveillance study, which was carried out in Bandung. Included as clinically suspected DHF/ DSS cases were all patients with a DHF/DSS diagnosis on admission and discharge, according to the opinion of the attending physician.

The medical records of clinically suspected DHF/DSS patients, hospitalized from April 1994 until June 1995 in four major hospitals in Bandung, Indonesia, the Dr. Hasan
Sadikin General Hospital (HSH), the St. Boromeus Hospital (SBH), the Immanuel Hospital (IH) and the St. Yusuf Hospital (SYH), were reviewed. Recorded were: the age of the patients, duration of fever before admission, result of the dengue serological test, platelet count on admission and during hospitalization, the presence of severe bleeding manifestations and the date of the onset of the bleeding, the administration of platelet transfusions and the date of the transfusions. Severe bleeding manifestations included haematemesis, melena, haematemesis-melena, and disseminated intravascular coagulation (DIC). Since epistaxis is commonly observed during febrile illness, epistaxis was not used as a criteria of severe bleeding, except if it was massive.

Dengue serological tests included the haemaglutination inhibition (H.I.) test, using the Clarke and Cassal microtechnic modification (Clark and Casals 1958), the IgG dengue blot (GeneLab, Kalbe) and the IgM dengue blot test (GeneLab, Kalbe) (Chan, 1990). The H.I. test was performed on paired sera, the IgG and IgM dengue blot tests were performed on acute sera only.

**Statistical analysis**

The $X^2$ analysis for trend by the Mantel Extension Method was used for comparison between each level and the first level of the variable. The Pearson $X^2$-test was performed on a 2-way frequency table to test for a difference between 2 variables. The calculated p-values were Yates-corrected. For all analysis a p-value lower than 0.05 was considered significant. Statistics were performed using EPI-INFO 6.

**Results**

Of the 1348 cases diagnosed as DHF/DSS patients on admission, 1300 patients were still considered clinically suspected DHF/DSS cases upon discharge. In the other 48 patients the discharge diagnoses included measles, typhoid fever, and fever of unknown origin. Of the clinically suspected dengue cases, 1198 (92%) were considered to have
DHF and 102 (8%) DSS; 673 (52%) were male and 627 (48%) female. The mean age of the patients was 13 years (Table 1).

For 168 cases (13%) there was no information about the duration of the fever in the medical records. Where information was available, 673 (66%) had 3-5 days of fever prior to admission. Seventy-one DSS patients (70%) developed shock after 3 to 5 days of fever, most of them were admitted in shock, only 2 patients (2%) developed shock during hospitalization.

A dengue serological test was performed on the sera of 1100 patients (85%). This gave a positive result in 763 patients (69%), including a positive H.I. test in 243 patients (22%), a positive IgG dengue blot test in 489 patients (44%) and a positive IgM dengue blot test in 25 patients (2.3%). A negative IgG dengue blot result was observed in 45 of 72 children (62%) under 6 years of age.

Of all clinically suspected DHF/DSS patients a thrombocytopenia less than 100.000/µl was present in 445 cases (34%) on admission and in 637 cases (49%) during hospitalization. Among DHF cases thrombocytopenia less than 100.000/µl was present in 561 (47%) of them and among DSS cases in 76 (74%) of them. The majority of cases developed thrombocytopenia less than 100.000/µl between the third and seventh day of illness with no difference between DHF and DSS cases.

Severe bleeding was recorded in 76 of all the 1300 clinically suspected DHF/DSS cases (6%) and included haematemesis on its own in 44 of them (58%), melena on its own in 16 of them (21%), both haematemesis-melena in 12 of them (16%) and DIC in 4 of the cases (5%). Severe bleeding occurred more often in patients with severe thrombocytopenia < 25.000/µl ($X^2$ trend = 51,406, $p<0.001$) (Table 3). Such bleeding was particularly frequent in patients with a thrombocyte count < 15.000/µl (occurred in 5 (36%) of the 14 patients).
One hundred and fifty-six (12%) of all 1300 clinically suspected DHF/DSS cases: 152 with a thrombocyte count of less than 100,000/µl and 4 with a thrombocyte count of more than 100,000/µl, received a platelet transfusion. No difference in the frequency of bleeding was observed comparing patients who received or did not receive a platelet transfusion (even in those with a platelet count < 25,000/µl) (Table 4). Only 30 (19%) of those who received a platelet transfusion had a thrombocyte count below 25,000/µl.

Seventeen of the 1248 clinically suspected DHF/DSS cases, for which follow-up data were available, died (1%), 8 (47%) within 24 hours and 9 (53%) more than 24 hours after admission. The fatality rate of the 48 cases, discharged against medical advice and the 4 cases, transferred to other hospitals, could not be traced.

Discussion

DHF is a major health problem in Indonesia. Bandung is one of the big cities in Indonesia where DHF is endemic. In this study the majority of DHF cases were children, with the largest proportion in the age group of 6 – 10 year olds (table 1).

Early in the infection, it may be difficult to differentiate DHF from other febrile illnesses. Later, usually after three or four days, when thrombocytopenia and haemoconcentration are present, DHF is easier to diagnose. In this study, 432 Dengue cases (42%) were admitted before day four of their illness. In a high number of cases 200 (15%) of the 1300 cases with a clinical diagnosis of DHF on admission, a Dengue serological test was not performed. Of the remaining 1100 patients serological evidence of a present or previous dengue infection was found in 763 (58.7%) of them. Ideally to confirm a diagnosis of dengue you need to perform either HI tests or IgG tests on paired sera or an IgM test or an Antigen test/viral culture on acute sera. Because of the difficulties however to confirm outside a research setting all DHF and DSS cases, we included in this
study all clinically suspected DHF and DSS cases according to the opinion of the attending physicians.

Similar to other studies thrombocytopenia was found in the majority of clinically suspected DHF/DSS cases between day three and day seven after the onset of fever (most often day five) (WHO 1997; Chairulfatah et al. 1996; Sugianto et al. 1994). Severe bleeding occurred significantly more often in patients with more severe thrombocytopenia. In this study a similar percentage of patients developed severe bleeding whether or not they received a platelet transfusion. Platelet transfusions are generally only beneficial to patients with platelets below 25,000/µl. The number of patients in this category may have been too small to detect significant differences in the incidence of bleeding. To clearly define the role of platelet transfusions in patients with DHF/DSS a randomized clinical trial should be performed.

In conclusion, a large number of patients with clinically suspected DHF/DSS in Bandung hospitals receive platelet transfusions, even if thrombocyte counts are above 25,000/µl. This study suggests that the majority of these platelet transfusions did not prevent subsequent bleeding. Treatment costs for DHF/DSS cases could be reduced if these unnecessary platelet transfusions were not given.
Acknowledgements

This study was made possible with the financial support from the Belgian Ministry of Development Cooperation (ABOS), as part of an Interuniversity Program of Cooperation between the Flemish Interuniversity Council (VLIR) and the Padjadjaran University, Bandung, Indonesia.
References


Table 1: Number of clinically suspected Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) cases by age and sex

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>8</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>2-5</td>
<td>78</td>
<td>79</td>
<td>157</td>
</tr>
<tr>
<td>6-10</td>
<td>161</td>
<td>166</td>
<td>327</td>
</tr>
<tr>
<td>11-14</td>
<td>111</td>
<td>98</td>
<td>209</td>
</tr>
<tr>
<td>15-20</td>
<td>105</td>
<td>84</td>
<td>189</td>
</tr>
<tr>
<td>21-30</td>
<td>115</td>
<td>126</td>
<td>241</td>
</tr>
<tr>
<td>31-40</td>
<td>55</td>
<td>46</td>
<td>101</td>
</tr>
<tr>
<td>41-50</td>
<td>26</td>
<td>19</td>
<td>45</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>14</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>673</td>
<td>627</td>
<td>1300</td>
</tr>
</tbody>
</table>
Table 2: The degree of thrombocytopenia and the presence of severe bleeding in clinically suspected DHF/DSS cases

<table>
<thead>
<tr>
<th>Platelet count (000)</th>
<th>Total n</th>
<th>DIC</th>
<th>H</th>
<th>M</th>
<th>H-M</th>
<th>n</th>
<th>%</th>
<th>OR*</th>
<th>95% CI</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>59</td>
<td>-</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>11</td>
<td>18.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-49</td>
<td>164</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>16</td>
<td>9.8</td>
<td>0.55</td>
<td>0.21-1.09</td>
<td>0.1</td>
</tr>
<tr>
<td>50-74</td>
<td>205</td>
<td>1</td>
<td>14</td>
<td>3</td>
<td>5</td>
<td>23</td>
<td>11.2</td>
<td>0.45</td>
<td>0.25-1.21</td>
<td>0.1</td>
</tr>
<tr>
<td>75-100</td>
<td>209</td>
<td>1</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>17</td>
<td>8.1</td>
<td>0.39</td>
<td>0.17-0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;100</td>
<td>663</td>
<td>-</td>
<td>8</td>
<td>-</td>
<td>1</td>
<td>9</td>
<td>1.3</td>
<td>0.06</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>1300</td>
<td>4</td>
<td>44</td>
<td>16</td>
<td>12</td>
<td>76</td>
<td>5.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DIC : Disseminated Intravascular Coagulation
H : Haematemesis
M : Melena
H-M : Haematemesis – Melena
*
: comparison X²-test (Yates corrected)
Table 3: Bleeding in clinically suspected DHF/DSS cases with or without a prophylactic platelet transfusion

<table>
<thead>
<tr>
<th>Platelet count (000)</th>
<th>YES</th>
<th>NO</th>
<th>OR</th>
<th>95% CI</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n</td>
<td>n</td>
<td>%</td>
<td>Total n</td>
<td>N</td>
</tr>
<tr>
<td>&lt;25</td>
<td>23</td>
<td>3</td>
<td>13</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>25-49</td>
<td>62</td>
<td>2</td>
<td>3</td>
<td>102</td>
<td>14</td>
</tr>
<tr>
<td>50-74</td>
<td>31</td>
<td>1</td>
<td>3</td>
<td>174</td>
<td>22</td>
</tr>
<tr>
<td>75-100</td>
<td>13</td>
<td>1</td>
<td>8</td>
<td>196</td>
<td>16</td>
</tr>
<tr>
<td>&gt;100</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>661</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>131</td>
<td>7</td>
<td>5</td>
<td>1169</td>
<td>69*</td>
</tr>
</tbody>
</table>

* 25 of these patients received also a platelet transfusion but after the onset of the bleeding
** comparison X²-test (Yates corrected)