SHORT REPORT

VITAMIN K INJECTION IN SPONTANEOUS BLEEDING AND COAGULOPATHY IN SEVERE MALARIA: PROS AND CONS

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Abstract. Not all clinicians give vitamin K to severe malaria patients with systemic bleeding. Vitamin K injections may not be useful to stop bleeding in severe malaria patients with predominant hepatocellular jaundice. However, vitamin K may be justified in bleeding patients who have prolonged fasting of more than 3-7 days, underlying malnutrition, or predominant cholestatic jaundice. The decision to give vitamin K to severe malaria patients with systemic bleeding should be based on underlying diseases, type of jaundice, risk for vitamin K deficiency, and allergy to the drug.

Key words: severe malaria, vitamin K, spontaneous bleeding, coagulopathy

Spontaneous bleeding in severe malaria may come from upper gastrointestinal bleeding, such as seen with gastric erosion or gastritis, but this has declined since the discontinuation of high dose corticosteroids in cerebral malaria. Other overt bleeding continues, including epistaxis, hematuria and hemoglobinuria, hypermenorrhea, and increased postpartum hemorrhage (Wiwanitkit, 2008).

Kochar *et al* (2006) reported that 25.5% of malaria cases had bleeding tendencies. Viscas *et al* (2005) mentioned that bleeding or disseminated intravascular coagulation (DIC) was found in 4.2% of cases imported to the USA. White (2009) found that less than 5% of patients with severe malaria develop clinically significant DIC. The WHO (2006, 2009) recommended the transfusion of screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets if available) and vitamin K injection in spontaneous bleeding and coagulopathy.

The pathogenesis of malarial bleeding includes thrombocytopenia and platelet dysfunction. Abnormal platelet adhesion was reported in malaria (Tandon *et al*, 1991). Cytohaderence and sequestration in capillaries and venules by parasitized and non-parasitized red blood cells causes changes in the deep capillaries of the viscera. An immune reaction, associated with complement activation in malarial infection is believed to contribute to injuries of

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red cells and platelets and promotes DIC development. Rojanasathien *et al* (1992) found most coagulation abnormalities of clotting factors V, VII, and IX are due to liver involvement.

In management of spontaneous bleeding in malaria due to thrombocytopenia, platelet concentrate is recommended. However, in the management of spontaneous bleeding from DIC in severe malaria, apart from specific antimalarial treatment and managing accessible bleeding lesions (*eg*, the use of endoscopy to manage gastric bleeding due to stress ulcers and gastritis), measures to stop consumptive coagulopathy and thrombocytopenia should be attempted, including correcting hypovolemia and shock, metabolic acidosis, and concomitant bacterial sepsis, general supportive management of DIC, including blood component therapy and fibrinolysis inhibitors [*eg*, fresh frozen plasma, cryoprecipitate, recombinant F VIIa, DDAVP (desmopressin), antithrombin III (ATIII) concentrate, antifibrinolytic agents, and platelete concentrate]. In patients with liver failure, vitamin K deficiency may occur and cause bleeding since vitamin K is a cofactor for clotting factors II, VII, IX, X, protein C and protein S. In one African setting, 8% of patients with fulminant liver failure had falciparum malaria as the cause (Mudawi and Yousif, 2007). Vitamin K is lipid soluble. Vitamin K_1 (phylloquinone) is from vegetable and animal sources, and vitamin K_2 (menaquinone) is synthesized by bacterial flora and found in hepatic tissue (Russell and Suter, 2008). Patients who cannot take food, who have malabsorption (biliary tract obstruction or chronic diarrhea), or have been fasting for 3-7 days may have vitamin K deficiency. Moreover patients who are given β-lactam antibiotics which inhibit vitamin K epoxide reductase may also have vitamin K deficiency and possibly contributing to intracranial, gastrointestinal or skin bleeding. Broad-spectrum antibiotic treatment can precipitate vitamin K deficiency by reducing gut bacteria which synthesize menaquinones, and by inhibiting the metabolism of vitamin K. In patients admitted to the ICU who are fasting, on parenteral feeding or who are given β-lactam antibiotics may have vitamin K deficiency by 3-7 days.

The patients may present with ecchymosis, bleeding at puncture sites and elevated prothrombin time and reduced clotting factors. Intravenous injection of vitamin K may correct bleeding and prothrombin time which should become normal in 4-6 hours. However, if a patient has severe bleeding FFP will rapidly stop bleeding. In adult patients in the ICU who are fasting or on antibiotics, vitamin K 10 mg intavenously may be given weekly as bleeding prophylaxis. The serious adverse effects of vitamin K injection include hypotension, trouble breathing, slow heart rate or anaphylaxis, thus injections should be given slowly. Some patients have no previous allergies to this drug since they have never been given vitamin K before. Liver involvement in severe malaria patients is predominantly hepatocellular rather than cholestasis (Wilairatana *et al*, 1994).

In general, hepatocellular disease will not respond to vitamin K due to a defect in gamma-carboxylation (Blanchard *et al*, 1981) and the patients may have no prior vitamin K deficiency before the malarial illness. Therefore, vitamin K injection may not correct bleeding in some severe malaria patients. Heavy parasitemia leading to occlusion of liver microcirculation leads to abnormalities in synthesis and secretion of coagulation factors and their inhibitors.

In severe falciparum malaria, there is activation of the blood coagulation system

along with thrombocytopenia, even before widespread DIC and coagulopathies occur (Ghosh and Shetty, 2008). If patients with severe malaria and bleeding have underlying malnutrition, concomitant intrahepatic obstruction and bile salt excretion defects, injections with vitamin K 10 mg intravenously daily for 3 days may be useful to correct coagulation defects in bleeding patients with elevated prothrombin time >1.5 x normal (Arruda and High, 2008). Some severe malaria patients with shock or unexplained deteriorating conditions (WHO, 2006) may be given broad-spectrum or β-lactam antibiotics as prophylaxis for bacterial sepsis. Vitamin K, in combination with blood component therapy, may be useful if the patients have clinical spontaneous bleeding.

In conclusion, vitamin K injections should not be given to "all" severe malaria patients with spontaneous bleeding. The risks and benefit of vitamin K administration should be considered. Bleeding in severe malaria patients with hepatocellular jaundice may not respond to vitamin K. Vitamin K may be useful and justified in bleeding patients who have prolonged fasting more than 3-7 days, underlying malnutrition, or concomitant obstructive biliary tract diseases.

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