Acute Kidney Injury Caused by *Bothrops* Snake Venom

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Key Words

Acute renal failure · Acute kidney injury · Acute tubular necrosis · Snake venom · *Bothrops*

Abstract

Medically important venomous snakes in Latin America belong to the genus *Bothrops*, *Crotalus*, *Lachesis* and *Micrurus*. The *Bothrops* genus is responsible for the majority of accidents. The WHO globally estimates 2,500,000 poisonous snakebites and 125,000 deaths annually. In its last report in 2001, the Brazilian Ministry of Health accounted 359 deaths due to snakebites, of which the *Bothrops* genus was responsible for 185. Snake venoms cause local and systemic damage, including acute kidney injury, which is the most important cause of death among patients surviving the early effects of envenoming by the *Crotalus* and *Bothrops* genera. Venom-induced acute kidney injury is a frequent complication of *Bothrops* snakebite, carrying relevant morbidity and mortality.

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Introduction

José de Anchieta, an important Jesuit leader in colonial Brazil, had already referred to the variety of snakes in the new territory in his letter to the Portuguese Crown

dating from 1560, recording for the first time an accident by these animals. During the colonial period the reports on accidents and deaths caused by poisonous snakes were scarce, which were found only on death certificates or even in personal dairy notes [1].

In the early 20th century, in 1901, ophidism was introduced as a scientific approach. At that time, Vital Brasil carried out the first epidemiological study about snakebites in the state of São Paulo, Brazil, and produced the first anti-venom available for human use. An organized data collection on venomous snakebites was made through a specialized journal, '*Boletins para Observação de Accidentes Ophidicos*' (Ophidic Accidents Observation Bulletin), which provided official information about venomous snakebites and was published in Brazil for nearly 50 years [2]. Subsequently, the information collected developed into detailed studies, including both patient profiles and a survey on the areas where the highest number of accidents occurred. Meanwhile, special attention was drawn to studies assessing venom-induced cell damage. In fact, snake venoms are extremely complex substances. They have proteic and non-proteic fractions, and may produce local changes, such as acute inflammatory activity, edema, ecchymosis, blisters and necrosis, and systemic changes, such as hemorrhage, blood pressure alteration, neurotoxicity, hemolysis, rhabdomyolysis and acute kidney injury (AKI). Renal injury is the leading cause of death among patients surviving the ear-

ly effects of venom, and the most frequent renal histological injury found in venom-induced AKI is acute tubular necrosis [1, 3–6].

Official Data on Accidents by Venomous Snakes

The WHO globally estimates 2,500,000 poisonous snakebites and 125,000 related deaths annually [6, 7]. The Brazilian Ministry of Health's information on snake accidents covering the period from January 1990 to December 1993 [8] accounted for 81,611 snakebite accidents notified. These numbers mean an accident annual average of around 20,000 and an incidence coefficient of 13.5 per 100,000 inhabitants. Among these accidents, 65,911 were caused by venomous snakes. The highest number of occurrences was in the south and southeastern regions, probably due to their larger populations as well as their better organized public health and information system, allowing a more efficient data collection. On the other hand, the precarious access to health services in the north and northeastern regions is likely related to undernotification of accidents in those areas.

Seasonal Incidence of Accidents

Bothrops snakes are active in the night and prey during this time. Conversely, they are ectothermic reptiles and several biological processes as moving, digesting, sperm and egg cell production and embryo evolution are much more effective during the daytime due to warmer temperatures.

Ophidic accidents are related to climate factors suitable to soil preparation, planting and harvesting, when there are larger numbers of farm workers in the fields. In the south, southeastern and central-western regions, a higher incidence occurs between September and March. In the northeastern region, the highest incidence happens from January to May, while in the northern part of the country, occurrences take place throughout the year. These data are consistent with the snakes' liveliest activity during the hottest time of the year in each region [1, 8, 9].

Snake Genus

Venomous snakes produce a toxic substance and inoculate it through a specialized apparatus. In snakes, envenoming is made through their hollow fangs which

communicate with the venom-producing glandules. Clinically relevant venomous snakes in Latin America belong to the genus *Bothrops*, *Crotalus*, *Lachesis* and *Micrurus* [6, 10]. The *Bothrops* genus is responsible for the majority of accidents. In Brazil, 65,911 out of 81,611 snakebite notifications were related to identified venomous snakes, and 59,619 (73.1%) were caused by *Bothrops* genus snakes [8]. This larger prevalence is probably due to the vast and abundant geographic distribution and the aggressive behavior of these snakes [1, 2, 6, 8, 9, 11, 12].

The *Bothrops* genus comprises over 30 species and subspecies spread out from the South of Mexico to Argentina and some Caribbean Islands. The most important species are *Bothrops asper*, *Bothrops atrox* and *Bothrops jararaca*. Interestingly, most *Bothrops* species are found in large numbers all over Latin and South America, while others are limited to a specific region, like the *Bothrops insularis* on Ilha da Queimada Grande, on the São Paulo state coast [1].

Victim Profile

A 30-year-old male farm worker arrives at an emergency service after having been bitten by a *B. jararaca* in the foot about 2 h earlier. This episode, so common nowadays, could have been written by Vital Brasil over 100 years ago. In fact, several studies have shown that the ophidic accident epidemiological profile has suffered few changes. 15- to 49-year-old male farm workers remain the most common victims, and feet and legs are the most affected sites [13, 14].

Bothropic Accident Clinical Picture

Snake venoms are composed of over 20 different components whose functions and interactions have not been entirely studied. 90–95% of a snake venom net weight is composed of proteins (enzymes, non-enzyme toxins and non-toxic proteins). The non-proteic fraction is made up of carbohydrates, lipids, metals, biogenic amines, free amino acids and nucleotides [1, 6, 8, 9]. The bothropic venom varies in its composition among the same species from different geographic regions, due to dietetic availability, and even in the same animal, depending on its age [1, 9, 15–20]. Despite venom variability, some basic actions are universal to all *Bothrops* species.

Local Manifestations

Venom inoculation may occur via the subcutaneous or intramuscular route. Fang perforations may be single or even invisible. Site bleeding is common. Local pain which is induced by bradykinin and histamine, venom biogenic amines, is usually immediate. Early development of edema is frequent. It is usually tense and lilaceous, due to subcutaneous bleeding caused by small peptides and phospholipase A₂. The venom causes hemolysis, platelet aggregation, myonecrosis, vascular endothelium rupture and extracellular matrix component degradation [1, 6, 8, 9, 21–23]. In up to 24 h, the whole limb may be impaired due to extracellular leaking. Infections such as abscess and cellulite may occur, due to contamination by the snake's oral bacterial flora [8, 9]. Tissue necrosis caused by venom proteolytic action associated to vascular injury is a feared complication, which might be worsened by tourniquet use and treatment delay. Compartmental syndrome caused by the inflammatory and hemorrhagic processes in the injured area is unusual, demands rapid medical intervention when it occurs and makes patient management particularly difficult. Intense pain, paresthesia, cyanoses and temperature changes may occur as a result of the nervous-vascular bundle compression by the edema present in the affected area [1, 8, 9].

Systemic Manifestations

Hemorrhagic manifestations such as gingival bleeding, microscopic hematuria, purpura and recent wound bleeding are frequent. Macroscopic hematuria, hemoptysis, epistaxis, conjunctival bleeding, hematemesis and central nervous system hemorrhage have been reported [6, 8, 9, 24]. Shock and hypotension have been described following the bite [6, 8, 14, 23]. Kidney injury is a frequent complication, causing high morbidity and mortality [1, 6, 9, 11, 12, 24–36].

Hemorrhage results from venom action causing coagulant system activation and intravascular fibrin formation. Such an action, known as 'thrombin-type coagulant action', is not neutralized by heparin. The final result is fibrinogen consumption and subsequent non-clotting. The venom, when activating factor X, also consumes the factors V, VII and platelets causing capillary microthrombi formation, which contribute to the AKI genesis [1, 8, 9, 14, 21, 22]. *Bothrops* venom also has high esterases activity. These proteases are responsible for hemorrhagic manifestations and kinin release [1, 8, 9, 21].

Table 1. Snakebite severity and treatment classification

	Mild	Moderate	Severe
Site manifestations: pain, edema, ecchymosis	absent or discrete	evident	intense
Systemic manifestations: serious hemorrhage, shock, anuria	absent	absent	present
Clotting time (CT) ¹	normal or altered	normal or altered	normal or altered
Anti-venom therapy (quantity of ampoules)	2–4	4–8	8–12
Route	IV	IV	IV

Normal CT: up to 10 min, prolonged CT: from 10 to 30 min, non-clotting CT: >30 min.

Data from the manual on diagnosis and treatment of accidents caused by poisonous snakes, Brazilian Ministry of Health, 2001.

Treatment

The specific and early anti-venom application is essential and decisive, considering that a fast specific treatment represents an extremely important positive prognostic factor. The accident classification under mild, moderate or severe is based on the patient's clinical status which determines the proper serum therapy proposed by Vital Brasil more than a century ago (table 1). Monitoring of blood pressure, respiratory condition, cardiac rate and adequate hydration should be performed. Attention to bite site injury and systemic bleeding is of high importance for treatment success [1, 4, 8, 9, 12–14, 37–41].

Bothrops Venom-Induced AKI

AKI, characterized by oliguria and serum creatinine increase, has been described to develop early after a *Bothrops* bite and may be severe requiring dialysis [1, 6, 11, 13, 14, 23–35]. Data from retrospective series reported an AKI prevalence of 1.4–38%, depending on the species [11, 14, 26, 29–35]. It is the leading cause of lethality among patients surviving the early effects of the venom [2, 6, 12, 14, 25], with mortality ranging from 13 to 19% [25, 27, 28, 35]. Published data suggest that the patient's age and body surface area, the snake's age, amount of inoculated venom, bite site and the time elapsed until anti-venom treatment all influence AKI prevalence. Children under 10

years of age have been shown to be more likely to develop complications [1, 4–6].

Besides the classical variables involved in AKI genesis, such as dehydration and hypotension, baseline diseases such as ischemic coronary artery disease, hypertension, diabetes, previous nephropathies, tobacco and alcohol use could be present, making these patients more vulnerable to the effects of snake venom.

The mechanisms of *Bothrops* venom-induced AKI have been attributed to the venom's direct action on the kidney, to its hypotensive effect, myoglobinuria, hemoglobinuria and to glomerular microthrombi deposit. Most of the available information on the mechanisms involved in AKI development after *Bothrops* snakebite comes from experimental studies [3, 4, 42–50]. *Bothrops* venom undergoes renal elimination. *Bothrops alternatus* venom has been detected in renal tissue 30 min after and in urine 3 h after intravenous inoculation in rats [49]. *B. jararaca* venom injection in rats caused AKI characterized by decreases in urinary output, glomerular filtration rate, renal plasma flow, and by an increase in renal vascular resistance [3]. The venom induces hemolysis and serum fibrinogen consumption. Kidney histology showed fibrin microthrombi deposits in the glomerular capillary [3], which has also been observed in recent studies on *Bothrops neuwiedii* venom [47]. Similar results have been found following intraperitoneal infusion of bothropic venom in rats [48]. Recent studies have observed a direct *Bothrops* venom-induced tubular and glomerular injury [4, 42, 43, 50]. *Bothrops moojeni*'s venom fractions studied in isolated kidney preparations promoted increased renal vascular resistance and urinary volume, glomerular filtration rate and renal perfusion flow decreases [45]. Acute tubular necrosis is the most frequent histological finding in AKI following a bothropic accident, but cortical necrosis, acute interstitial nephritis and glomerular alterations have also been described [3–6, 36].

Considering the high chance of developing kidney impairment after *Bothrops* snakebite, the immediate care must include patient's adequate hydration, aiming at a maximum renal protection. However, the most important treatment to prevent AKI is early and specific anti-venom application at the recommended doses. In an experimental study on bothropic venom-induced AKI, de Castro et al. [4] demonstrated optimal kidney protection only when the venom and anti-venom were given simultaneously. In a prospective clinical study on *Crotalus* snakebite, a time longer than 2 h for anti-venom administration has been identified as an independent factor for AKI development [51]. Data available on dialysis treat-

ment for *Bothrops* venom-induced AKI are very scarce. Either peritoneal treatment or hemodialysis have been used in 33–75% of the cases described [25, 28, 52].

Anti-Venom Treatment

The conventional option for venomous snakebite treatment is the anti-venom produced from horse antibodies (produced in Brazil by the Instituto Butantan, Fundação Ezequiel Dias, and the Instituto Vital Brazil). However, this anti-venom is not considered ideal since it does not prevent local damages caused by the snake venom, it can induce hypersensitivity reactions and is sometimes difficult to find in remote areas [4, 13, 23, 53–56].

Da Silva et al. [55] have evaluated the capacity of serum preincubated with *Bothrops jararacussu* and *B. jararaca* venom in antagonizing venom-induced myonecrosis and hemorrhage in rats. They have found that preincubation with *B. jararacussu* venom was able to antagonize 40–95% of the venom myotoxicity and that the same procedure with *B. jararaca* venom antagonized 70–95% of the hemorrhagic activity of the venom. Theoretically, such a protocol might be useful in risk exposition situations or as a preventive therapy for people living in densely populated *Bothrops* areas.

Other authors have investigated marsupial serum application as a treatment against *Bothrops erythromelas* venom [57]. They concluded that marsupial serum features venom-neutralizing properties against hemorrhagic, myonecrotic, hyperalgesic and edematogenic effects of the venom. *Didelphis marsupialis* serum was also able to inhibit venom-induced effects in an isolated kidney preparation [57], representing a promising choice for venomous snakebite treatment.

Brazilian researchers have recently assessed the effects of a regional popular medicine against snake venom which is commonly used in the central region to treat snakebites [58, 59]. They evaluated the effect of the administration of *Schizolobium parahyba* (Fabaceae) infusion and its fractions against the pharmacological and toxic activity of *Bothrops* venom in rats. This native plant from the Brazilian forest, popularly known as guapuruvú, was effective in protecting against some of the *B. alternatus* and *B. moojeni* venom-induced enzymatic and biological activities. Animal lethality was reduced to zero and the venom hemolytic, hemorrhagic and coagulation system effects were attenuated [58, 59]. Studies aiming at Brazilian forest phytotherapy are a sustainable research choice. This new 'ancient' approach would meet both spe-

cies preservation goals and cost-effectiveness, considering that animals would not be harmed and medicinal plants could be cultivated in different environments. Barone et al. [60] obtained partial renal protection using simvastatin and lipoic acid in a model of *B. jararaca* venom-induced AKI.

Conclusions

Clinical and experimental data clearly show that the bothropic venom leads to AKI, which is a major cause of death following snakebite accidents. Several educational and preventive actions should be taken in order to protect farm workers, who are the main victims of such acci-

dents. The adverse effects of tourniquet use should be clarified, the 'homemade' formula limitations pointed out and, furthermore, the need for ready expert treatment should be remarked. Above all, the lyophilic anti-venom should be made available in remote areas, and health agents should be trained to spread information as well as treatment routines which would both help and educate in case of snakebite accidents.

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Editorial Comment

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The review by Sgrignolli and colleagues highlights the issue of *Bothrops* snakebite nephrotoxicity with emphasis on Brazil. Envenoming by snakebites is an important public health concern in tropical and subtropical regions. According to the WHO, in excess of 20,000 occur annually due to snakebites. Consequently, snakebites were added by the WHO in 2009 to the list of neglected tropical diseases. Whilst Brazil and Latin America are commonly affected, the highest numbers of envenoming are estimated to be in South Asia (121,000) followed by South-East Asia (111,000) and East Sub-Saharan Africa (43,000).

Of interest, Papua New Guinea has one of the world's highest incidence rates of snakebites. The range of systemic and renal manifestations is well described in the minireview by Sgrignolli, Burdmann and their colleagues. Clearly, snakebite is an underestimated and ignored public health problem that causes considerable illness, death, and socioeconomic hardship to poor populations living in rural tropical regions of the globe. It is likely to be an additional cause of AKI and possibly CKD in the tropics along with poverty, infections and the growing impact of globalization.