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Original Article

Dengue hemorrhagic fever: Clinical efficacy of vitamin K

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ABSTRACT

Background: At present dengue is the most significant viral infection affecting public health and survival. Bleeding in dengue due to many reasons can cause significant anemia and death. Elevation of prothrombin time (PT) in dengue points to liver failure and consequent bleeding. **Objective:** Ability of vitamin K to stop bleeding in dengue hemorrhagic fever (DHF) is examined in this study. **Methods:** It is a retrospective review of medical records of children admitted with confirmed and clinical DHF. Children in the age group of 1 month to 15 years from June to November of 2015 at the Institute of Child Health, Niloufer Hospital, Hyderabad, were included in the study. WHO guidelines were used to define clinical and confirmed DHF cases. Cessation of bleeding within 24 h of vitamin K administration without recurrence was taken as clinical evidence of efficacy of vitamin K. **Results:** Of the 100 patients with confirmed DHF, 26 met the inclusion criteria, and of the 133 clinical DHF, 27 met the inclusion criteria. The presentation of bleeding in decreasing order of frequency was malena, epistaxis, hematuria, hematemesis, gum bleed, ecchymoses, and hematochezia. Deranged PT was seen in nearly 100% of the patients, and hepatomegaly was seen in 77% patients, while thrombocytopenia was seen in 80% patients. Clinical response to vitamin K was seen in 80.8% of confirmed (95% confidence interval [CI]: 60-92.7%) and 92.6% of clinical DHF (95% CI: 74.2-98.7%). **Conclusions:** In the study group, presentation of bleeding suggests coagulation failure as the main contributor to bleeding rather than thrombocytopenia. Overall response rate to vitamin K was 86.8% (95% CI: 74-94%). Early institution of vitamin K in DHF may prevent anemia, and reduce the need for transfusions.

Key words: *Clinical efficacy, Dengue hemorrhagic fever, Prothrombin time-international normalized ratio, Thrombocytopenia, Vitamin K*

At present dengue is the most rapidly spreading arthropod-borne viral disease of human beings with significant morbidity and mortality. Dengue viral infection is mostly asymptomatic, but in some, it produces a wide spectrum of clinical manifestations. All the four virus serotypes were found producing epidemics in India [1]. Coagulopathy associated with dengue fever is well observed, but unfortunately, underlying mechanisms still remain unclear. Thrombocytopenia is unlikely to produce spontaneous bleeding in dengue. Thrombocytopenia associated with coagulopathy increases the severity of hemorrhage.

The listed causes of bleeding in dengue hemorrhagic fever (DHF) are abnormal coagulation profile, thrombocytopenia, platelet dysfunction, prothrombin complex deficiency secondary to liver involvement, endothelial injury, prolonged aPTT and disseminated intravascular coagulation (decrease in fibrinogen level, increased level of fibrinogen degradation product, increased level of D-Dimer, consumptive coagulopathy, activation of mononuclear phagocytes), sequestration of platelets, acidosis, hemorrhagic gastritis, and ulceration. Bleeding may present as spontaneous bleeding in skin, black tarry stool, epistaxis, gum bleed, hematuria, hematemesis, intracranial bleed, and increase in menstrual flow. Packed cell transfusion/fresh frozen plasma (FFP) along with platelets may be required in cases of severe bleeding with coagulopathy. In some patients, the aspartate aminotransferase/alanine aminotransferase level may be very high and prothrombin time (PT) may be prolonged. If PT is prolonged intravenous vitamin K1 may be initiated in such conditions [1]. In bleeding if HCT is low or not rising, blood transfusion and vitamin K1 intravenously should be considered [2].

Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X [3]. If the PT is prolonged by 4-6 seconds or more (international normalized ratio [INR] ≥1.5), and there is any evidence of altered sensorium or INR >2 without encephalopathy, the diagnosis of acute liver failure (ALF) is established. Vitamin K (5-10 mg subcutaneously) should be administered routinely at least once since vitamin K deficiency has been reported in patients with ALF [4,5]. The most common site of bleeding in ALF is from superficial gastric erosions. To a lesser extent bleeding also presents spontaneously from nasopharyngeal, pulmonary, and genitourinary sources [6].

Pharmacodynamic activity of vitamin K is seen in its deficient state only. Its intravenous administration controls hemorrhage

within 3-6 h. A normal prothrombin level may often be obtained in 12-14 h. Repeated large doses of vitamin K are not warranted if the initial response is unsatisfactory. Although a 30-day supply of vitamin K is stored in the normal liver, acutely ill patients can become vitamin K-deficient within 7-10 days [7]. There is no known toxicity associated with large doses of vitamin K1 [8]. PT is an insensitive marker of vitamin K deficiency. Prothrombin must decrease to approximately 50% of normal levels before a change in PT status is noted. Proteins induced by vitamin K absence for factor II (PIVKA-II), a highly sensitive and specific marker is increasingly being used to assess vitamin K status. PIVKA-II values >3 ng/mL are indicative of vitamin K deficiency.

There is a paucity of evidence regarding the efficacy of vitamin K in DHF. Search using words dengue, and vitamin K in PubMed, Cochrane, Index Copernicus, Embase, Lilacs yielded no relevant results. Although WHO included vitamin K in the necessary drugs list for dengue management in its guidelines, routine administration of vitamin K in DHF was not advocated [9]. Vitamin K is advised in hepatic failure and hepatic encephalopathy associated with dengue in few guidelines. Recombinant Factor VIIa has been tried and advocated at some centers [10,11]. However, it is prudent to study the utility of vitamin K in DHF before going for such costly and short-lived therapies. Therefore, we planned this study with an objective to assess the clinical efficacy of vitamin K to control bleeding in children with DHF.

METHODS

It is a retrospective study conducted at the Institute of Child Health, Niloufer Hospital, Hyderabad, from June to November of 2015. Medical records of children from 1 month to 15 years of age admitted with confirmed and clinical DHF were reviewed. Only children having clinical features of dengue with documentation of the status of bleeding before and after the intravenous vitamin K administration were included in the study. Evaluation of the history, physical examination findings and/or full blood count and hematocrit was done. According to the WHO guidelines, patients admitted with clinical features of dengue with negative serological evidence were included in the clinical DHF group. Patients with serological evidence of dengue (positive NS1 antigen and/or anti-dengue IgM, and/or anti-dengue IgG) along with clinical features of DHF were included in the confirmed group.

Patients underwent NS 1 Ag testing with RDT kits at the time of admission while IgM and IgG testing for dengue was done by Alere SD BIOLINE Dengue IgG/IgM rapid immunochromatographic test after 5 days of fever. Records without clinical evidence of dengue, with clinical and laboratory evidence of other causes of bleeding, without serial documentation of bleeding, and with no vitamin K administration were excluded from the study. It is emphasized above that thrombocytopenia alone is not likely to cause bleeding in dengue, and the previous studies mentioned by WHO showed that correction of platelet count with transfusion failed to prevent bleeding. Thus, thrombocytopenia cannot be considered as an independent factor. Hence, cases with bleeding and thrombocytopenia due to dengue were also included in the study. Those who had bleeding and were not tested for PT, were also included if they had other evidence of dengue and no evidence of other cause of bleeding. Clinical and laboratory data from the DHF case records were subjected to statistical analysis with SPSS software.

Based on the pharmacokinetics of vitamin K, cessation of bleeding within 24 h of vitamin K administration without recurrence was taken as clinical evidence of efficacy of vitamin K. Cessation of bleeding as a clinical benefit due to treatment is clinically relevant, sensitive (responsive to change) and is both recognized and used by physicians. Temporal correlation of response to blood products was assessed and wherever vitamin K was independently clinically effective, it was taken as response.

RESULTS

About 26 of the 100 patients with confirmed DHF and 27 of the 133 clinical DHF met the inclusion criteria. In confirmed group, 10 were male, 16 were female, and in clinical group 17 were male, 10 were female. The details of the patients are presented in Table 1.

The presentation of bleeding in the decreasing order of frequency was malena, epistaxis, hematuria, hematemesis, gum bleed, ecchymoses, and hematochezia. 11 children (20.7%) had bleeding from more than one site. Deranged PT-INR (≥1.3) was seen in 96.9% of tested patients (31 of 32 tested) and one child had an INR of 1.28. Hepatomegaly was seen in 77% total patients. Patients were not tested for coagulation after improvement. This makes it difficult to compare parameters from admission to improvement. Thrombocytopenia was seen in 80% of the total patients.

Confirmed DHF patients (n=74) who were not included in the group had a mean hospital admission duration of 4.46±2.15 (Range - 0.5-9 days). Clinical DHF patients (n=106) who were not included in the group had a mean hospital admission duration of 4.53±3.2, (Range - 0.25-27 days). Both these groups had lesser admission duration than the study groups because of patients in the study groups had to stay long due to more significant bleeding. As there are no guidelines yet to give routine vitamin K to DHF, only patients with significant bleeding received vitamin K.

Clinical response to vitamin K was observed in 80.8% of confirmed (95% confidence interval [CI] with continuity correction: 60-92.7%) and 92.6% of clinical DHF (95% CI with continuity correction: 74.2-98.7%).

DISCUSSION

In the study group, presentations of bleeding suggest coagulation failure as the main contributor to bleeding than the thrombocytopenia. Elevated PT suggests that liver dysfunction is the major contributor to bleeding. At our institute, FFP could not be given 6 hourly or as an infusion and bleeding continued in spite of 1 or 2 infusions of FFP. Two such children responded to vitamin K. As thrombocytopenia was not the main cause of

Table 1: Observations in children with DHF who received vitamin K

Observation	Confirmed DHF (n=26)	Clinical DHF (n=27)
	n (%) or positive/tested	n (%) or positive/tested
Fever	26	26
Mean±SD	5.35±1.81	4.35±3.17
Vomiting	18 (69.2)	14 (51.8)
Malena	18 (69.2)	16 (59.2)
Epistaxis	8 (30.8)	5 (18.5)
Hematuria	3 (11.5)	4 (14.8)
Gum bleed	1 (3.8)	0
Ecchymoses	0	1 (3.7)
Hematemesis	0	2 (7.4)
Red stools	0	1 (3.7)
Petechiae	1 (3.8)	1 (3.7)
>1 site of bleeding	8 (30.8)	3 (11.1)
Jaundice	1 (3.8)	1 (3.7)
Hepatomegaly	24 (92.3)	17 (62.9)
Liver tenderness	18 (69.2)	10 (37)
Hypotension	21 (80.8)	17 (63)
Thrombocytopenia	24 (92.3)	18 (66.6)
High PCV	6 (23)	9 (33.3)
Leucopenia	5 (19.2)	4 (14.8)
Hyperbilirubinemia	2/6	1/7
Elevated AST	1/2	
Elevated ALT (range)	4/4 (129-2790)	2/3 (233-479)
Elevated PT (INR≥1.3)	14/14	17/18
PT-INR 1.3-2	6	11
PT-INR 2-5	4	3
PT-INR>5	4	3
Hospital stay (days)		
Mean±SD	5.61±2.04	5.31±2.63
Range	3-12	2-11
FFP received	4 (15.4)	1 (3.7)
Platelet transfusion	8 (30.8)	3 (11.1)
PRBC received	2 (7.7)	0
Anemia with CCF	1 (3.8)	0
Vitamin K received	26	27
Response to vitamin K	21 (80.8)	25 (92.6)

FFP: Fresh frozen plasma, DHF: Dengue hemorrhagic fever, PCV: Packed cell volume, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PT: Prothrombin time, INR: International normalized ratio, SD: Standard deviation, PRBC: Packed red blood cells, CCF: Congestive cardiac failure

bleeding, 7 children who continued to bleed in spite of platelet transfusion responded to vitamin K. One child who needed PRBC for anemia due to prolonged bleeding stopped to bleed after vitamin K. Clinical course of the above mentioned 10 patients (18.9%), demonstrates the role of vitamin K in the cessation of bleeding as more likely than the spontaneous recovery from dengue illness. In the rest 36 patients who had cessation of bleeding after vitamin K, the possibility of spontaneous recovery as the cause of cessation of bleeding is difficult to exclude, and this can be answered in a large, well-designed randomized controlled trials. 5 of 7 children who failed to respond to vitamin K, received further transfusions. Of the remaining two children who did not respond to vitamin K, one recovered with spontaneous recovery of platelet count, and another one was taken away against medical advice by parents. Overall response rate to vitamin K was 86.8% (95% CI: 74-94%).

A large body of clinical and experimental evidence points to the involvement of the liver in the pathobiology of dengue virus infections of humans. The balance of evidence suggests that hepatocytes are directly involved as the sites of dengue replication, adding to the total viral burden [12]. In ALF, about 25% can have subclinical vitamin K deficiency, which can be corrected by intravenous vitamin K. In clinical practice, a decrease in PT by 30% following intravenous vitamin K confirms vitamin K deficiency [13]. Failure to observe an increase in circulating levels of the vitamin K-dependent factor VII by 25% after intravenous vitamin K suggests inadequate hepatic synthetic reserve [14]. Response to vitamin K was less in the confirmed group, owing to more severe involvement of liver than the clinical group. Routine use of vitamin K in DHF may control bleeding if liver dysfunction is not very severe. Early institution of vitamin K in DHF may prevent anemia, and reduce the need for transfusions.

High prevalence of anemia in children of developing countries is further burdened by recurrent epidemics of DHF. With this in mind, it may be justified to give at least one dose of vitamin K to all children with DHF at the earliest notice of bleeding as there is no evidence of toxic effects due to vitamin K in children. This response to vitamin K can be observed prospectively by the clinicians while managing DHF. Since the response to vitamin K, if present is not short-lived as in other therapies like FFP, rFVIIa, vitamin K may be considered as the initial priority over these.

If very little is known about a subject, sequence of research designs will efficiently build up reliable information. As cause-effect conclusions in retrospective and observational studies are difficult to arrive at, randomized controlled studies are necessary using serial monitoring of bleeding, vitamin K by high pressure liquid chromatography, PIVKA II estimation, Factor VII, and PT before and after vitamin K administration in children with DHF, which can serve as definite evidence.

CONCLUSIONS

As can be seen, vitamin K is clinically effective in controlling bleeding in DHF. Routine administration of vitamin K to children with DHF at the earliest may reduce the need for blood transfusions and the burden of anemia. For cause-effect conclusion well designed randomized controlled trials using vitamin K administration in DHF, measurement of response to vitamin K with factor VII levels, and serial monitoring of bleeding, coagulation profile, and estimation of vitamin K, and PIVKA II levels are needed.

REFERENCES

1. WHO, Country Office for India. National Guidelines for Clinical Management of Dengue Fever. Geneva: WHO; 2015.
2. Kalayanarooj S. Clinical Manifestations and Management of Dengue/DHF/DSS. Trop Med Health. 2011;39 4 Suppl:83-7.
3. Shearer MJ, Newman P. Recent trends in the metabolism and cell biology of vitamin K with special reference to vitamin K cycling and MK-4 biosynthesis. J Lipid Res. 2014;55(3):345-62.
4. Lee WM, Larson AM, Stravitz RT. AASLD Position Paper: The Management of Acute Liver Failure: Update; 2011.
5. Bhatia V, Bavdekar A, Yach SK. Management of acute liver failure in infants and children: Consensus statement of thepediatric gastroenterology chapter. Indian academy of pediatrics. Indian Pediatr. 2013;50:477-82.
6. Munoz SJ, Stravitz RT, Gabriel DA. Coagulopathy of acute liver failure. Clin Liver Dis. 2009;13(1):95-107.
7. Kasper DL, Braunwald E, Hauser S, Longo DL, Jameson JL, Fauci AS. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw Hill; 2005. p. 683.
8. UK Expert Group on Vitamins and Minerals: Safe Upper Levels for Vitamins and Minerals-May; 2003.
9. WHO. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. 2009 Edition. Geneva: World Health Organization; 2009.
10. Epidemiology Unit, Ministry of Health-Sri Lanka. National Guidelines: Guidelines on Management of Dengue Fever and Dengue Haemorrhagic Fever in Children and Adolescents. November, 2012.
11. Chuansumrita A, Wangruangsatidb S, Chuad YL, Capedinge MR, Bechf OM. Dengue study group. Control of bleeding in children with dengue hemorrhagic fever using recombinant activated factor VII: A randomized double-blind, placebo-controlled study. Blood Coagulation Fibrinolysis. 2005;16:549-55.
12. Smith DR, Khakpoor A. Involvement of the liver in dengue in fections. Dengue Bull. 2009;33:75-86.
13. Ginès P, Kamath PS, Arroyo V. Chronic Liver Failure: Mechanisms and Management. New York: Springer; 2010. p. 65, 460.
14. Cho SM, Murugan R, Al-Khafazi A. Fulminant hepatic failure. In: Vincent JL, Abraham E, Kochanek P, Moore FA, Mitchell PF, editors. Textbook of Critical Care. 6th ed. Philadelphia, PA: Elsevier Health Sciences; 2011. p. 775.

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