EXCESSIVE FIBRINOLYSIS: THE COAGULOPATHY FOLLOWING MERREM’S HUMP-NOSED VIPER (HYPNALE HYPNALE) BITES

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Abstract. In 56 patients with proven hump-nosed viper (Hypnale hypnale) bites, 12 (21.4%) developed continued oozing of blood from the site of the bite and a prolonged clotting time. Further investigations showed low fibrinogen levels and increased fibrinogen degradation products in plasma. The bleeding time, platelet count, prothrombin time, and partial thromboplastin time with kaolin were normal. The bite of this snake can be complicated with a coagulopathy in which excessive fibrinolysis seems to be the main abnormality.

The hump-nosed viper (Hypnale hypnale) is a snake found in India and Sri Lanka. It is considered to be moderately venomous when compared with the Krait, Russell’s viper, and the cobra. Most bites cause predominantly local effects such as pain and swelling at the site of bite. Hemorrhagic blisters at the site of bite and regional lymphadenopathy occur in a minority of patients. There are conflicting reports on the potential for systemic envenomation by hump-nosed viper bite, and one study of 62 consecutive admissions showed no significant features of systemic toxicity. However, several case reports suggest potential nephrotoxicity of the venom, and two cases of death following hump-nosed viper bite have been reported. Coagulation defects following hump-nosed viper bites are thought to be rare. There are two case reports of this complication in the literature, both of which suggest excessive fibrinolytic activity. This study prospectively investigated hemostatic dysfunction following hump-nosed viper bites.

PATIENTS AND METHODS

A prospective study was performed of all admissions following hump-nosed viper bites admitted to the University Medical Unit at the Colombo North General Hospital in Ragama, Sri Lanka, between August 1995 and July 1996. Only patients who brought the incriminated snake with them to hospital were included in the study. Written informed consent was obtained from the patients to use part of the blood collected for routine testing and for analysis of fibrinogen degradation products. The study was approved by the Ethical Committee of the Faculty of Medicine, University of Kelaniya. After verification of the species of snake, initially by the authors and subsequently by the Department of Parasitology of the University of Kelaniya, patients bitten by the snake were examined for evidence of local envenomation: pain, swelling, hemorrhagic bullae, gangrene at the site of bite, and systemic envenomation. A detailed clinical examination and urine microscopy were performed. Hemoglobin level, white cell count, platelet count, reticulocyte count, erythrocyte sedimentation rate, whole blood clotting time, bleeding time, and levels of serum creatinine, blood urea, and serum electrolytes were determined in all patients. Further hematologic investigations were done on patients who developed oozing of blood from the site of bite or those who had a prolonged whole blood clotting time (> 10 min); prothrombin time, partial thromboplastin time with kaolin (in all except four patients), plasma fibrinogen, and plasma fibrinogen degradation products (in all except two patients). Whole blood clotting time was measured using the bedside test, which involves assessing the time required to clot 3 ml of whole blood collected into a glass tube. The bleeding time was tested using a modified Ivy method by measuring the time of bleeding from a prick to the ear lobe. The prothrombin time was measured using the Thromboerol S (Behring Diagnostics, Frankfurt, Germany) thromboplastin test, and partial thromboplastin with kaolin was measured using the Thrombosol I (Ortho Diagnostic Systems, Raritan, NJ) reagent. Plasma fibrinogen and fibrinogen degradation products (uncross-linked) were measured by an automated analyzer using Human Diagnostics (Taunusstein, Germany) and Sigma Laboratories (St. Louis, MO) test kits, respectively. Patients who had initial evidence of excessive oozing of blood from the site of bite, or who had an abnormal coagulopathy screen test results had the whole blood clotting time determination repeated every 6 hr until it became normal. The patients were treated symptomatically with analgesics (acetaminophen) for pain and antibiotics (intravenous crystalline penicillin or oral erythromycin) when wound infection or cellulitis was suspected. Tetanus toxoid was given on admission to all patients and polyspecific antivenom (Haffkine Laboratories, Bombay, India) was given to the first four patients with the bites, but not to the rest because this has been the common practice in Sri Lanka, and also because no studies proving the lack of an effect were available until recently. However, because of the lack of benefit in the first few patients, this antivenom preparation was not used thereafter.

RESULTS

The total number of snake bite patients admitted to our unit during the one-year study period was 139. In 80 (57.5%), the bite was positively identified. Hump-nosed viper bites accounted for 56 of the 80. Of the patients bitten by a hump-nosed viper, 50 (89.2%) were bitten on the legs, and six (10.7%) were bitten on the hands. A local reaction at the site of bite in the form of swelling developed in all 56 patients. In 40 (71.4%), the swelling was intense, involving more than half of the limb. Digital gangrene requiring amputation of a digit occurred in one patient. Hemorrhagic bullae were observed at the site of bite in 10 (17.8%) patients and oozing of blood from the site of bite was seen in 12 (21.4%) patients. These 12 patients also had prolonged whole blood clotting time as measured by the bedside test.
However, none of them developed clinical evidence of generalized bleeding. None of the 56 patients developed renal or neurologic complications. The results of the routine biochemical tests performed mentioned were normal in all patients. The coagulation profiles of the 12 patients with prolonged whole blood clotting time are shown in Table 1. Fibrinogen degradation products were increased in the 10 of these 12 patients in whom it was tested. Plasma fibrinogen was reduced in seven of the 10 patients. Bleeding time, platelet count, prothrombin time, and partial thromboplastin time with kaolin (done in eight patients) were normal. The time required for the whole blood clotting time to return to normal showed no difference between those treated with antivenom and those not treated.

**DISCUSSION**

The hump-nosed viper is widely distributed in Sri Lanka, being present from coastal areas up to an altitude of 1,250 meters. Its bite accounts for an important proportion of all snake bites in this country. In one study, it was shown to account for 27% of all snake bites, and in the present study it accounted for 70%.

The ability of the venom of the hump-nosed viper to produce coagulopathy is poorly documented. The first case report of a coagulopathy following a hump-nosed viper bite was in a five-year-old boy from Kandy (in central Sri Lanka) who developed severe coagulopathy with overt gastrointestinal hemorrhage and acute renal failure needing dialysis. The investigators also demonstrated procoagulant fibrinolytic, and platelet aggregating activity of hump-nosed viper venom in vitro. We reported an abnormal bleeding tendency in a 55-year-old man bitten by a hump-nosed viper who developed oozing of blood from the site of the bite and in vivo evidence of excessive fibrinolysis with hypofibrinogenemia. The present study confirms that coagulopathy can occur in a proportion (21%) of patients bitten by the hump-nosed viper. It also confirms that excessive fibrinolysis is the most consistent hematologic defect and that hypofibrinogenemia occurs in most patients with coagulopathy. The grossly prolonged clotting times in some patients suggests that no clot formed. However, this is difficult to explain in the presence of the normal prothrombin time and the partial thromboplastin time with kaolin values. The results may in fact be due to excessive fibrinolysis causing rapid lysis of any clot formed. There seems to be no significant abnormality of platelets following envenomation, as demonstrated by the normal platelet count and the normal bleeding time. Although none of the patients in our study developed clinically significant bleeding that required urgent medical attention, the potential for such a situation should not be ignored. The currently available Haffkine Laboratories polyspecific antivenom has no proven benefit against the venom of *H. hyspanae*. The first four patients in this study were each treated with 20 vials (each vial contains 10 ml) of antivenom as an intravenous infusion without any effect on the clotting time. The use of this antivenom preparation in cases of hump-nosed viper bites is not uncommon in Sri Lanka, and until recently, studies demonstrating definite lack of effect were not available. In view of the potential hazards of such treatment and lack of convincing benefit in the earlier patients, it was not used thereafter. The whole blood clotting times returned to within the normal range spontaneously between 36 and 120 hr in all 12 patients.

We suggest that evidence of coagulopathy should be actively looked for in all suspected hump-nosed viper bites. We used the whole blood clotting time test, in addition to clinical evaluation, for the purpose of screening for coagulopathy. Although this is admittedly a crude test of coagulation and lacks standardization when done at the bedside, it is often the only test available for most third-world clinicians who manage snake bite victims in the acute setting. We suggest that patients with a prolonged clotting time following a hump-nosed viper bite be investigated further. In view of the evidence of a coagulopathy following its bite, a specific antivenom against hump-nosed viper venom needs to be developed.

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