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Extracorporeal Support in a Patient With Acute Kidney Injury and Coagulopathy Due to Snake Bite: Case Report

*Ballesteros-Castro DA1,2, Mantilla-Villareal AC1,2, Barrera-Robledo ME3, Santiago-Ausecha DR4.**

1. Internal Medicine-Nephrologist, San José University Hospital, Popayán, Colombia.
2. Lecturer, Department of Internal Medicine, University of Cauca, Popayán, Colombia.
3. Second-year Resident of Internal Medicine, University of Cauca, Popayán, Colombia.
4. Nephrology Service Physician, San José University Hospital, Popayán, Colombia.

Abstract: Snake bites are one of the main causes of morbidity and mortality in rural communities in the tropics, as well as being an important public health problem. In general, the main clinical features of snakebites are: local edema, tissue necrosis, shock, spontaneous hemorrhage, coagulopathy, paralysis, rhabdomyolysis, and acute kidney injury; this being one of the most serious complications. These manifestations are the result of complex biochemical components of the venom that include cytotoxins, hemotoxins, neurotoxins, myotoxins, and other low-molecular-weight substances in snake venom, which is why recent studies have been conducted in search of complementary therapies for the treatment of snakebites and it has been evidenced within the molecular weight range of the toxins, which can be eliminated by means of hemoperfusion with the HA230 acute poisoning cartridge, which establishes a new therapeutic measure for snakebites.

Keywords: Snake bites, Snake bites, Bothrops, Acute kidney injury, coagulopathy, hemoperfusion.

Introduction Snake bites remain a significant public health issue due to their high frequency and severity. There are four genera of clinically relevant venomous snakes in Latin America: Bothrops, Crotalus, Lachesis, and Micrurus (Pinho et al., 2008). Bothrops snakes are responsible for most accidents, partly due to their wide geographical distribution and aggressive behavior when threatened (Sgrinolli et al., 2011). In Colombia, they account for 80-85% of all venomous snakebites (Instituto Nacional de Salud, 2022). Bothrops snakes can cause severe systemic reactions, and due to its high vascularization, the kidney is very susceptible to their toxins (Sitprija et al., 2012), making acute kidney injury one of the most serious complications of snakebites (Amaral et al., 1986), leading to proteinuria and hematuria, which can be associated with acute tubular necrosis, resulting in greater severity (Sitprija, 2006). Interstitial nephritis, cortical necrosis, and glomerular changes have also been described (Pinho et al., 2008; Sgrinolli et al., 2011).

Snake venom consists of more than 20 different substances, the effects of which are not yet fully understood. The protein fraction (enzymes, non-enzymatic toxins, and non-toxic proteins) constitutes 90-95% of its weight. Bothrops venom, despite the variability in its composition between species from different regions and within the same species, shows a mechanism characterized by proteolytic, coagulant, and hemorrhagic action, leading to characteristic local and systemic manifestations (Sgrinolli et al., 2011). The action of proteases, hyaluronidases, phospholipases, and inflammatory mediators leads to local tissue injury, with early onset of pain, edema, bleeding, and blistering lesions,

which can be complicated by abscesses and tissue necrosis. Among the systemic manifestations, hemorrhagic events (epistaxis, gingival bleeding, hematuria, hemoptysis, bleeding from the central nervous system) are associated with coagulation abnormalities secondary to activation of factor X and an action similar to thrombin, leading to consumption of coagulation factors, as occurs during the process of intravascular coagulation (Amaral et al., 2001; Gutiérrez et al., 2006). These cytotoxins, cardiotoxins, neurotoxins, selective enzymes, and low molecular weight compounds of snake venom are within the molecular weight range of toxins that can be eliminated by hemoperfusion through the HA230 acute poisoning cartridge (Sherry, 2020), which is an extracorporeal procedure for eliminating drugs and circulating toxins, being the treatment of choice for the elimination of high molecular weight toxins, highly protein-bound, and liposoluble substances (Ronco and Bellomo, 2022).

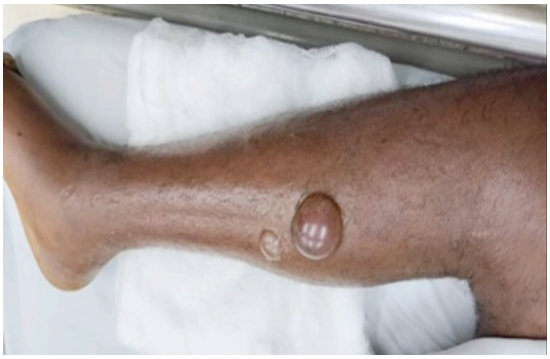
With this review, we aim to present the case of a patient with severe late bothropic ophidian accident that develops Acute Kidney Injury (AKI) which required hemoperfusion, hemoadsorption, and hemodialysis, with a good clinical outcome. The importance of this case lies in the few studies available in the literature on this type of extracorporeal therapy in bothropic ophidian accidents and its good outcome.

Case description

A 23-year-old male farmer from Timbiquí, with no pathological history, admitted to the hospital with an 8-day clinical picture consistent with a bite by a Bothrops Atrox snake (equis) on the right lower limb, with subsequent edema and pain, managed with natural medicines, without improvement; subsequently, he presented hematuria and confusion, so he consulted on the sixth day at level I of care, where extensive edema, warmth, erythema, perilesional blisters, liver involvement, and leukocytosis were found, so he was referred to a higher level.

He enters the emergency department disoriented, dehydrated, hemodynamically stable, without respiratory difficulty. With vital signs: blood pressure 131/85 mmHg, heart rate 77 beats per minute, respiratory rate 20 breaths per minute, oxygen saturation 97%, temperature 36ºC, oliguric < 0.4 cc/kg/hour, on initial examination, the patient with jaundiced sclerae and dry mucous membranes, Grade II edema and coldness in the right lower limb, presence of blisters on the middle third of the inner leg and on the outer face of the proximal third and lateral region of the gastrocnemius, showing bite lesions with mild active bleeding, capillary refill 3 seconds (Figure 1).

Figure 1: Findings on physical examination: Edema, erythema, and perilesional blisters.



The noteworthy analytical parameters at admission were leukocytosis with neutrophilia, microcytic - hypochromic anemia, altered renal function (creatinine 11.56 mg/dl, urea nitrogen 194 mg/dl), severe hypovolemic hyponatremia (Sodium 123 mmol/L), severe hyperkalemia (potassium 6.69 mmol/L), Hyperphosphatemia (6.7 mmol/L), elevated lactate dehydrogenase (593 U/L), coagulopathy (PT: >145 sec PTT: >260 sec INR: Cannot be calculated), Fibrinogen (Below detection limit) indirect hyperbilirubinemia (total bilirubin 6.47 mg/dl

– direct bilirubin 3.98 mg/dl), elevated liver enzymes (AST 61 Units and ALT 83 Units) - elevated CPK (916 U/L) and metabolic acidosis with pH 7.33, pO2 85, pCO2 25 mmHg, Bicarbonate 13.1 mmol/L, BE -11.7, PaFI 421 mmHg, and lactic acid 1.23 mmol/L, APACHE 21 points, ECG sinus rhythm, normal axis 30°, normal AV conduction, sharp T waves in precordials, stable ventricular repolarization, with soft tissue ultrasound of the right lower limb reporting a fusiform image between the gastrocnemius and soleus muscles with defined hypoechoic heterogeneous contours with presence of thin and thick septa inside measuring 223x30x62mm, with a collection of similar characteristics in relation to the posterior tibial muscle measuring 85x11x27mm, poorly defined areas of increased echogenicity and loss of fibrillar pattern with presence of irregular laminar anechoic collections in the lateral gastrocnemius belly, especially at its proximal and distal end, normal arterial Doppler of the right lower limb, assessed by orthopedics, who ruled out compartment syndrome, without urgent surgical criteria.

Hydric management was initiated, anti-hyperkalemic measures given by nebulizations with B2, Polarizing solution, ASA diuretic, and membrane stabilizer, antibiotic management with ceftazidime and metronidazole, polyvalent antivenom serum from the National Institute of Health (12 vials), transfusion of blood products, transferred to the ICU for multiorgan failure (hematological, hepatic, and renal), secondary to severe ophidian accident, evaluated by nephrology indicating initiation of hemoperfusion therapy with Jafron HA230 filter with the aim of toxin removal (molecular weight > 25,000 daltons) and continued hemoadsorption therapy to restore internal homeostasis, correction of severe hyperkalemia, acidemia, and reduction of azotemia, as well as lesser hemodynamic impact and early promotion of renal function recovery (Figure 2, 3).

Subsequently, he presented adequate evolution, reduction of azotemia, correction of severe hyperkalemia and acidemia, as well as improvement of coagulopathy, however, they considered performing a second cycle of hemoperfusion with Jafron HA230 filter with the aim of continuing toxin clearance and inflammation management, and later starting hemoadsorption with oXiris filter, after 24 hours of filter, continued in diffusion and convection mode. Then he presented a high risk of filter and extracorporeal circuit coagulation, as he was without anticoagulation due to the patient's clinical condition, so at the end, continuous venovenous hemodiafiltration with ST150 filter was initiated with the aim of maintaining and recovering homeostasis, recovering the internal environment, and promoting renal recovery with lesser hemodynamic impact.

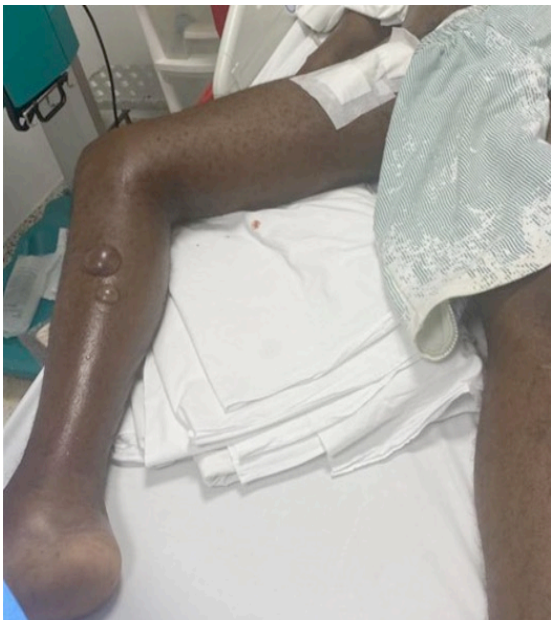


Figure 2: Patient in ICU with a 24 cm Mahurkar catheter, straight, in the right femoral vein.

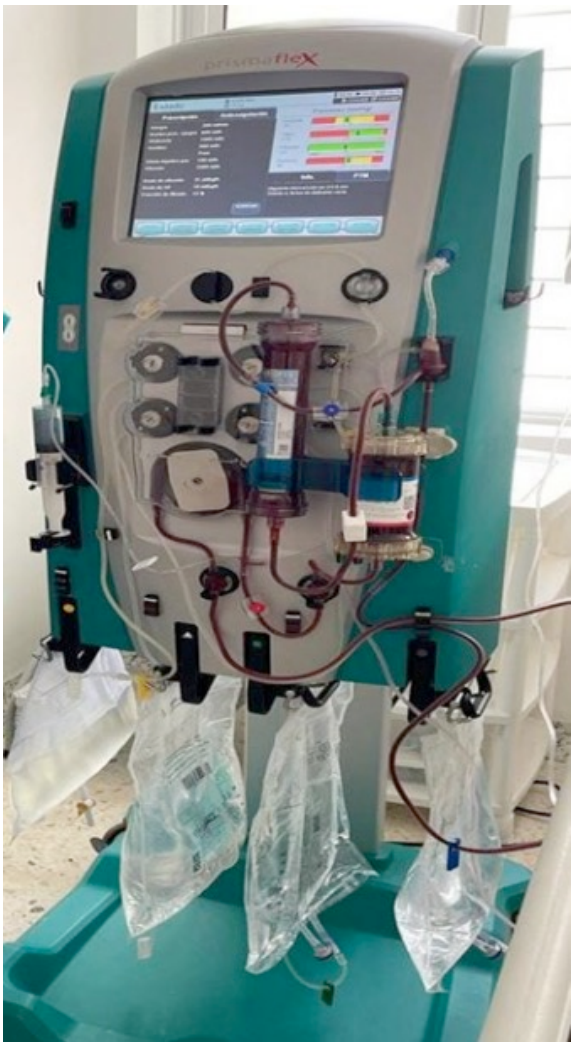


Figure 3: HA-230 hemoperfusion cartridge with oXiris filter in Prismaflex machine.

During the stay, the patient presented with purulent drainage in the right lower limb, leading to an escalation in antibiotic management to imipenem and linezolid. The patient was reassessed by orthopedics, who diagnosed abscessed cellulitis with partial improvement, indicating the need for surgical intervention for drainage. A washout and debridement were performed, and subsequently, the patient was transferred to the Intermediate Care Unit (ICU) to continue the recovery process of renal function, evidenced by stable azotemia levels and preserved diuresis. Clinically, the patient showed improvement, so hemodialysis therapy was deferred. The patient was able to remain without renal replacement therapy for 5 days, with diuresis exceeding 1000 cc without diuretics, and a decreasing trend in azotemia levels, leading to the removal of the hemodialysis catheter (Figures 1, 2).

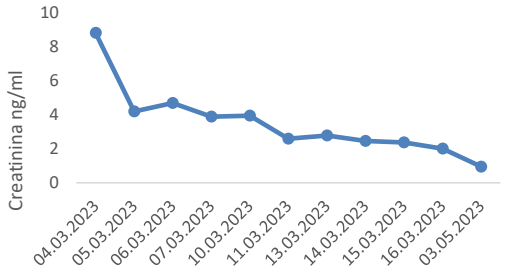


Figure 1: Creatinine levels over time

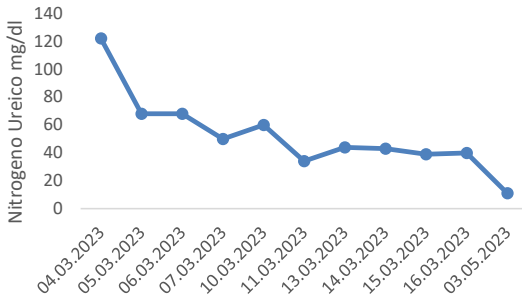


Figure 2: Blood Urea Nitrogen levels over time

Discussion

Most snakebite accidents in Latin America are caused by species of the Bothrops genus (Segura et al., 2010). In Colombia, the genera Bothrops, Porthidium, Bothriopsis, and Bothriechis are responsible for 90-95% of snakebite incidents (Otero et al., 2002).

According to the World Health Organization (WHO), the presence of venomous snakes is a global issue and a public health problem, especially in tropical regions. Snakebite envenomation is considered one of the major neglected tropical diseases, affecting poor rural populations in Africa, Asia, Latin America, and Oceania (Gutiérrez et al., 2006).

VARIABLE	Day 0	Day 2	Day 4	Day 6	Day 12	Discharge
CPK	916	208	50		70	
Total Bilirubin (mg/dl)	6.47	3.1	2.1		1	
Direct Bilirubin (mg/dl)	3.98	1.75	0.95		0.5	
CRP (mg/dl)	11.2	7.95	11.3		1.73	0.12
Albumin (g/dl)	3.3					

Source: Own

Table 1. Laboratory test follow-up

VARIABLE	Day 0	Day 2	Day 4	Day 6	Day 12	Discharge
Leukocytes (x 10^3/ul)	26.4	24.3	31.1	27.6	10.7	9.2
Hemoglobin (g/dl)	7.4	7.5	6.1	8.3	8.3	12.6
Platelets (x 10^3/ul)	245	259	336	389	634	327
Fibrinogen (mg/dl)	Not measurable	285	378	450		
D-dimer (ug/ml)	985	0.5				
PT (sec)	>145	13.3	14.4	14.6	14.1	13.2
INR	Not measurable	1.18	1.29	1.31	1.25	1.15
aPTT (sec)	>260	25.5	26.1	26.8	26	27.3
Na+ (mEq/L)	129	134	137	132	137	137
K+ (mEq/L)	6.9	5.5	5.2	4.7	4.8	4.5
Cl (mEq/L)	92	100	104	96	105	105
Ca+ (mg/dl)	8.6	7.9	8.2		9.4	
Mg (mg/dl)	3.74	2.5	1.89		1.54	1.72
Phosphorus (mg/dl)	6.7	4.8	5.9		3.5	
AST (U/L)	61	38	31		27	
ALT (U/L)	83	51	37		30	
Alkaline Phosphatase (U/L)	67	67	74		85	
LDH (U/L)	593	413	402		395	

Renal injury is a common complication of snakebite accidents and a leading cause of mortality, sometimes requiring renal replacement therapy, with case variability between 0.7% and 50%, and even a potential cause of chronic kidney disease development (Abuabara et al., 2022). Known risk factors favoring renal injury include the patient's age, body surface area, amount of venom injected, specimen age, injury site, and time between the bite and antivenom administration (Albuquerque et al., 2019).

The pathophysiology of acute kidney injury induced by snakebite is not completely understood. Renal injuries can be caused by the unique or combined action of different ischemic or nephrotoxic mechanisms triggered by the venom's action in the body (Amaral et al., 2001). Experimental studies suggest that the pathogenesis of this type of acute kidney injury is multifactorial and includes renal ischemia due to hypovolemia and hypoperfusion, thrombotic microangiopathy due to fibrin deposition in glomerular capillaries, and toxic effects on direct cytotoxicity of renal tubules (Gutiérrez et al., 2009).

Bothrops venom contains several biologically active peptides, and this composition can vary among the same species from different geographic regions, depending on the snake's age and diet. The biochemical family of toxins in Bothrops species venom includes snake venom metalloproteinases, snake venom

serine protease, L-amino acid oxidase, and phospholipase A2, which can trigger an inflammatory response and contribute to cellular and tissue damage, as well as hemostatic abnormalities. It can even activate coagulation factor X, prothrombin, and destroy fibrinogen, leading to hypofibrinogenemia and the production of fragile fibrin. Consequently, consumption coagulopathy can occur, which can be fatal (Albuquerque et al., 2019).

Cytotoxins, cardiotoxins, neurotoxins, selective enzymes, and low molecular weight compounds in snake venom fall within the molecular weight range of toxins that can be removed by the HA230 filter. Part of the snake venom is not neutralized by standard snake antivenom, so a new treatment therapy currently exists through extracorporeal therapies to eliminate the venom. Hemoperfusion can be used on a hemodialysis machine or continuous renal replacement therapy. A study using the HA230 hemoperfusion cartridge along with standard treatment for 15 patients with severe venomous snake bites showed it is safe and reliable and can directly remove toxins from patients' blood to achieve blood purification, significantly reducing lactate and inflammatory markers. Its incorporation into the clinical treatment of venomous snake bites is therefore useful (Sherry, 2020).

An exploratory experimental study in rats involving snake venom injection with or without subsequent hemoperfusion or antivenom administration showed that groups undergoing hemoperfusion designed for protein adsorption (using granular charcoal) and protein precipitation (using tannic acid) protected rats against the lethal effects of the venom (Oliveira et al., 2020).

Hemoadsorption therapy with oXiris, which uses the principle of adsorption to remove inflammatory mediators produced during cytokine storms, employs principles of diffusion, convection, ultrafiltration, and adsorption. It lasts for 24 hours and, depending on filter viability, can be extended up to 72 hours using convection and diffusion (Monard et al., 2019).

Regarding hemodialysis, some authors mention that it is required in 30% of patients, but a recovery rate of 54.8% at discharge is observed (Albuquerque et al., 2014; Castro et al., 2004). Studies conducted in India have identified early oliguria (which can occur up to 96 hours after exposure) and hematuria as predictors of dialysis requirement (Zamora et al., 2010).

Additional prognostic factors related to renal therapy requirements include the severity of the snakebite classification (severe) and paraclinical

Additional prognostic factors related to renal therapy requirements include the severity of the snakebite classification (severe) and paraclinical changes due to multiorgan involvement or disseminated intravascular coagulation (DIC), prolonged INR, hyperbilirubinemia, thrombocytopenia, proteinuria, and delayed antivenom administration (Zuluaga et al., 2022).

Conclusion

Snakebite accidents are a frequent issue that should not be overlooked, with the Bothrops genus being the main group of snakes in Latin America and one of the leading causes of mortality and morbidity. The most severe clinical complication is acute kidney injury. Therefore, we must consider that although there is antivenom serum, some severe cases may require additional support.

The development of extracorporeal therapies has improved the prognosis in patients like the case presented. Although the patient had a late arrival to the emergency service for treatment initiation, the consumption coagulopathy induced by venom was corrected, sepsis-induced complications were addressed, and complete renal function recovery was achieved. It is essential to highlight the positive impact of these

interventions on clinical outcomes so that more patients can benefit from such extracorporeal therapies.

Declaration of Conflicts of Interest

The authors declare no conflicts of interest. Ethical approval was obtained from the institution's ethics committee and the university.

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