https://doi.org/10.15446/cr.v11.111939

FATAL INTRACEREBRAL HEMORRHAGE ASSOCIATED WITH *BOTHROPS ASPER* ENVENOMATION IN COLOMBIA. CASE REPORT

Keywords: Snake bites; Bothrops; Cerebral Hemorrhage.
Palabras clave: Mordeduras de Serpientes; Bothrops; Hemorragia cerebral.

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Received: 03/11/2023 **Accepted:** 27/03/2024

ABSTRACT

Introduction: Snakebite envenoming is a medical emergency that, if not treated promptly, can lead to complications such as acute kidney failure, hypovolemic shock, compartment syndrome, and bleeding disorders, with intracerebral hemorrhage being a rare but highly fatal complication. Therefore, knowing the clinical symptoms and treatment options for these events is essential for achieving a good prognosis in patients.
Case presentation: An 80-year-old man was admitted to the emergency department of a primary care hospital in the municipality of San Carlos, Antioquia (Colombia), after being bitten by a *Bothrops asper* snake on his left hand. He was administered six vials of polyvalent antivenom serum within the first hour after admission, but his condition deteriorated, so he was transferred to a quaternary care center in Rionegro (Antioquia), where he was admitted with hypertensive crisis, bleeding gums, and altered state of consciousness. Laboratory tests and a plain CT scan of the skull were performed, showing hemispheric cerebellar hemorrhage, diffuse subarachnoid hemorrhage, and generalized cerebral ischemic changes. In view of the findings, nine hours after the first dose, four additional vials of polyvalent antivenom serum and a single dose of 1 500 Ul of prothrombin complex concentrate (4F-PCC) were administered, leading to an improvement in coagulation times. However, due to the general deterioration of his condition and the severity of the intracerebral hemorrhage, the patient died 19 hours after admission to the second institution.
Conclusion: Early detection of complications and timely initiation of appropriate treatment reduce mortality in patients treated for snakebite envenomation. However, there are still shortcomings in the management and reversal of intracerebral hemorrhages in these cases, making this report a significant contribution to the existing medical literature.

RESUMEN

Introducción. Los envenenamientos por mordedura de serpiente son una emergencia médica que si no se trata a tiempo puede traer complicaciones como insuficiencia renal aguda, choque hipovolémico, síndrome compartimental y trastornos hemorrágicos, siendo el sangrado intracerebral una complicación poco frecuente, pero de gran mortalidad. Por lo cual, conocer los síntomas clínicos y las opciones de tratamiento de estos eventos es fundamental para lograr un buen pronóstico en los pacientes.
Presentación de caso. Hombre de 80 años, quien ingresó al servicio de urgencias de un hospital de primer nivel de atención del municipio de San Carlos, Antioquia (Colombia), tras haber sido mordido por una serpiente *Bothrops asper* en su mano izquierda. Se le administraron 6 ampollas de suero antiofídico polivalente en la primera hora después de su ingreso, pero presentó deterioro general, por lo que fue trasladado

a una institución de cuarto nivel de atención en Rionegro (Antioquia), donde ingresó con crisis hipertensiva, sangrado en encías y alteración del estado de conciencia. Se realizaron exámenes de laboratorio y tomografía de cráneo simple que mostró hemorragia cerebelosa hemisférica, hemorragia subaracnoidea difusa y cambios isquémicos encefálicos generalizados. Dados los hallazgos, 9 horas después de la primera dosis se administraron 4 ampollas adicionales de suero antiofídico polivalente y una dosis única de 1 500Ul de concentrado de complejo protrombínico (4F-PCC), con lo cual se logró mejoría en los tiempos de coagulación; sin embargo, debido al deterioro general del estado de salud y a la gravedad de la hemorragia intracerebral, el paciente falleció 19 horas después de su ingreso a la segunda institución.
Conclusión. La detección temprana de complicaciones y el inicio oportuno de un tratamiento adecuado reducen la mortalidad en pacientes con envenenamiento por mordedura de serpiente. Sin embargo, aún existen vacíos en el manejo y la reversión de hemorragias intracerebrales en estos casos, por lo que el presente reporte constituye un importante aporte a la literatura médica existente.

INTRODUCTION

Snakebite envenomation, or envenoming (1,2), refers to the inoculation of toxins that can cause injury to a wide variety of tissues, as well as physiological alterations (3). Estimates suggest that approximately 5.4 million cases of snakebites are reported worldwide every year and that between one third and one half of these cases are related to envenomation, resulting in between 80 000 and 140 000 deaths attributable to this phenomenon (1).

The incidence of snakebites, regardless of the species, varies from country to country and between regions of the same country depending on factors such as climate, ecological parameters, biodiversity, distribution of venomous snakes, human population density, economic activities, types of dwellings, among others. In Latin America, the overall incidence of snakebite envenomation ranges from 5 to 62 cases per 100 000 inhabitants per year (4).

In Colombia, according to the Instituto Nacional de Salud (National Institute of Health), the annual average number of ophidian accidents between 2007 (the year in which these events began to be reported) and 2021 was 4 349 cases (1), with an incidence of 6.2 cases per 100 000 inhabitants in less populated regions and 20 cases per 100 000 inhabitants in more populated areas and an overall mortality rate of 5-9% (2).

Snakes of the *Bothrops* genus are involved in most of the envenomation cases reported in Brazil, Ecuador, French Guiana, Colombia, Argentina, Costa Rica, and Panama (5). In a study on the prevalence of cerebrovascular complications due to *Bothrops* envenomation, Mosquera *et al.* (cited by Larréché *et al.* (5) and Del Brutto *et al.* (6)) found that 2.6% of the victims suffered a cerebrovascular event, with nearly 60% of them dying and 40% presenting sequelae.

Bothrops asper, popularly known in these areas as *cuatronarices*, *mapaná*, *equis*, *rabiseca*, *tapa*, *pudridora*, *terciopelo*, or *barba amarilla*, inflicts the majority of snakebites in Central America and northern regions of South America, affecting mostly young agricultural workers in rural settings. Local effects of *B. asper* poisoning include pain, local edema, hematomas, blisters, dermonecrosis and myonecrosis, systemic hemorrhage, hypotension, renal alterations, among others (4). In turn, systemic complications include hypovolemic shock, compartment syndrome, acute renal failure, and bleeding disorders (4).

The following report describes the case of a patient with intracerebral hemorrhage (ICH) secondary to a *B. asper* bite in order to assess the value of using antivenom and implementing other early management strategies to reverse coagulopathy.

CASE PRESENTATION

An 80-year-old male farmer, residing in a rural area of the department of Antioquia (Colombia), was admitted to the emergency department of a primary care hospital in the municipality of San Carlos (Antioquia) after being bitten by a *mapaná* snake on his left hand. His only relevant medical history was chronic paralysis of the left upper limb of unknown etiology prior to the bite; the family reported that he was not a regular user of medications.

Based on his accounts and the presence of 2 puncture wounds on the thumb, the patient was diagnosed with moderate local snakebite envenomation, which resulted in the administration of 6 vials of polyvalent antivenom within the first hour after being admitted to the hospital. However, given the overall deterioration of his condition and state of consciousness, he was transferred to a more complex institution 9 hours after admission.

The patient was taken to the emergency department of a quaternary care hospital in the municipality of Rionegro (Antioquia). Upon admission to the second institution, the physical examination revealed that the patient had altered consciousness, an abnormal breathing pattern (gasping), elevated blood pressure (189/128 mmHg), bleeding gums, and 2 puncture wounds on the thumb of the left hand (Figure 1) with edema, associated with snakebite envenomation, and extending to the middle third of the forearm.

On neurological evaluation, reduced pupil size was observed, with no reaction to light, and a Glasgow Coma Scale score of 6/15. In view of these findings, immediate orotracheal intubation was performed, ventilatory support was started, and complementary studies were performed to reevaluate the severity of the envenomation.

Figure 1. Injuries to the base of the left thumb.
Source: Image obtained while conducting the study.

Laboratory tests showed leukocytosis (21,400x1 000/µL), neutrophilia (18,510x1 000/µL), moderate hypokalemia (2.9mmol/L), elevated D-dimer (115,219ng/mL), hyperlactatemia (4.2mmol/L), and reduced fibrinogen levels (96mg/dL). Moreover, prolonged clotting times were observed in coagulation factor tests: prothrombin time (PT) of 19.1 seconds, international normalized ratio (INR) of 1.62, and partial thromboplastin time (PTT) of 33.5 seconds.

A non-contrast axial computed tomography scan of the skull, performed within the first hour of admission, showed ICH involving the right frontal and parietal lobes and extending into the lateral ventricles, with signs of acute hydrocephalus. Bleeding in the cerebellum and diffuse subarachnoid hemorrhage showing generalized cortical ischemic changes were also observed (Figure 2).

After confirming the diagnosis of ICH, 4 additional vials of polyvalent antivenom (9 hours after the first dose) and a single dose of 1 500Ul of four-factor prothrombin complex concentrate (4F-PCC) were administered. The patient was assessed by the neurosurgery service, which concluded that, due to the extent of the ICH, surgical treatment offered no benefits and posed a high risk of short-term mortality, so this approach was ruled out.

Shortly after the treatment was administered, the patient was transferred to the intensive care unit for continued ventilatory support and hemodynamic monitoring. Seven hours after the administration of the antivenom, the coagulation tests normalized (PT: 14.4 seconds, INR: 1.2, PTT: 31.4 seconds); however, due to the clinical condition and the severity of the ICH, he died 19 hours after admission to the second institution.

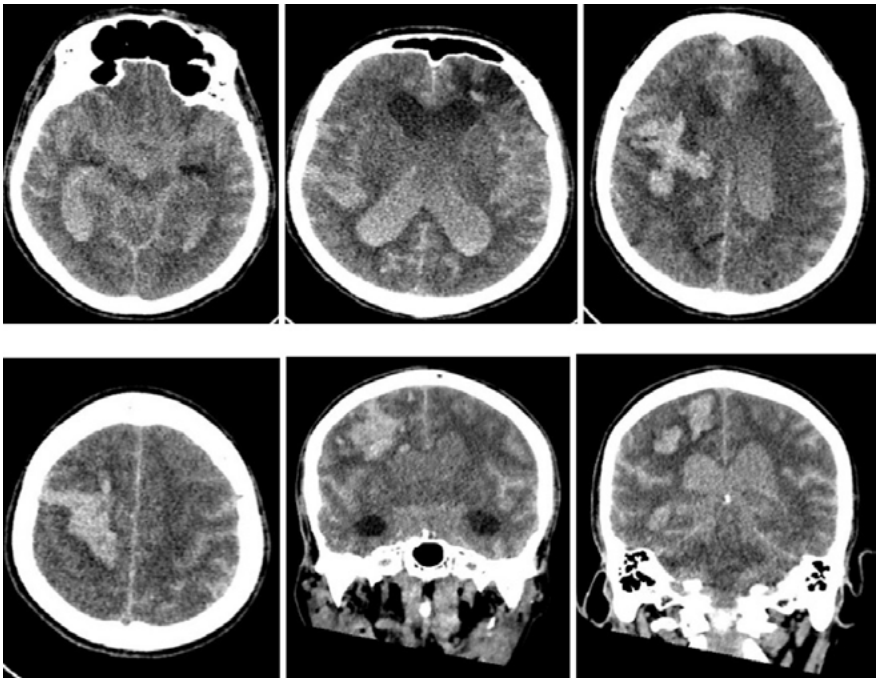

Figure 2. Non-contrast computed tomography of the skull showing extensive intracerebral hemorrhage.

Source: Image obtained while conducting the study.

DISCUSSION

In the Americas, Brazil, Mexico, Venezuela, and Colombia are the countries with the highest number of cases of snakebite envenomation reported (1). In the latter, over 300 snake species have been recorded, although only 18% of them are venomous, with species belonging to the *Viperidae* family, made up of the so-called true vipers (genera *Bothrops*, *Crotalus*, *Lachesis*, *Porthidium*, and *Bothriechis*) causing the majority of snakebite envenomation cases, which are characterized by hemorrhagic disorders, edema, and tissue damage (1).

In Colombia, 92% of snakebite cases reported between 2007 and 2021 were classified as envenomation and 82% of them were treated using antivenom (1). Snakebites affect predominantly men (74%), residents of rural areas (71%), and individuals involved in agricultural activities at the time of the event (48%); the most affected age group is 60 years of age or older (1).

Local symptoms of *B. asper* envenomation include severe pain at the site of the bite, progressive edema, blistering and, in some cases, dermonecrosis (4). Some of the main systemic complications caused by envenomation from this species include hypovolemic shock, compartment syndrome, acute renal failure, and hemorrhagic disorders; the latter two are the main causes of death (4).

Snake venoms contain a highly potent mixture of bioactive molecules known as toxins. *Bothrops* snake venom toxins can be classified as enzymatic proteins (snake venom metalloproteinases, snake venom serine proteases, phospholipases A2, and L-amino acid oxidases), and non-enzymatic proteins (disintegrins and C-type lectin proteins) (5). Given that metalloproteinases, serine proteases, and C-type lentins have anticoagulant or procoagulant activity and may be either agonists or antagonists of platelet aggregation, bites by these species can cause ischemic or hemorrhagic strokes and infarction (6,7), as in the reported case.

The pathophysiology of ICH secondary to *Bothrops* bite envenomation has not been fully elucidated; however, it has been demonstrated that patients who have been envenomed by snakebite have low platelet counts, decreased fibrinogen levels, and prolonged PT and TTP (6,8-9), manifestations that were largely evident in our patient. Similarly, prothrombotic states secondary to venom-induced consumption coagulopathy (VICC) are also documented, resulting in bleeding of the gums (as in the reported case), gastrointestinal tract hemorrhage, hematuria, and ICH, the latter being the most dangerous as it is usually fatal (8).

Central nervous system hemorrhages secondary to *Bothrops* bite envenomation are serious complications; they may be intracerebral, intraventricular, cerebellar, lobar, medullary, subarachnoid, subdural, or extradural (5). In general, ICH is caused by the rupture of a penetrating vessel causing extravasation, which leads to clinical manifestations related to its location and extent such as cognitive impairment, hemiparesis, paralysis, aphasia, dysarthria, and impaired consciousness (5,10-11), most of which were observed in our patient.

The diagnosis of ICH due to *Bothrops* envenomation is initially based on a high clinical suspicion supported by epidemiological background (bite in an endemic area) and early clinical manifestations such as hemorrhagic disorders (7,10). Diagnostic confirmation requires imaging studies, with cranial computed tomography being the study of choice due to its wide availability and good diagnostic performance (12). In the reported patient, extensive ICH was documented, suggesting a poor prognosis.

In this case, the patient presented with central nervous system involvement and limited local manifestations due to severe envenomation. This particular event has already been described in the medical literature, especially in cases of envenomation caused by young *Bothrops* specimens, which are characterized by a higher proteolytic activity compared to adult specimens, contributing to a greater severity of symptoms (4,9,10,13).

The treatment recommended for the management of snakebites is the administration of antivenom to neutralize the circulating venom and the venom being released at the site of inoculation (1). This intervention must be implemented as soon as possible, since it has been reported that administering

it in a period longer than 6 hours, as well as in patients over 65 years of age, are independent risk factors associated with mortality (14). In Colombia, there are two polyvalent antivenoms of whole immunoglobulin G (IgG) and one of fragmented IgG (F(ab′)2) available (4). The official guideline recommends administering 10 to 12 vials of the polyvalent serum manufactured by the Instituto Nacional de Salud in cases of severe envenomation, which has the capacity to neutralize 70mg of *B. asper* venom per 10 mL vial (4,9).

In cases of inadequate response to the antivenom, fresh frozen plasma (FFP) administration has been proposed to help reverse the coagulopathy, but the results have been controversial. For example, Brown *et al.* (15) retrospectively analyzed the use of clotting factors (FFP and/or cryoprecipitate) to treat VICC in snakebite patients in Australia, finding that factor replacement within 4 hours after initiation of antivenom treatment was associated with earlier improvement of clotting function in individuals who were bitten by Australian elapid snakes. Likewise, Isbister *et al.* (16) demonstrated that although FFP administration after antivenom administration leads to faster restoration of coagulation in most patients, it does not shorten the length of hospital stay. Furthermore, these authors concluded that early administration of FFP (<6-8 hours) following the bite is less likely to be effective (16).

In the reported case, as an alternative to the use of FFP, 4F-CCP was used. It contains therapeutic amounts of at least 4 coagulation factors: FII, FVII, FIX and FX, which are precisely the most affected in the pathophysiology of snakebite envenomation. In this regard, Sarode *et al.* (17) found that 4F-PCC is an effective alternative to FFP transfusion for urgent reversal of vitamin K antagonist therapy in major hemorrhagic events. Similarly, 4F-PCC has been used in cardiac surgery, major trauma, and hepatic dysfunction for the treatment of hemorrhage due to its efficacy in normalizing hemostasis (18,19).

It is noteworthy that at the time of writing this report there were no studies or reports on the use of 4F-PCC in snakebite envenomation patients with bleeding disorders. In any case, it should be noted that even though there was evidence of coagulation time normalization after the administration of 4F-PCC in the case presented, the delay in the administration of the drug (more than 12 hours after the bite), the age of the patient, his clinical condition, and the significant intracerebral involvement led to his death.

CONCLUSION

Snakebite envenomation is an important cause of morbidity and mortality in the Colombian population. A large number of these events occur in rural areas that do not have sufficient resources for the care of patients or for their referral to more complex institutions, so proper diagnosis, early initiation of treatment, and timely

detection of complications could help to avoid fatal outcomes. However, even with all the knowledge acquired to date, there are still gaps in the management and use of tools focused on the reversal of ICH in cases of snakebite envenomation, as well as in policies and prevention measures.

ETHICAL CONSIDERATIONS

The bioethics committee of the Hospital San Vicente Fundación (Rionegro, Colombia) approved the publication of this case report.

CONFLICTS OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGMENTS

To the Hospital San Vicente Fundación in Rionegro and its ethics committee for granting us access to the documents necessary for the preparation of this publication.

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