TRANSFUSION REQUIREMENTS IN PATIENTS WITH DENGUE HEMORRHAGIC FEVER

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Abstract. Dengue viruses are endemic in Thailand and Southeast Asian countries. A retrospective study of 175 patients with dengue virus infection admitted at the Department of Pediatrics, Ramathibodi Hospital in 1997 was carried out. Fifteen and 160 patients were clinically diagnosed with dengue fever and dengue hemorrhagic fever (DHF), respectively. DHF was commonly found in patients whose ages ranged from 10 to 14 years. The mean body weight was at the 54th percentile for age. In the management, 10.6% of patients with DHF required blood component therapy which included platelet concentrate (64.7%) in patients who exhibited active bleeding, packed red cells (47%) in patients who exhibited a rapid drop in the hematocrit and fresh frozen plasma (29.4%) in patients with circulatory failure who did not respond to intravenous fluid. The transfusion requirement was significantly correlated with the occurrence of bleeding ($p < 0.008$) and bleeding in the gastrointestinal tract ($p < 0.0001$) but not correlated with the number of platelet counts ($p = 0.207$). As a result, physicians in charge should be aware of the transfusion requirement and communicate this to the blood bank in advance for the preparation of appropriate blood components.

INTRODUCTION

Dengue infection has been identified as a clinical entity since 1780 (Rush, 1989). Clinical descriptions of an 1897 Australian outbreak reported 30 children died (Hare, 1898). The dengue virus, which is endemic in Southeast Asian countries is mosquito-borne by the *Aedes aegypti* and *Aedes albopictus*. It has been identified among four types, I to IV (Halstead, 1990). Infection by the dengue virus may result in the mild manifestation of dengue fever or the serious manifestation of dengue hemorrhagic fever (DHF). The two major serious problems in the management of DHF are peripheral circulatory failure and bleeding. In severe cases of circulatory failure, the volume expander of plasma or plasma substitutes should be added and in cases of massive bleeding, platelet concentrate should be given.

We conducted a retrospective study to determine the transfusion requirements among patients with dengue infection admitted to the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Bangkok in 1997.

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MATERIALS AND METHODS

Patients

One hundred and seventy-five patients (90 males, 85 females) were enrolled in the study. The diagnostic criteria of dengue infection depend upon the clinical manifestations and laboratory tests. Dengue fever is characterized by fever, malaise, headache, retroorbital pain and myalgia. Platelet counts are normal. The diagnosis of DHF depends upon the following (WHO, 1986): (1) high fever for 2 to 7 days (2) hemorrhagic manifestations such as a positive tourniquet test or bleeding at other sites (3) thrombocytopenia, platelet counts 100,000 / μl or less (4) increased vascular permeability, which is indicated by the presence of pleural effusion or hemoconcentration (increased hematocrit more than 20%). The clinical manifestations of DHF are defined by febrile, toxic and convalescent stages.

The severity of DHF is classified into 4 grades (Nimmanitya *et al*, 1969): grade I, undifferentiated fever, the only hemorrhagic manifestation is a positive tourniquet test; grade II, bleeding phenomena such as spontaneous petechiae, ecchymoses, epistaxis or gastrointestinal hemorrhage and there is no association with hypotension; grade III, circulatory failure is manifested by rapid and weak pulse with the narrowing of the pulse pressure (20

torr or less) and/or hypotension; and grade IV, profound shock, weak and rapid pulse, no measurable blood pressure and/or massive hemorrhage.

The patients with dengue infection received management according to the guidelines of the Department of Pediatrics, Ramathibodi Hospital (Pongpanich *et al*, 1980). Those with dengue fever, or DHF, grade I or II, and exhibited dehydration, received fluid replacement therapy. Those with grade III or IV DHF received half or full strength normal saline in 5% dextrose solution at a rapid rate of 10 to 20 ml/kg/hour for 1 to 2 hours. In severe cases of circulatory failure, other volume expanders such as plasma or plasma substitutes must be added. However, the total fluid administered per day should not exceed the maintenance plus 5 to 10% of the deficit. Packed red cells were transfused in patients who manifested a rapid drop in the hematocrit. In cases of active bleeding or bleeding in vital organs, platelet concentrate, prepared from either single donor or multiple donors, was given in the dose of 0.2 to 0.4 U/kg bw.

Methods

The complete blood count, coagulogram, fibrin degradation products, and serological confirmation of dengue infection were performed by the standard methods.

Statistics

The association between two variables was calculated by chi-square test; a p-value of less than 0.05 was considered a statistically significant difference.

RESULTS

The retrospective study was conducted in 175 patients whose ages ranged from 9 months to 16 years and 5 months with a mean of 9 years and 6 months. Most of the patients (54%) were in the age group of 10 to 14 years. Patients with dengue infection were found all year round but its prevalence was particularly high during August to December. The patients stayed in Bangkok (84.6%) and other provinces nearby Bangkok (15.4%). Most of them were hospitalized at the febrile stage with a mean duration of fever for 4.6 days. Fifteen and 160 patients were clinically diagnosed with dengue fever and DHF, respectively. The severity of DHF was classified into 4 grades: grade I, 48 cases; grade II, 69 cases; grade III, 25 cases and grade IV, 18 cases. The tourniquet test was found positive in 25 out of 26 tested patients. The serological results were confirmed in 16 tested patients. One-fourth of them (46/175=26%) exhibited rash in the convalescent stage. The mean body weight was at the 54^{th} percentile for age. The patients whose body weight exceeded the 50^{th} percentile for age had a higher chance to develop grade III or IV DHF than those with lesser body weight ($p = 0.039$) (Table 1).

The patients with dengue fever manifested a benign syndrome but those with DHF manifested more serious clinical manifestations. Hemorrhagic manifestations were found in 88 cases of DHF (50.2%) as shown in Table 2. Two-thirds of the patients had bleeding at a single site while one-third had bleeding at two to three sites. Three patients exhibited menorrhagia, which required hormonal therapy. Replacement therapy of blood components was given to 17 out of 160 patients with DHF (10.6%) as shown in Table 3. Nine patients were classified as grade III or IV while the rest were classified as grade II. All except two patients with beta thalassemia/HbE disease and G6PD deficiency, exhibited bleeding episodes commonly found in the gastrointestinal tract. The required blood component included platelet concentrate (11/17=64.7%) in patients who exhibited active bleeding, packed red cells (8/17=47%) in patients who exhibited a rapid drop in the hematocrit and fresh frozen plasma (5/17=29.4%) in patients with circulatory failure, who did not respond to the intravenous fluid. The platelet concentrate was mainly prepared from random donors while packed red cells were prepared by conventional methods without reducing the contaminated white blood cells, by inverted centrifugation or leukocyte filter except in one patient with beta thalassemia/HbE disease. Although an extensive amount of blood component was used for exchange transfusion and plasmapheresis was carried out in two patients with profound shock complicated by liver failure and disseminated intravascular coagulation, both of them died. The case-fatality rate was 1.14% (2/175).

The transfusion requirement was significantly correlated with the occurrence of bleeding ($p < 0.008$) and bleeding in the gastrointestinal tract ($p < 0.0001$). The mean number of platelets decreased in the more severe patients as follows: grade I, 78,020 /μl; grade II, 66,527 /μl; grade III, 55,687 /μl and grade IV, 44,937 /μl without any

Table 1
Body weight expressed by percentile for age and the different grades of spacing not appropriate too wide dengue hemorrhagic fever.

Body weight (percentile)	Grade I and II		Grade III and IV	
	No.	%	No.	%
< 25	29	76.3	9	23.7
> 25 – 50	37	86	6	13.9
> 50 – 75	15	55.6	12	44.4
> 75	35	67.3	17	32.7

Table 2
Hemorrhagic manifestations found in 88 patients with dengue hemorrhagic fever.

Manifestations	%
Petechiae	37.9
Epistaxis	31.5
Hematemesis	11.2
Melena	9.2
Gums, teeth	4.6
Menorrhagia	2.8
Ecchymosis	1.9
Retina	0.9

statistical difference. The occurrence of bleeding was not correlated with the number of platelets ($p = 0.207$): patients with marked thrombocytopenia did not bleed but those with moderate thrombocytopenia had acute bleeding.

DISCUSSION

The aim of the management of DHF is to maintain vital organ functions during the critical period. Over- or under-treatment will result in an unfavorable outcome. Close observation by the clinician and constant nursing care are essential for a favorable outcome. If the patient is in full sensorium and has an adequate urine output but the blood pressure is slightly low with a narrow pulse pressure, aggressive fluid replacement therapy should be undertaken with caution. Excessive administration of fluid, plasma or plasma expanders will cause serious respiratory embarrassment. In addition, a rapid rise in blood pressure after circulatory collapse may aggrevate bleeding by a sudden increased blood flow to the area of vascular damage such as gastric mucosa, although the patient's platelet counts are not markedly decreased.

At present, DHF is commonly found in patients whose ages range from 10 to 14 years. Most of them are healthy with a hypersthenic build. The occurrence of DHF in grade III or IV is more prominent in patients whose body weight exceeds the 50th percentile for age. However, the body weight was measured at the febrile stage of DHF where the extravascular leakage occurred. Even though these were not accurate body weights, they reflected the trend of high body weights in the studied patients. Consequently, the required blood component (which depends upon the body weights) is proportionally increased. For example, the requirement of platelet concentrate in patients with thrombocytopenia and bleeding should be at least 10 Units of platelet concentrate prepared from multiple donors or one unit of single-donor platelet concentrate.

Even though the abnormal hemostasis in DHF includes vasculopathy, thrombocytopenia, platelet dysfunction and coagulopathy (Hathirat *et al*, 1993), 10.6% of the hospitalized patients with DHF in this study required blood component therapy. The transfusion requirement was correlated with the occurrence of bleeding, and bleeding at the gastrointestinal tract, but was not correlated with the number of platelets. Physicians in charge should be aware of the transfusion requirements and communicate this to the blood bank in advance for the preparation of appropriate blood components. Although the blood bank has been routinely screened for various infectious markers, such as VDRL, HBsAg, anti-HCV, anti-HIV and HIV antigen, the recipients are still vulnerable to contract transfusion-transmitted diseases. Transfusion-transmitted AIDS has been reported in a boy with Glanzmann's thrombasthenia who received platelet concentrate prepared from multiple donors

Table 3
Descriptive data of patients receiving replacement therapy.

Age	BW (kg)	Grade of DHF	Bleeding	Laboratory		Blood components			
				Hct (%)	Platelet (/μl)	FFP (ml)	Platelet conc unit	Platelet conc donor	PRC (ml)
12y,9m	46	IV	petechiae, epistaxis	52	24,000	200	-	-	-
10y,8m	44	II	epistaxis, hematemesis, melena	42→34	58,000	-	10	single[d]	-
9y,1m[a]	19	II	-	14.7	36,000	-	-	-	390
11y[b]	106	II	-	48→22	49,000	-	-	-	250
10y,2m[c]	36	II	hematemesis	43→37	98,000	-	10	single[d]	-
11y,11m	34	III	melena	52	23,000	410	-	-	-
10y, 4m	44	III	ecchymosis, melena	40→29	11,200	800	20	multiple	400
13y, 2m	41	II	epistaxis, hematemesis	61	46,000	-	4	multiple	-
14y, 5m	91	III	menorrhagia	35	115,000	-	5	multiple	-
4y	14	III	petechiae	39→27	28,000	-	5	multiple	120
12y	49	II	hematemesis	45	32,000	-	10	multiple	-
12y, 9m	80	II	epistaxis	48	32,000	-	10	multiple	-
14y	45	II	gum and teeth	57	9,000	-	20	multiple	-
2y, 8m	18	III	melena	39	35,000	180	4	-	360
16y, 4m	42	III	melena	27→22	24,000	-	-	-	250
2y, 10m[e]	13	IV	melena	54	56,000	40,400	120	single[d]	6,500
3y[e]	16	IV	melena, hematemesis	41→25	45,000	5,000	34	multiple	5,000

[a] Patient with β-thalassemia/Hb E disease exhibited markedly anemia.
[b] Patient with G6PD deficiency exhibited hemoglobinuria.
[c] Patient with hemophilia B (FIX 2.6%) also received prothrombin complex concentrate 3,000 Units.
[d] One unit of single-donor platelet concentrate is equal to 10 Units of random - donor platelet concentrate.
[e] Patients with profound shock and bleeding received exchange transfusion and plasma exchange.

(Chuansumrit *et al*, 1996). Therefore, the number of blood donors should be minimized as far as possible. If the parent is able to afford single-donor platelet concentrate whose efficacy and safety is better than platelet concentrate prepared from multiple donors, the risk of transfusion-transmitted diseases will be decreased. In addition, the contaminating white blood cells in the packed red cells can induce HLA alloimmunization and non-hemolytic febrile transfusion reaction (Decary *et al*, 1984). If the leukocyte filter is not affordable, inverted centrifugation should be performed in order to reduce the residual white blood cells to 10^8 cells/unit of packed red cells (Kaewkamol *et al*, 1993). The non-hemolytic febrile transfusion reaction and the occurrence of HLA alloimmunization will also be minimized.

In conclusion, patients with DHF who manifested bleeding episodes especially at the gastrointestinal tract, commonly required blood component transfusion. Physicians should be aware when preparing the appropriate blood components in order to achieve a favorable outcome.

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