Kidney International, Vol. 67 (2005), pp. 659–667

Acute renal failure after *Crotalus durissus* snakebite: A prospective survey on 100 patients

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Acute renal failure after *Crotalus durissus* snakebite: A prospective survey on 100 patients.

Background. Acute renal failure (ARF) is the main cause of death after the South American crotalid snakebite. The aim of this study was to assess the prevalence, risk factors, and characteristics of *Crotalus durissus* venom-induced ARF.

Methods. One hundred cases of *Crotalus durissus* bite were studied from hospitalization to discharge or death. Creatinine clearance (GFR) <60 mL/min/1.73m^2 in the first 72 hours after snakebite was defined as ARF. Data are expressed as median (range of variation) or %, and were analyzed by univariate analysis and logistic regression.

Results. Twenty-nine patients developed ARF. Of those, 24% required dialysis and 10% died. ARF patients had smaller body surface [1.55 (0.6–2.3) vs. 1.7 (0.6–2.1) m^2, $P = 0.0097$], received antivenom (AV) later [12 (2–48) vs. 2 (1–14) hours, $P < 0.0001$], received more AV [190 (90–536) vs. 158 (75–500) mg/m^2, $P < 0.0001$], presented lower diuresis at admission [62 (0–182) mL/hr vs. 100 (25–325) mL/hr, $P = 0.0004$], and showed a striking creatine kinase (CK) increase [50,250 (69–424,120) vs. 1108 (88–133,170) U/L, $P < 0.0001$]. Age <12 years (OR 5.6, $P = 0.026$), time for AV >2 hours (OR 11.1, $P = 0.032$), CK at admission >2000 U/L (OR 12.7, $P = 0.0009$) were identified as independent risk factors for ARF, whereas diuresis at admission >90 mL/hr (OR 0.20, $P = 0.014$) was an independent protector factor.

Conclusion. C. durissus venom-induced ARF had high prevalence (29%). Delay for AV treatment, CK at admission >2000 U/L, and age <12 years were independent risk factors for ARF development. Diuresis at admission >90 mL/hr was a protective factor.

Poisonous snakebites are a serious health challenge in tropical regions due to their incidence, morbidity, and mortality [1, 2]. The World Health Organization (WHO) estimates there are approximately 125,000 deaths out of 2,500,000 poisonous snakebites a year worldwide [2].

In Brazil, there are 20,000 poisonous snakebites a year, a mean incidence of 13.5 bites/100,000 inhabitants and a mortality rate of about 0.45% [3]. The *Crotalus* gender, of the *Viperidae* family and *Crotalinae* subfamily, is represented in Brazil by a single species, *Crotalus durissus*, or the South American rattlesnake. It is responsible for 7.7% of the notified cases, and for a mortality rate of 1.9%, the greatest among all Brazilian poisonous snakes [3].

The crotalic venom is a complex mixture of enzymes, toxins, and peptides. The main identified toxins are crotoxin, crotamine, giroxin, convulxin, and an enzyme similar to thrombin [4, 5]. Crotoxin is responsible for the high toxicity of the venom [5] and has neurotoxic [6], myotoxic [7–10], and nephrotoxic [11–13] activity.

The clinical picture of *C. durissus* snakebite is characterized by mild local injury and systemic manifestations, which are frequently severe. Eyelid ptosis, blurred vision, and/or double vision, ophthalmoplegia, and paralysis of facial muscles are examples of the venom neurotoxic activity. Its myotoxic action induces rhabdomyolysis, characterized by generalized myalgia and myoglobinuria. The coagulant activity triggered by the thrombin-like enzyme may lead to afibrinogenemia and blood incoagulability in 40% to 50% of the cases [1, 3].

Acute renal failure (ARF) is the major complication in patients surviving the initial effects of *C. durissus* envenomation, and is considered the major death cause in these accidents [14, 15]. The crotalid accident is approximately 10 times less frequent than the bothropic, but the absolute number of ARF cases reported in literature with both snake genders is similar [16]. Recent experimental studies suggest the pathogenesis of crotalid-induced ARF is related to rhabdomyolysis, renal vasoconstriction, and a direct nephrotoxic effect of the venom [11–13, 17, 18].

Although the reported prevalence of ARF after *C. durissus* snakebite is high [1, 19, 20], all available studies are retrospective and used parameters with poor

Key words: snakebite, acute renal failure, Crotalus, rattlesnake, rhabdomyolysis.

Received for publication June 12, 2004
and in revised form August 3, 2004
Accepted for publication August 18, 2004

sensitivity, such as serum creatinine [15, 19, 20], or that were not very specific, such as diuresis [1, 14, 21, 22], to evaluate renal function.

The objective of this study was to assess the prevalence, risk factors, and characteristics of ARF after envenomation by the South American crotalid.

METHODS

Victims of *C. durissus* snakebite admitted at the Hospital de Doenças Tropicais (HDT), Goiânia, Goiás (GO), were prospectively studied. HDT is a reference center for the treatment of snake envenomation in the State of Goiás, Brazil.

The diagnosis was based on the snake identification and/or by a clinical picture consistent with *C. durissus* envenomation within the first 24 hours after hospitalization. A typical clinical picture was defined as the presence of neurotoxic face (lid ptosis, flaccid paralysis of facial muscles, ophthalmoplegia), blurred and/or double vision, myalgia, and mild injury at the bite site.

Acute renal failure (ARF) was defined as endogenous creatinine clearance (GFR) <60 mL/min/1.73m^2 in the first 72 hours after envenomation with subsequent recovery of GFR. Patients who did not improve their GFR were carefully screened, and if there was clinical and/or laboratory evidence of chronic kidney disease they were excluded from the analysis. Chronic kidney disease was defined as baseline serum creatinine (previous to the accident) over 2 mg/dL, renal ultrasound with decreased kidneys or loss of the corticomedullary distinction, and/or history of active or past renal disease.

The study was approved by the Ethics Committees of the Tropical Diseases Hospital of Goiânia and Hospital das Clínicas, University of São Paulo Medical School. Patients were only included in the study after signing the informed consent. If the patient was younger than 18 years of age, informed consent was signed by the legal guardian.

All of the patients received specific crotalid antivenom (Instituto Butantan, São Paulo, Brazil) at HDT admission if adequate treatment had not been carried out previously. The crotalid antivenom (CAV) was administered intravenously, following the dosages recommended by the Health Ministry (HM), according to the classification of the accident (Table 1) [3]. Patients with changes in coagulation time 12 hours after antivenom administration received an additional CAV dose of 150 mg. Tetanus prophylaxis was used when required.

At admission, all patients were hydrated with an alkalinizing solution (500 mL of glucose 5%, 25 mL of mannitol 20%, 10 mL of sodium chloride 20%, and 20 mL of sodium bicarbonate 8.4%), 3 to 6 L/day, according to clinical picture. This solution was used to prevent renal injury by rhabdomyolysis. If the urinary flow remained satisfactory (1–2 mL/kg/hr in children and 30–40 mL/hr in adults), the solution was maintained for 48 to 72 hours. If the patient remained oliguric (diuresis <400 mL/day), the solution was discontinued and furosemide was administered (240 to 480 mg/day). When necessary (uremia and/or hypervolemia), intermittent peritoneal dialysis (IPD) was used.

Table 1. Classification of crotalid snakebite severity and recommended antivenom dosage

	Classification of the accident (initial evaluation)		
	Mild	Moderate	Severe
Myasthenic face and blurred vision	None or late	Mild or evident	Evident
Myalgia	None or mild	Mild	Intense
Dark urine	None	None or little evident	Present
Oliguria or anuria	None	None	None or present
Antivenom *mg/no. of vials*	75 mg	150 mg	300 mg
CAV-BCAV[a]	(5 vials)	(10 vials)	(20 vials)

Modified from National Health Foundation (FUNASA), 2001.
[a]CAV, crotalid antivenom; BCAV, bothropic-crotalid antivenom.

Clinical parameters

The bite site, severity of envenomation (Table 1), the type and the amount of antivenom given per body surface, the time elapsing between the snakebite, and the administration of specific antivenom were evaluated.

Age, gender, body surface, history of chronic diseases (heart failure, hypertension, or diabetes mellitus), use of concomitant drugs, hospitalization time, dialysis treatment, and mortality were recorded. The presence of myalgia and urinary abnormalities (volume and color), as assessed by the patient, and the occurrence of lid ptosis and bleeding were also screened.

Weight (kg), systolic and diastolic blood pressure (mm Hg), intravenous hydration volume (mL/kg/hr), and diuresis (mL/hr) were evaluated daily.

Laboratory evaluation

A blood specimen was collected at admission and daily until 72 hours after the snakebite. When the patient developed ARF, blood specimens were collected every three days until discharge or death. Blood samples were used to measure sodium, potassium, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and lactic dehydrogenase (LDH) (Autoanalyzer Mega Merck 1.0; Merck, Darmstadt, Germany), to determine blood coagulation time (CT) (Lee White Method), hematocrit, hemoglobin, and platelets (Cell-Dyn 3.000–5.4, San Francisco, CA, USA).

On admission day, urine was collected for at least six hours to a maximum of 24 hours, depending on the time of hospitalization and the patient's urinary volume. It was then collected and analyzed daily in all patients (12-hour urinary volume) until 72 hours after the snakebite.