Therapeutic Value of Antivenoms in the Treatment of Snakebite Envenoming in Latin America: A Scoping Review

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Abstract

Introduction: Snakebites are an underestimated public health problem in rural areas of tropical and subtropical regions, with impoverished rural populations being the most affected due to their limited access to health services.

Objective: Realize a scoping review to synthesize the available evidence and identify knowledge gaps in therapeutic management and the efficacy of antivenoms for the treatment of snakebites in Latin America.

Results: Eleven selected studies showed that both monovalent and polyvalent antivenoms were effective in the treatment of snakebite envenoming.

Conclusions: All antivenoms evaluated in the studies were effective and safe for treating snakebite envenoming. It is important that hospitals and health centers have effective, affordable, and safe antivenoms to reduce patient care times.

Keywords: Snakebite, antivenom, therapy

Introduction

Snakebite envenoming is an underestimated public health problem in rural areas of tropical and subtropical regions (1–3), affecting more than five million people each year, with approximately 2.7 million cases of envenoming, 130,000 deaths, and 400,000 cases of permanent disability, according to the World Health Organization (WHO) (4–6). In Latin America and the Caribbean, an estimated 57,000 snakebite cases occur annually, with an approximate case fatality rate of 0.6% (6,7). The most affected populations are impoverished rural communities due to their limited access to health services (8,9).

The incidence and fatality of snakebite envenoming vary according to geographic and environmental factors such as climate, altitude, and population density (1,8). For example, in Venezuela, nearly 5,700 bites and 32 deaths are reported each year, while in Brazil approximately 27,200 bites and more than 115 deaths occur annually (10,11). In the Amazon region, the highest incidence is associated with the genus *Bothrops*, the main cause of reported cases (6). In Central America, Panama reports an average of 1,900 bites annually (55 per 100,000 inhabitants) and 15 deaths (0.5 per 100,000), while in Nicaragua around 650 bites (56 per 100,000 inhabitants) and seven deaths are reported each year. In Colombia, approximately 4,500 cases are reported annually, with a case fatality rate below 1% (12–14).

Although research on venoms has advanced significantly, there remains a substantial gap between scientific knowledge and its clinical application (15). Antivenom therapy, which continues to be the only specific and effective treatment for snakebite envenoming (6,13,16), faces serious challenges of availability and distribution, particularly in rural and remote regions (17). In Latin America, several countries have the capacity to produce antivenoms; however, this activity faces limitations associated with low commercial interest, underscoring the need to strengthen production processes, optimize distribution systems, and improve health personnel training (3,15,18).

In response to this problem, the WHO has included snakebite envenoming in its list of priority neglected tropical diseases and has set a goal of reducing mortality and disability by 50% by 2030 (7). Complementarily, the Pan American Health Organization (PAHO) supports antivenom production and distribution through the Network of Public Antivenom-Producing Laboratories (RELAPA) and promotes community education programs aimed at reducing morbidity and mortality. In this context, the present scoping review

was conducted with the objective of synthesizing the available evidence on the therapeutic value of antivenoms in Latin America and identifying the main existing knowledge gaps (7).

Materials and Methods

A scoping review was conducted following the guidelines of the PRISMA-ScR framework. The protocol was registered on the Open Science Framework (OSF) platform on September 6, 2024, under the registration code available at https://osf.io/7d4hq (19). The search for relevant studies was performed in PubMed, LILACS, and Scopus databases, using MeSH and DeCS descriptors related to the efficacy and treatment with antivenoms in the context of snakebite envenoming in Latin American countries, with no restrictions on year of publication.

Inclusion criteria were defined as studies published in Spanish, English, or Portuguese that evaluated the therapeutic efficacy of antivenoms in the management of snakebite envenoming in Latin America. Exclusion criteria included expert opinions lacking empirical support, research based exclusively on animal models, incomplete publications or those available only in abstract form, and studies focusing solely on preclinical efficacy without clinical data.

The study selection process was conducted in three stages: first, the removal of duplicate records; second, screening of titles and abstracts to identify potentially eligible studies; and finally, full-text assessment based on the predefined criteria. Additionally, a manual search of the reference lists of the selected articles was carried out to identify other relevant works not retrieved in the electronic search.

Data extraction was performed using a structured Microsoft Excel form, which included general study information, participant characteristics, type of antivenom and therapeutic regimen administered, as well as outcomes related to clinical efficacy and reported therapeutic endpoints.

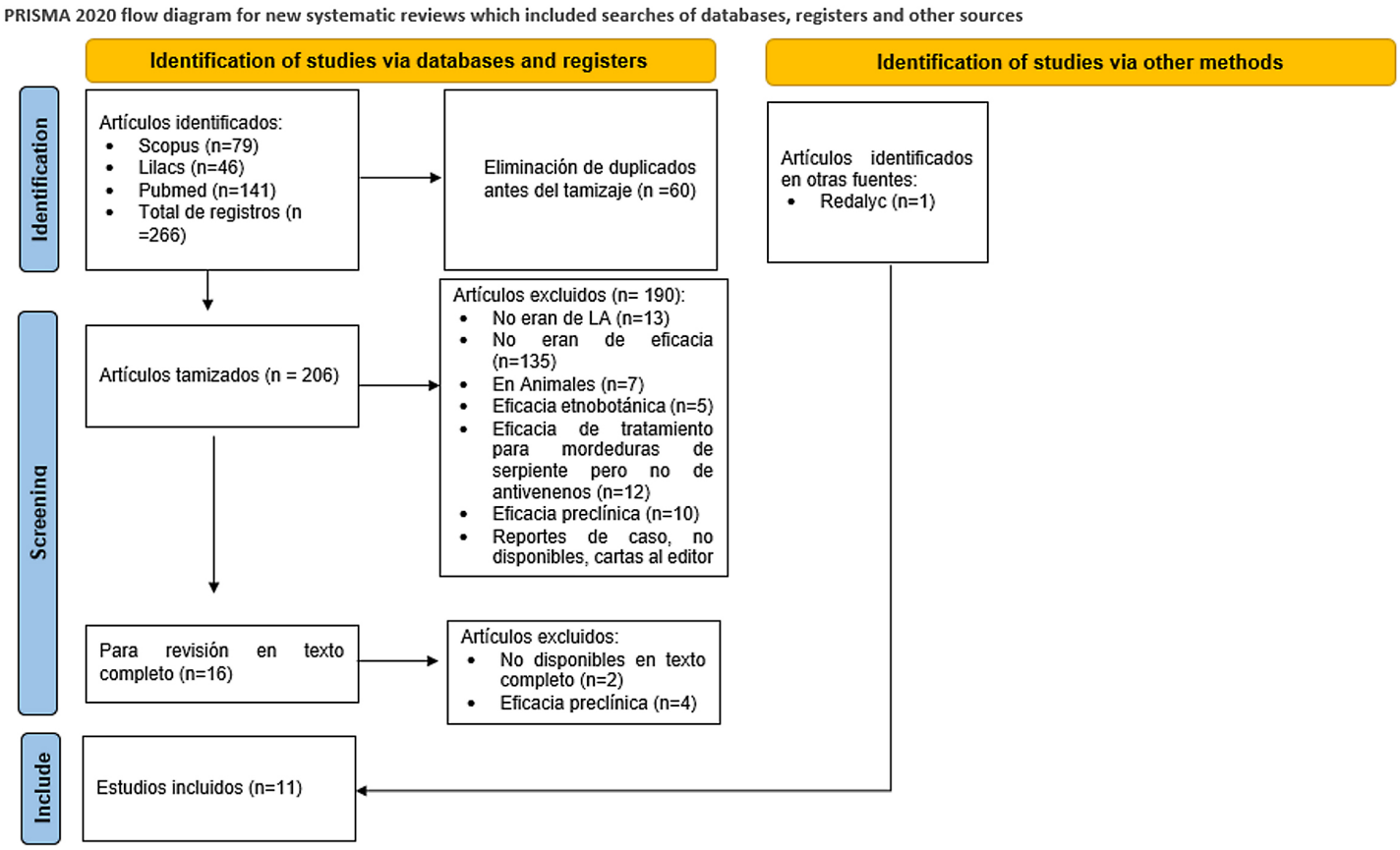
Results

A total of 266 potentially relevant references were identified, comprising 141 records from PubMed, 46 from LILACS, and 79 from Scopus. After removing duplicates, 206 records were screened by title and abstract review. Of these, 16 were selected for full-text evaluation, and ultimately 11 studies met the established eligibility criteria.

Most of the included studies (n = 5) were conducted in Brazil and Colombia, with publication dates ranging from 1993 to 2020. Only one study

was published in Spanish. Of the total, ten were clinical trials and one was a prospective observational study, all focusing on the evaluation of the therapeutic efficacy of antivenoms against snakebite envenoming caused by *Bothrops atrox*.

Figure 1. PRISMA Flow Diagram.



Source: Page MJ, et al. BMJ 2021;372:n71. DOI: 10.1136/bmj.n71.

Regarding the characteristics of the participants, the studies applied severity classification systems for snakebite envenomation in order to group patients and adjust the therapeutic antivenom regimen. In addition, clinical aspects such as the administered dose, the presence of adverse effects or early reactions associated with the treatment, and coagulation times as an indicator of therapeutic response were evaluated. Detailed information on the characteristics of the included studies, the population treated, and the therapeutic management employed is presented in Table 1.

Table 1. General information of the included studies and characteristics of therapeutic management.

Article	Type of study	Type(s) of snake(s) identified	Sample size	Bite classification	Type of antivenom administered by group		Administered dose		Coagulation times	Side effects / early reactions	
					Group A	Group B	Group A	Group B		Group A	Group B
Cardoso, J.L.C.,et al. (17)	Double-blind randomized clinical trial	*B. jararaca* y *B. jararacussu*	170	They stratified two groups: less severe and more severe, according to the 3 types of antivenoms	Liquid, pepsin-digested, refined, polyspecific antivenoms prepared from equine sera using virtually identical techniques.		Less severe: 4 ampoules (40 mL) intravenous administration	More severe: 8 ampoules (80 ml) of antivenom administered intravenously	The antivenom rapidly restored clotting and stopped bleeding in most patients, with fibrinogen levels returning to normal within 12 hours, although some cases presented purpura and increases in leukocytes and neutrophils.	Early reactions: Chills: 20 Nausea or vomiting: 13 Hives: 20	Early reactions: Chills: 9 Nausea or vomiting: 9 Hives: 5
Jorge, M.T. et al. (25)	Double-blind randomized clinical trial	*Bothrops*	121 according to the 3 types of antivenoms	No	Multipurpose commercial equine antivenom against Bothrops	Commercial multipurpose equine antivenom against Bothrops diluted at 50%	4 ampoules of 10 mL undiluted, at full concentration.	4 ampoules of 10 mL, diluted 50%	Reversal of blood coagulability (of all patients) 6 hours: 40 patients 12 hours: 57 patients 24 hours: 60 patients	Does not report	Does not report
Otero, R., et al. (26)	Double-blind randomized clinical trial	*B. atrox* *B. nasutus* *L. kuta* *serpiente coral*	39	Mild: 15 Moderate: 15 Severe: 15	Monovalent anti-B antivenom. atrox	Polyvalent anti-B antivenom. atrox	The antivenoms were dispensed in 10 mL vials and packaged in cardboard boxes containing 9 vials labeled A or B.		Significant improvement in blood coagulation was observed at 6 hours in 17 of 33 patients with initially compromised coagulation, and at 12 hours in 31 of them.	Urticaria: 5 Facial flushing: 1 Generalized rash: 3 Fever: 3 Chills: 3 Nausea: 1 Vomiting: 1 Medium hypotension: 2 Bronchospasm: 1	Urticaria: 2 Fever: 2 Chills: 1 Nausea: 2 Cramps: 1 Medium Hypotension: 2

Article	Type of study	Type(s) of snake(s) identified	Sample size	Bite classification	Type of antivenom administered by group		Administered dose		Coagulation times	Side effects / early reactions	
					Group A	Group B	Group A	Group B		Group A	Group B
Otero, R., et al. (23) intravenous administration	Double-blind randomized clinical trial	*B. atrox* *B. nasutus* *L. kuta* *serpiente coral*	53	They were classified according to severity, the data is not presented.	Commercial polyvalent equine antivenom. Compound of complete IgG obtained by fractionation with caprylic acid.	Monovalent anti-B. atrox antivenom, composed of complete IgG obtained by fractionation with ammonium sulfate.	Does not describe the dosage		100% of patients showed improvement in coagulation and bleeding within 24 hours, with 80% showing improvement within the first 6 hours, although some required additional doses.	Urticaria: 6 Facial flushing: 3 Generalized rash: 3 Fever: 3 Chills: 3 Nausea: 1 Vomiting: 7 Medium hypotension: 2 Bronchospasm: 1 Cramps: 4	Urticaria: 2 Generalized rash: 1 Fever: 1 Chills: 1 Nausea: 1 Vomiting: 1 Bronchospasms: 0 Cramps: 4 Angioedema of the face: 1
Smalligan R, et al. (24)	Double-blind randomized clinical trial	*B atrox* *B. bilineatus* *B. taeniatus* *L. muta* *B. brazili*	210	No	GROUP A: Antivenom from Colombia GROUP B: Brazilian antivenom GROUP C: Antivenom from Ecuador		Most patients (n=180): Initial dose of 20 mL of antivenom by intravenous injection over 10 minutes. Minority of patients (severely poisoned): Higher initial doses of up to 70 mL		The Colombian antivenom restored coagulation in 64% of patients at 6 hours and in 99% at 24 hours, being most effective with initial doses less than 70 mL, although 45% required additional doses.	Skin rashes, vomiting, abdominal pain, fever and chills, pruritus and dyspnea, and hypotension.	

Article	Type of study	Type(s) of snake(s) identified	Sample size	Bite classification	Type of antivenom administered by group		Administered dose		Coagulation times	Side effects / early reactions	
					Group A	Group B	Group A	Group B		Group A	Group B
Pardal PP, et al. (22)	Randomized, open-label, single-blind clinical trial*	*B. atrox /B. marajoensis L. m. muta Lachesis*	74	LMild: 43 Moderate: 27 Severe: 4	Standard Bothrops-Lachesis antivenom, produced by a different laboratory than group B	B. atrox-Lachesis antivenom	4 to 12 ampoules of antivenom depending on this assessment of severity.		Blood coagulation abnormalities observed at admission were reversed within 24 hours after antivenom treatment in both groups.	Hives: 3 Nausea/Vomiting: 2 Itching: 1 Cough: 1 Dyspnea: 1	Hives: 5 Nausea/ vomiting: 1 Itching: 1 Cough: 1
Otero R, et al. (21)	Mild: 17 Moderate: 35 Severe: 15	*B. asper*	67	Mild: 17 Moderate: 35 Severe: 15	IgG antivenoms fractionated by caprylic acid precipitation or by caprylic acid precipitation and α-propiolactone treatment		Patients in phase II received variable doses (three vials (n = 7); four vials (n = 7); five vials (n = 4); six vials (n = 4); eight vials (n = 7); and ten vials (n = 8)) of antivenom according to the degree of poisoning at admission.		Ninety-seven percent of patients recovered coagulation within 24 hours with no differences between antivenoms, and an additional dose at 6 hours prevented recurrences of coagulopathy within 48 hours.	Thirteen patients had early reactions to the antivenom within the first 2 hours of treatment, all of which were mild (cutaneous, gastrointestinal, chills).	
Patiño, R., et al. (15)	Therapeutic clinical trial	*B. asper* *B. atrox*	60	Of 36 patients: Mild: 5 Moderate: 23 Severe: 8	Lyophilized polyvalent antivenom antibothropic, anticrotal, and antilachesic (Antivipmyn-Tri®) digested with pepsin		Mild or moderate poisoning: 5 vials of antivenom. Severe poisoning and those bitten by a snake longer than 1 meter: 10 vials of antivenom.		In 96.2% of patients, coagulation normalized within 24 hours; two cases of hypoprothrombinemia and two recurrences of coagulopathy were corrected with additional doses, suggesting that lower initial doses may be associated with recurrences.	Nine patients were considered to have mild early adverse reactions to the antivenom, such as skin reactions, fever, and gastrointestinal symptoms. One moderate reaction, such as hypertension.	

Article	Type of study	Type(s) of snake(s) identified	Sample size	Bite classification	Type of antivenom administered by group		Administered dose		Coagulation times	Side effects / early reactions	
					Group A	Group B	Group A	Group B		Group A	Group B
Otero-Patiño, R., et al. (20)	Double-blind randomized clinical trial	*B. asper*	72	Mild: 19 Moderate: 36 Severe: 17	Composed of F(ab')2 fragments, generated by pepsin digestion and caprylic acid precipitation	Complete IgG molecules produced by caprylic acid precipitation followed by ion exchange chromatography.	According to severity: No poisoning: no need for antivenom, observe the patient for 6 hours and repeat the coagulation test. Mild: 5 vials Moderate: 10 vials Severe: 15 vials		Eleven patients recovered coagulation within 48 hours after an additional dose of antivenom 24 hours later; one experienced a recurrence without external bleeding but with pleural effusion. There was no relationship between the initial dose and recovery time.	Urticaria: 5 Nausea/vomiting: 4 Generalized rash: 3 Facial flushing: 3 Cramps: 2 Fever/chills: 1 Diarrhea: 1 Angioedema of the face: 1	Hives: 3 Nausea/ Vomiting: 2 Generalized Rash: 2 Cramps: 1 Fever/Chills: 1
Mendonça-da-Silva, I., et al. (11)	Prospective, randomized, open-label trial	*Bothrops* *Crotalus* *Lachesis*	116	The groups were stratified by type of snake	Antivenoms available for Bothrops, Bothrops-Lachesis and Bothrops-Crotalus		Bothrops bites: 2 vials for mild cases and 4 vials for moderate cases. Lachesis bites: 5 vials for mild cases. Crotalus bites: 2.5 vials for mild cases and 5 vials for moderate cases.	Bothrops bites: 4 vials for mild cases and 8 vials for moderate cases. Lachesis bites: 10 vials for mild cases. Crotalus bites: 5 vials for mild cases and 10 vials for moderate cases.	Most patients' clotting improves within 6-12 hours after receiving antivenom, returning to normal within 24 hours. However, some with pre-existing kidney damage may not recover, as the damage may have occurred before treatment.	Does not report	

Article	Type of study	Type(s) of snake(s) identified	Sample size	Bite classification	Type of antivenom administered by group		Administered dose		Coagulation times	Side effects / early reactions	
					Group A	Group B	Group A	Group B		Group A	Group B
Silva de Oliveira, S., et al. (10)	Prospective study of patients bitten by snakes	*B. atrox.*	100	LMild: 27 Moderate: 59 Severe: 14	Bothrops antivenom or Bothrops-Lachesis antivenom		It only describes the administration of doses corresponding to clinical severity (mild, moderate, severe)		Most patients' clotting improves within 6-12 hours after receiving antivenom, returning to normal within 24 hours. However, some with pre-existing kidney damage may not recover, as the damage may have occurred before treatment.	Does not report	

In general, the studies included both pediatric and adult populations, with a higher frequency of snakebite accidents in men, mainly involving bites localized on the feet and legs. The most frequently reported local signs at the time of admission were inflammation, pain, edema, bleeding, and blister formation, while among the systemic signs, gingival bleeding, nausea, and vomiting were identified (20,21).

The reviewed studies highlight the therapeutic value of various antivenoms in the treatment of envenomation by snakes of the *Bothrops* genus (11), without finding significant differences in terms of efficacy for restoring coagulation, controlling edema, or preventing systemic and local complications. However, some antivenoms, such as the one produced by the Butantan Institute, showed a higher incidence of adverse reactions, which required the administration of complementary treatment and affected its safety profile. The findings suggest that halving the conventional dose could be sufficient in mild and moderate cases, thereby reducing the risk of anaphylactic reactions.

Both monovalent and polyvalent antivenoms demonstrated high efficacy in neutralizing venom effects during the first 6 to 12 hours after the accident (20,21). In the context of Ecuador, although three antivenoms evaluated were effective, the Colombian antivenom showed faster correction of coagulopathy, while the Ecuadorian product presented a lower adverse reaction profile. Nonetheless, no relevant differences were observed in the resolution of local complications such as necrosis and infection (10,22). Specifically, antivenoms directed against *Bothrops* asper were safe and effective, with high percentages of coagulation recovery within the first 24 hours (22,23), although some patients required additional doses. Likewise, Brazilian antivenoms and others formulated from equine plasma showed the ability to normalize coagulation times within a period of up to 48 hours (20). For its part, Antivipmyn-Tri® demonstrated efficacy in the treatment of *Bothrops* envenomation in Colombia (14,24).

Discussion

This scoping review analyzed the therapeutic management and efficacy of the antivenoms used for the treatment of snakebite envenomation in Latin America, based on eleven studies—two prospective and nine randomized clinical trials—that evaluated antivenoms produced in Brazil, Costa Rica, Colombia, Ecuador, and Mexico. In terms of geographic distribution, five studies were conducted in Colombia, one in Ecuador, and five in Brazil. The

results show that both monovalent and polyvalent antivenoms are effective in the treatment of snakebite envenomation in the region (7,26).

The *Bothrops* genus continues to be responsible for more than 80% of snakebite cases in Brazil, Colombia, and Ecuador, clinically associated with local manifestations such as inflammation, hematomas, and, in many cases, systemic bleeding (21,22,23,25,26). Although snakebite envenomation represents a significant public health problem, mortality has decreased substantially with the availability of effective antivenoms (17,27). However, high rates of mortality and morbidity persist, mainly associated with factors such as delayed access to medical care and limited availability of these biologics in rural and remote regions.

In all studies, restoration of blood coagulability was considered a key marker of therapeutic efficacy. Data show that most antivenoms achieve normalization of coagulation times within 6 to 24 hours (26). Although no statistically significant differences in overall efficacy were observed among the products, the Colombian antivenom demonstrated faster correction of coagulopathy in the study conducted in Ecuador (24).

The management and dosage of antivenom have evolved from the initial recommendations formulated by Vital Brazil, which were based on calculating the dose from the maximum amount of venom injected by snakes of the *Bothrops* genus. Historically, up to 16 vials were administered in severe cases; however, more recent evidence supports an optimized dosing approach with fewer vials, maintaining therapeutic efficacy while reducing the incidence of adverse effects (17,25).

The safety of antivenoms remains a relevant concern. Early adverse reactions range from 10% to 87%, although most are mild and manageable (28). Antivenoms produced using caprylic acid purification, based on whole immunoglobulin G (IgG), have shown a better safety profile compared to other production processes (29). Consequently, the data suggest the need to move toward standardization of doses, as well as the adoption of production practices that prioritize safer formulations with lower reactogenic potential (30–32).

Conclusions

The studies included in this scoping review confirm that both monovalent and polyvalent antivenoms produced in Brazil, Colombia, Costa Rica, Mexico, and Ecuador are effective and safe for the treatment of snakebite envenomation caused by *Bothrops* species in Brazil, Colombia, and Ecuador.

The most recent formulations, particularly those purified by caprylic acid fractionation, present a better safety profile, with a lower incidence of adverse reactions.

The findings suggest the need to update clinical dosing guidelines, as well as to optimize the selection of available antivenoms in each region, in order to improve therapeutic efficacy and minimize treatment-associated risks. Likewise, it is essential that hospitals and health centers have access to effective, safe, and economically affordable antivenoms, ensuring their availability particularly in rural areas with high incidence. In addition, it is imperative to strengthen community education programs aimed at correcting misconceptions and promoting timely access to medical care, thereby supporting a comprehensive approach that combines biomedical knowledge with respect for local cultural practices.

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