Journal of Infectious Diseases and Immunity Vol. 3(7), pp. 124-133, July, 2011
Available online at http://www.academicjournals.org/JIDI
ISSN 2141-2375 ©2011 Academic Journals

Full Length Research Paper

A prospective clinical study of incidence of hepatorenal and hematological complications in dengue fever and management of symptomatic bleed in bundelkhand region of Northern India with fresh whole blood

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Accepted 17 June 2011

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. Besides bleeding, cases of hepatic and renal dysfunction in dengue fever are increasing in incidence. In management of hemorrhagic complications, fresh whole blood is far superior to platelet transfusion and fresh frozen plasma. This work is aimed at studying the incidence of hepatorenal and haematological complications and the management of symptomatic bleed with fresh whole blood in dengue fever. A prospective design was carried out with 62 Dengue positive patients either admitted in wards or attending Medicine Out Patient Department of MLB Medical College Jhansi were recruited in this study between 1st January 2010 and 31st December 2010. Patients were assessed for hepatorenal and haematological complications as well as management of symptomatic bleed were also studied. Incidence of jaundice in dengue fever was 15% of which one third cases were of direct hyperbilirubinemia and two third those of indirect hyperbilirubinemia. Serum glutamate pyruvate transaminase (SGPT) was raised in 68% patients while serum glutamate oxaloacetate transaminase (SGOT) was high in 71% patients. Incidence of renal failure in dengue fever was 16% (as per glomerular filtration rate (GRF) levels calculated by modified diet in renal disease formula). The leucopenia was seen in 31% and leucocytosis in 17%. Although the incidence of thrombocytopenia was observed in 92% while bleeding was seen in 32% cases only. All the cases were managed with fresh whole blood transfusion and 100% successful outcome. Incidences of hepatic and renal complications were present in 85 and 39% cases, respectively. Bleeding manifestations were seen in 32% cases, which do not correspond always to platelet counts and respond to fresh whole blood transfusion excellently.

Key words: Dengue fever, hepatorenal dysfunction, haematological complications, thrombocytopenia, whole blood transfusion.

INTRODUCTION

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and from urban to rural settings. An estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries (WHO Geneva, 2008a).

Since 2000, epidemics of dengue have spread to new areas and quantum has increased in the already affected areas of the South East Asia region. In 2003, eight countries namely: Bangladesh, India, Indonesia, Maldives, Myanmar, Sri Lanka, Thailand and Timor-Leste reported dengue cases. In 2004, Bhutan reported the country's first dengue outbreak. In November 2006, Nepal reported indigenous dengue cases for the first

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time. The Democratic Peoples' Republic of Korea is the only country of the South-East Region that has no reports of indigenous dengue. Dengue is not officially reported to World Health Organization (WHO) by countries in the African region. Dengue-like illness has been recorded in Africa though usually without laboratory confirmation and could be due to infection with dengue virus (DEN) or with viruses such as Chikungunya that produce similar clinical symptoms (WHO, Geneva, 2008b).

Dengue in India

India is endemic for dengue infections in various states and union territories which are reporting outbreaks. Highest numbers of dengue cases were reported in 2010, as 25725 cases and 99 deaths till November 2010. Maximum cases were reported from Delhi (6221) followed by Punjab (4022), Kerala (2501), Gujarat (2269) and Karnataka (2177). All the four serotypes have been isolated in India (Baruah and Dhariwal, 2011).

The various serotypes of the DEN are transmitted to humans through the bites of the infected aedes mosquitoes, principally *Aedes aegypti*. This mosquito is a tropical and subtropical species widely distributed around the world, mostly between latitudes 35 degree north and 35 degree south. These geographical limits correspond approximately to a winter isotherm of 10°C. Because of lower temperatures *A. aegypti* is relatively uncommon above 1000 m. The immature stages are found in water filled habitats, mostly in artificial containers closely associated with human dwellings and often indoors. People rather than mosquitoes, rapidly move the virus within and between communities. Dengue outbreaks have also been attributed to aedes albopictus, aedes polynesiensis and several species of the aedes scutellaris complex.

After an incubation period of 4-10 days, infection by any of the four virus serotypes can produce a wide spectrum of illness, although most infections are asymptomatic or subclinical. Primary infection is thought to induce lifelong protective immunity to the infecting serotype. Individuals suffering an infection are protected from clinical illness with a different serotype within 2-3 months of the primary infection but with no long-term cross-protective immunity. Individual risk factors determine the severity of disease and include secondary infection, age, ethnicity and possibly chronic diseases (bronchial asthma, sickle cell anaemia and diabetes mellitus). Young children in particular may be less able than adults to compensate for capillary leakage and are consequently at greater risk of dengue shock.

Complications of dengue infection include hemorrhagic shock, renal dysfunction, liver failure, encephalopathy, and Guillain-Barré syndrome. Although post-dengue infection complications are rare, isolated post-dengue infection phrenic neuropathy and diaphragmatic paralysis have been reported Chien et al. (2008). Hepatic dysfunction is associated with jaundice and encephalopathy. Reye's syndrome has rarely been reported. Macular oedema and haemorrhages and focal chorioretinitis with or without retinal vasculitis are known ocular complications of Dengue fever (Teoha et al., 2006).

Hemophagocytic syndrome in dengue fever can result in multi organ failure and poor prognosis. acute renal failure has been described in dengue hemorrhagic fever (DHF).

Fresh whole blood is better in dengue hemorrhagic fever (DHF)

WHO recommends fresh whole blood in DHF (Wiwanitkit, 2005) since stored blood looses 2,3 di phospho glycerate whose low levels impede the oxygen releasing capacity of Haemoglobin resulting in functional tissue hypoxia; whereas platelet concentrates may exacerbate fluid overload. Fresh whole blood is far more economical as compared to the platelet concentrates and fresh frozen plasma. Easy availability of fresh blood is another important consideration especially in peripheral hospitals where platelet separators are not available.

Our study

Aims and objectives

(1) To study the epidemiological pattern, clinical profile and incidence of hepatorenal and haematological complications in proven cases of Dengue fever;
(2) To study the management of symptomatic bleed with fresh whole blood

MATERIALS AND METHODS

The materials comprises of 80 cases admitted in Medicine Department of Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh-INDIA, from 1st January 2010 to 31st December 2010, with clinical history suggestive of dengue fever and were later on found to be dengue positive on serological testing, that is, enzyme linked immuno sorbent assay for dengue fever IgM positive or IgG positive or non structural antigen positive were studied. 18 cases were excluded on different grounds and final study comprised 62 cases of dengue fever. During their hospital admission, patients were studied for different complications arising because of index event, needed biochemical tests to be done and the data were analyzed in view of the following points:

1. Clinical profile especially in reference to incidence of hepatorenal and haematological complications in Dengue fever.
2. Study the outcome of management of symptomatic bleed with fresh whole blood. All values of biochemical and haematological parameters were taken from Harrison's Principles of Internal Medicine 17th Edition.

RESULTS

Of the total cases, that is, 62 collected in this study, 34% were females and 66% were male. 57% of the cases, that is, 35 are of age group 16-30 years and elderly population (age>65 years) affected by Dengue fever found to be only 3%. Majority of the Dengue fever cases occurred in months of June to August, that is, 83.8% cases.

During first time presentation, generalized body ache was present in 84%, headache in 77%, high grade fever in 73%, joint pain in 42%, symptomatic bleed in 32%, malaise in 27% and apparent jaundice in 15% of the dengue positive cases. Atypical complication seen in dengue fever was ascites in 10% and pleural effusion in 32% (Table 1).

At the time of hospital admission hepatic dysfunction in the form of raised serum bilirubin, that is, >1.3 mg% was present in 15% of cases (n=9) along with elevation of serum transaminases (SGOT and SGPT) in 68 and 71% of the cases (Figures 1, 2, and 3). Severe degree of hepatic dysfunction that is SGOT and SGPT> 200 IU/L were present in 13-16% of total dengue positive cases (Figures 2 and 3).

Renal failure in terms of raised serum creatinine levels (values > 1.2 mg% in males and > 0.9 mg% in females) were found to be high in 61% of the total cases (Table 2). Further on the basis of calculated GFR, it was found that in patients presented with renal dysfunction, mild and moderate degree of renal failure were present in 38 and 16% of the total cases (Table 3). It was found that 21% patients had oliguria (Table 4). In our study, the incidence of hypernatremia was 6% and that of hyponatremia was 38% (Table 5). It was found that the incidence of hyperkalemia was 10% and that of hypokalemia was 19% (Table 6). No case suffered from severe degree of renal failure and all patients of renal failure recovered fully by conservative management.

On analysis of haemoglobin level, anemia was found in 65% of the total cases in males and 62.5% in females (Table 7). Hematocrit level < 40% was present in 63% of male and hematocrit level of 40-45% was present in 17% of the male patients (Table 8). In females, normal hematocrit was present in 31.25% of total cases. In 18.75% of females, the hematocrit was between 35 and 40% and in 50% of the total females; the hematocrit was less than 35% (Table 9).

On analysis of total leukocyte count, leukopenia was found to be in 31% and leukocytosis in 17% of the cases (Table 10). Thrombocytopenia, that is, platelet count less than 150,000/mm^3 were found in 92% of the total cases (Table 11).

But at the time of presentation, symptomatic bleed were present in only 32% of the dengue positive cases, in spite of documented thrombocytopenia in 92% of the total cases (Table 12). In patients of symptomatic bleed, 65% presented with history of melena, 20% as hematuria, 10% as epistaxis, and 5% as hematemesis (Table 13). Treatment of symptomatic bleed by whole fresh blood was done in 32% of the cases, with full recovery in the form of improvement of the clinical features and stoppage of bleeding manifestation (Table 14).

In 10% of the cases, transfusion of fresh whole blood was done due to suspicion of masked bleeding that is, falling haemoglobin and hematocrit levels.

DISCUSSION

In this study, female to male ratio was 1:2.9 which is markedly varied from the 1.86:1 ratio in a study carried out by Yang et al. (2009) in Cixi, Zhejiang province, China in 2009 (WHO Geneva, 2008b). Whereas female to male ratio in a retrospective case control study carried out by Murray Smith et al. (2000) in Charters Towers, Queensland in 1996 was 1.7:1 this was somewhat close to this study.

In this study, the vast majority of patients, that is, 89% were in the age group 16-50 years. Similar findings were reported in a study carried out by Yang et al. (2009) in Cixi, Zhejiang province, China in 2009 (WHO Geneva, 2008b), in which he reported that 78.3% cases were between 20-50 years of age. It means Dengue fever mainly affects working class which is in continuous exposure to mosquito during his/her indoor and outdoor activities.

We found that liver dysfunction was present in the form of jaundice in 15% cases; of which one third cases were of direct hyperbilirubinemia and two third were those of indirect hyperbilirubinemia. Chhinaa et al. (2008) of Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana reported in 2006, the incidence of jaundice in dengue fever to be 19.5%. While Mohan et al. (2000) in the year 2000 reported the incidence of jaundice in dengue fever to be 25%. Incidence of hepatic dysfunction in our study was lower than both of these studies which may be attributed to timely diagnosis and management. On the other hand, Chandrakanta et al. (2008) reported the incidence of jaundice in dengue fever to be 2%. This finding supports our view that timely diagnosis and management may result in decrease incidence of hepatic dysfunction, which is on decreasing trend in recent years.

The rise of serum transaminases in the form of elevated serum levels of SGPT and SGOT were seen in 58% patients and 74% patients respectively. In our study, increased levels of serum bilirubin were noted in a smaller proportion of patients, in accordance with the results of Chhinaa et al. (2008); however described, the incidence of rise in SGOT and SGPT to be 97.7 and 93.9%, respectively. However, in a study by Souza et al. (2004), SGOT and SGPT were deranged only in 63.4 and 45% patients respectively. Mohan et al. (2000) reported the incidence of rise in serum transaminases to be

Table 1. Clinical presentation in dengue cases at the time of hospital admission.

S/N	Symptoms	Number of patients	% (n/62)
1	Bodyache	52	84
2	Headache	48	77
3	High grade fever	45	73
4	Joint pain	26	42
5	Bleeding	20	32
6	Malaise	17	27
7	Jaundice	9	15
8	Mild Pleural effusion	20	32
9	Mild Ascites	6	10

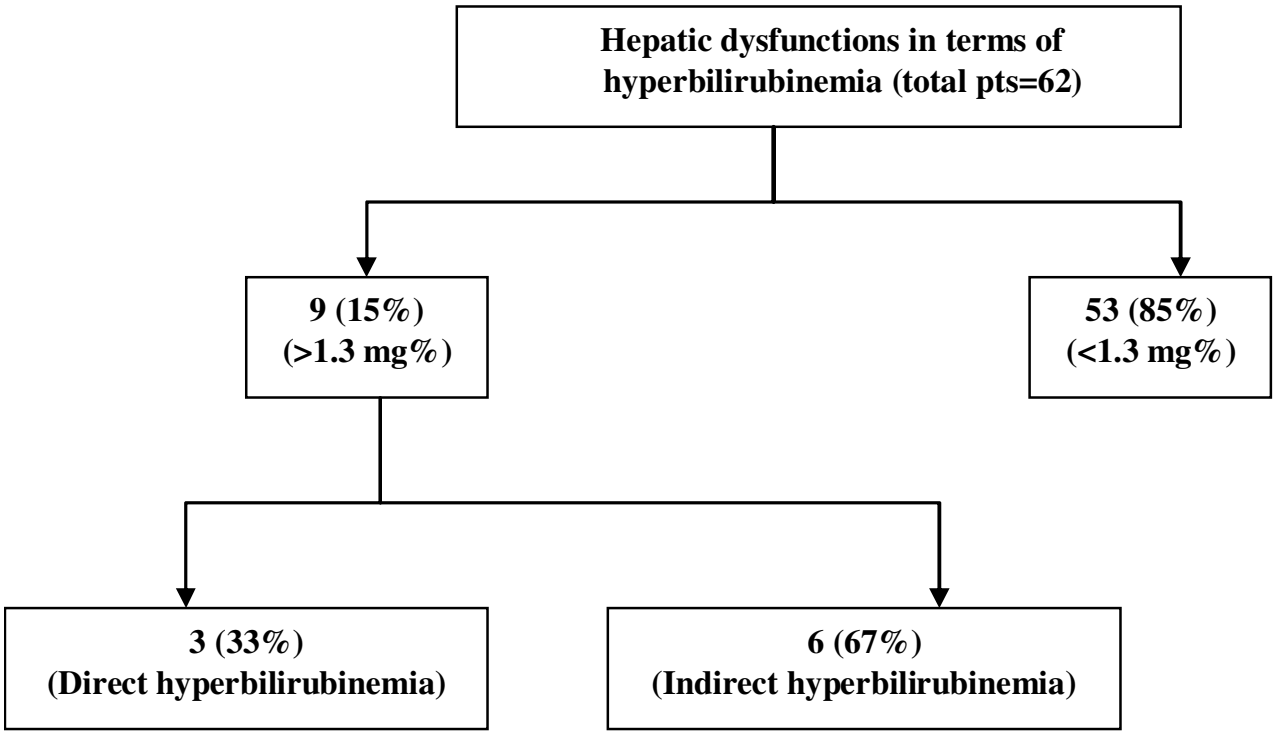

Figure 1. Hepatic dysfunction in dengue fever in terms of hyperbilirubinemia which was present in 15% patients of which one third had direct hyperbilirubinemia and two third indirect hyperbilirubinemia.

between 81-87%.

The SGOT level in dengue infection tends to be greater than SGPT (Souza et al., 2002; Mohan et al., 2000). This differs from the pattern in viral hepatitis but is similar to that seen in alcoholic hepatitis. The exact cause of this is uncertain, but it has been suggested that it may be due to excess release of SGOT from damaged monocytes during dengue infection.

The incidence of renal failure in dengue fever was seen in 16% (as per GFR value calculated by modified diet in renal disease formula) cases. Lee et al in (2009) reported that ARF occurs in 3.3% of patients with DHF. Acute kidney injury (AKI) is a poorly studied complication of DHF. The available information comes from small series of patients or case reports. Futrakul et al. (1973) reported 'mild elevation in serum creatinine' in 43% of 24 DHF cases in Thailand. Tanphaichitr et al. (2002) found one case of 'transient azotemia' and one case of 'acute renal shutdown' among 17 patients with DHF and glucose 6-phosphate dehydrogenase deficiency. Méndez and Gonzáles et al. (2003) found 1.6% of ARF among 617 children with DHF in Colombia. More recently, Lee et al. (2005) reported 4.9% of ARF in 81 Chinese patients suffering from DHF/ Dengue Shock Syndrome and

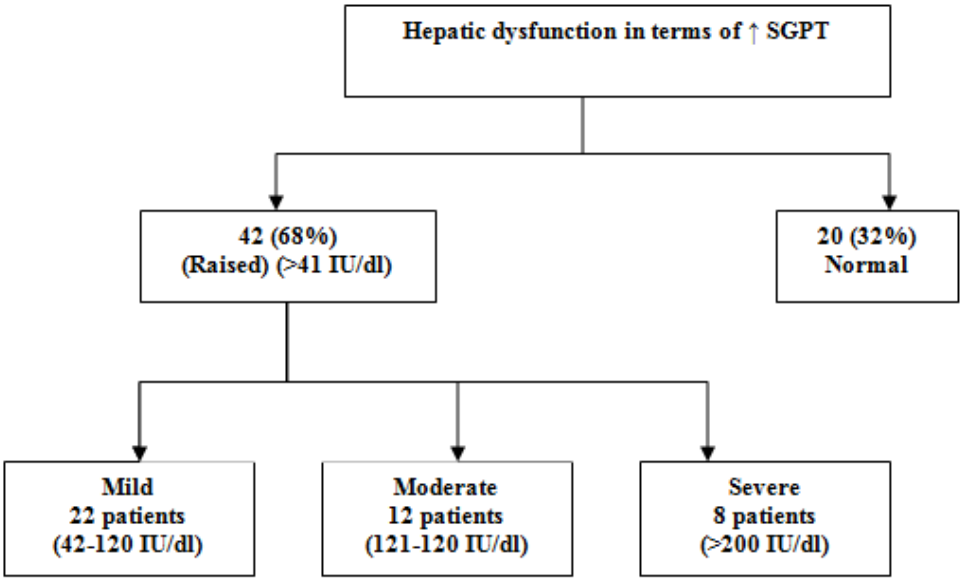

Figure 2. Hepatic dysfunction in terms of increase in SGPT levels which was present in 42 (68%) patients of whom 22 patients had mild elevation, 12 had moderate elevation and 8 had severe elevation in SGPT levels.

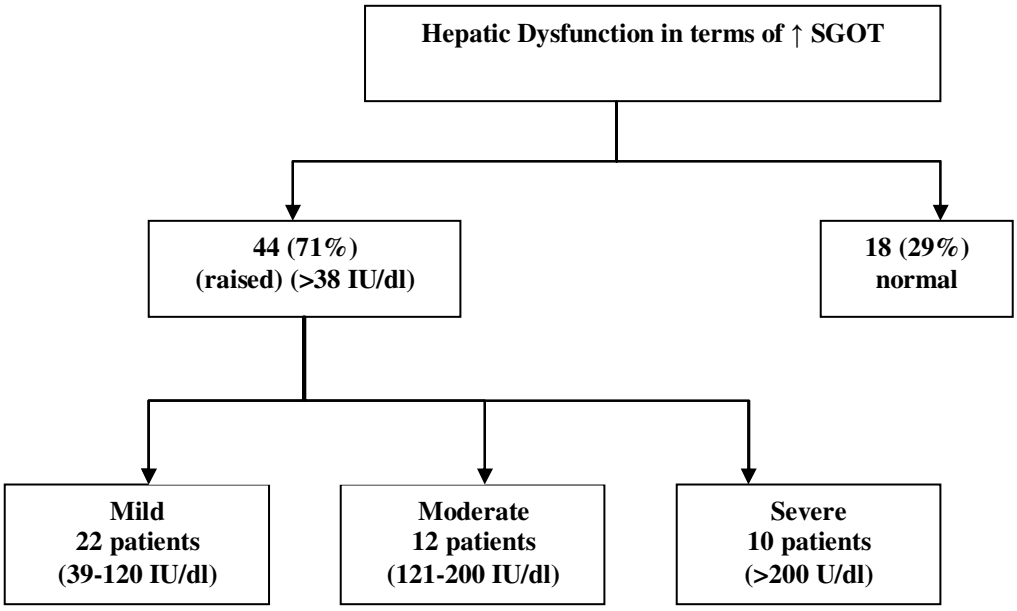

Figure 3. Hepatic dysfunction in terms of elevated SGOT levels which was present in 44 patients (71%) of which 22 patients had mild, 12 patients had moderate and 10 patients had severe elevation in SPOT levels.

Abboud et al. (2007) reported 5% of ARF in DHF. Wiwanitky et al. (2005) revised the literature concerning fatal cases of DHF in Thailand, finding 51 fatalities in a total of 6154 DHF cases. Among these patients, 17 had AKI, yielding a percentage of 33.3% of AKI in the patients who died and a percentage of 0.3% of AKI for all DHF cases (Wiwanitkit, 2005). Besides these series of patients, there are eight cases of AKI reported in patients with dengue fever (Kuo et al., 1992; Wiersinga et al., 2006; Gunasekera et al., 2000; Nair et al., 2005; Wiersinga et al., 2006) and 5 cases reported in DHF or DSS (Radakovic et al., 2002; Chacko et al., 2004; Davis

Table 2. Incidence of renal dysfunction on the basis of raised serum creatinine.

Serum creatinine	Number of patients	% (n/62)
Normal	24	39
Deranged	38	61
	62	

Elevated levels were seen in 61% of the cases. Normal level in males is 0.6-1.2 mg% whereas in females it is 0.5-0.9 mg%.

Table 3. Grading of severity of renal dysfunction on the basis of estimated GFR (modified diet in renal disease formula).

S/N	eGFR	Number of patients (n)	% (n/62)
1	<15	0	0
2	15-30	0	0
3	31-60	10	16
4	61-90	23	38
5	>90	24	38
6	NA	5	8

Mild renal dysfunction was present in 38% and moderate dysfunction was present in 16% of the dengue cases.

Table 4. Incidence of renal dysfunction in terms of oliguria (urine output < 500 ml/day).

Oliguria	Number of patients	% (n/62)
Present	7	11
Absent	55	89
Total patients	62	

11% patients had oliguria that is, urine output less than 500 ml per day.

Table 5. Incidence of disturbance in serum sodium levels.

Serum sodium levels	Number of patients	% (n/62)
Severe hyponatremia (<120 mmol/L)	3	5
Moderate hyponatremia (120-130 mmol/L)	6	10
Mild hyponatremia (131-135 mmol/L)	14	23
Eunatremia (135-145 mmol/L)	35	56
Hypernatremia (>145 mmol/L)	4	6
Total patients	62	

5% patients had severe hyponatremia, 10% had moderate hyponatremia and 23% had mild hyponatremia. 6% patients had hypernatremia.

and Bourke, 2004; Garcia et al., 2006; Karakus et al., 2007).

The incidence of leucopenia was found in 31% while leucocytosis was in 17% only. Lin et al. (1989) reported the incidence of leucopenia to be 76%. Chandrakanta et al. (2008) reported the incidence of thrombocytopenia to be 60% while in our study the incidence of thrombocytopenia was found to be 92%.

In the present study, bleeding occurred in 32% cases. Out of which 65% was presented as having malena, 20% as hematuria, 10% as epistaxis and remaining 5% as hematemesis. Chandrakanta et al. (2008) reported the incidence of bleeding in dengue fever to be 38.8% out of which 23.7% cases had gastrointestinal tract bleeding (61%).

In our study, only fresh whole blood was administered

Table 6. Incidence of disturbance in Serum Potassium levels.

Serum potassium	Number of patients	% (n/62)
Severe hypokalemia (<3 mmol/L)	4	6
Mild hypokalemia (3-3.5 mmol/L)	8	13
Eukalemia (3.5-5.5 mmol/L)	44	71
Hyperkalemia (>5.5 mmol/L)	6	10
Total patients	62	

6% patients had severe hypokalemia and 13% patients had mild hypokalemia. 10% patients had hyperkalemia.

Table 7. Incidence of anemia on the basis of haemoglobin levels.

S/N	Sex	Anemic (n)	% (n/62)	Normal (n)	%	Total
1.	Male	30	65	16	35	46
2.	Female	10	62.5	6	37.5	16

Anemia was seen in 46% of male and 16% of female cases. According to WHO, anemia is defined as Serum haemoglobin below 12 g% in females and below 13 g% in males.

Table 8. Haematocrit distribution in dengue cases (male).

S/N	Hematocrit (%)	Number (n)	% age (n/46)
1	<40	29	63
2	40-45	8	17
3	>45	9	20

Table 9. Haematocrit distribution in dengue cases (female).

S/N	Hematocrit (%)	Number (n)	% age (n/16)
1	<35	8	50
2	35-40	3	18.75
3	>40	5	31.25

Table 10. Total leukocyte count in dengue patients.

S/N	TLC (/cu mm)	Number of patients (n)	% (n/62)
1	<3540	19	31
2	3541-9060	32	52
3	>9060	11	17

Leukopenia was seen in 31 and 52% cases.

as per the current WHO guidelines (WHO Geneva, 2008a). We transfused fresh whole blood in 32% cases that bled and additionally, in 10% non bleeding cases with low hematocrit. Fresh whole blood transfusion was associated with 100% successful outcome. Prophylactic platelet transfusion was not given to any patient. Chairulfatah et al. (2003) concluded that most DHF/DSS cases, platelet transfusions do not influence the incidence of severe bleeding. Treatment costs for DHF/ DSS cases could be reduced if these unnecessary platelet transfusions are avoided (Chairulfatah et al., 2003). Lum et al. (2003) similarly concluded that

Table 11. Platelet level in dengue cases.

S/N	Platelet (/cu mm)	Number of patients(n)	%(n/62)
1	<165000	57	92
2	>165000	5	8

Normal value is 165000-415000 cells/cu mm.

Table 12. Incidence of symptomatic bleed in dengue cases.

S/N	Bleeding symptoms	Number of patients	% (n/62)
1	Bleeding	20	32
2	Asymptomatic	42	68

Symptomatic bleed was seen in 32% of cases.

Table 13. Types of symptomatic bleed in dengue cases.

S/N	Form of bleeding	Number of patients (n)	% (n/20)
1	Malena	13	65
2	Hematuria	4	20
3	Epistaxis	2	10
4	Hematemesis	1	5
Total		20	100

Majority of the cases were presented with malena.

Table 14. Treatment of symptomatic bleed by fresh whole blood.

S/N	Indication of BT	Number of patients (n)	% (n/62)	Outcome (bleeding stopped)
1	Symptomatic bleed	20	32	Yes
2	Other reasons (severe anemia or fall in PCV)	6	10	Yes
Total		26		

prophylactic platelet transfusions had no role in management of dengue fever.

DHF is a severe form of the disease characterized by fever, haemorrhagic phenomenon, thrombocytopenia and evidence of plasma leakage (increased haematocrit, pleural effusion, ascites and hypoalbuminaemia). DHF usually occurs in secondary dengue infections, although it may follow primary infections, particularly in infants (Malavige et al., 2004). In Southeast Asia, DHF affects predominantly in children, whereas in America, all age groups are involved (Guzman and Kouri, 2002; Gibbons and Vaughn, 2002; Fonseca and Fonseca, 2002). The differential diagnosis for DHF includes malaria, leptospirosis, hantavirus infection, typhoid fever, human immune virus (HIV), enteroviral infection, influenza and sepsis, as well as autoimmune disorders as polymyositis, dermatomyositis and vasculitis (Gibbons and Vaughn 2002; Malavige et al., 2004). In particular, leptospirosis and hantavirus infection may mimic DHF in almost all aspects, including renal injury and renal histology (Lement et al., 2007; Keyaerts et al., 2004).

In a study conducted in 2003 by Mendez et al. (2003) which states that prophylactic platelet transfusions for severe thrombocytopaenia in otherwise haemodynamically stable patients has not been shown to be effective and is not necessary. The incidence of pleural effusion in our study was 32% while that of ascites was 10%. Thulkar et al. (1999) reported the incidence of pleural effusion and ascites in grade III DHF to be 53 and 15%, respectively.

Conclusion

Dengue fever is the most rapidly spreading mosquito born viral disease. India is endemic for dengue infections

and various states/union territories are reporting outbreaks with maximum reported cases in Delhi that is 6221 in 2010. The clinical spectrum of disease is broad and ranges in severity from mild symptoms to death. It mainly affects adult age group with severe hepatic and renal dysfunction. About 1/3 cases presented with DHF, in which transfusion of whole fresh blood was found to have 100% successful outcome in the present study.

ACKNOWLEDGEMENTS

We acknowledge Professor Dr Ganesh Kumar, Principal and Dean, MLB Medical College, Jhansi, UP-India for helping us in publication of this article and providing adequate facilities for working on this study. The authors are highly thankful to the Residents of Postgraduate Department of Medicine, MLB Medical College, Jhansi, UP-India, for their ever tiring hard work for working on this study. We thank Mr Praveen Srivastava, computer assistant, for keeping the autonomic database.

Abbreviation: WHO, World Health Organization; **DEN,** dengue virus; **DHF,** dengue hemorrhagic fever; **DSS,** dengue shock syndrome; **ARF,** acute renal failure; **AKI,** acute kidney injury; **GFR,** glomerular filtration rate; **SGOT,** serum glutamate oxaloacetate transaminase; **SGPT,** serum glutamate pyruvate transaminase.

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