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ORIGINAL ARTICLE

FACTORS FOR UNFAVORABLE EVOLUTION OF SNAKEBITES IN CHILDREN

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ABSTRACT

Pediatric patients have particularities in the clinical manifestations and complications of snakebite envenomation (SBEs), and few studies have examined this population. The objective of this paper was to study snakebites in a pediatric age group treated at a reference hospital and to evaluate factors associated with unfavorable evolution. A cross-sectional study with a clinical-epidemiological description and identification of the factors related to unfavorable evolution in patients aged <19 years old seen from January, 2018 to November, 2019 was performed. Complications related to the SBE, such as compartment syndrome, secondary infection, extensive necrosis, hemorrhage, and kidney damage, were considered unfavorable evolution. From the 325 patients in the sample, 58 were aged <19 years old; 40 (69%), 0-12 years old; and 18 (31%), 13-18 years old. All patients had local manifestations (mild, moderate, and severe), and 36 (62%) had an unfavorable evolution. Fourteen (24.1%) patients had compartment syndrome, with a significant risk association between 0 and 12 years old ($p = 0.019$). Two factors significantly contributed to unfavorable evolution: the timing from the bite to medical care being ≥6 hours and additional antivenom therapy needed. We conclude that the younger the patient, the smaller body segment affected, leading to disproportionality between the affected area and the amount of inoculated venom, contribute to more frequent local manifestations and complications in children rather than adults. Because of the relationship between body area and vascular volume in children differs from that in adults, the same volume of venom inoculated by snakes will be disproportionate in these two groups. Therefore, in the treatment of pediatric patients, increasing the volume of antivenom therapy is possibly necessary. Furthermore, as in adults, six hours between the bite to medical care increases the risk of complications and mortality.

KEY WORDS: Snakebites envenomation; venom; antivenom; pediatric population.

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INTRODUCTION

Snakebite envenomation (SBE) is a neglected public health problem in tropical countries (Williams et al., 2019). In 2022, 4,522 snakebite cases were reported in Brazil; 185/4,522 (4%) cases occurred in the State of Goiás. From these individuals, 43/185 (23%) were between 0-19 years old (Data SINAN, 2023).

The medical literature suggests that SBE are more severe in children than adults. However, several studies in Brazil (Santiago et al., 2006), the United States (Parrish et al., 1965), and in Palestine (Sadan & Soroker, 1970) have shown a lower lethality, fewer systemic complications, and a greater propensity for local signs and complications for children than for other age groups (Santiago et al., 2006; Oliveira et al., 1999).

Children have a more disproportionate body surface area and blood volume than adults, and sometimes, children require higher antivenom dosages than adults to improve venom neutralization and to prevent complications (Seifert et al., 2022). However, current treatment protocols use the same dose for children and adults (FUNASA, 2001).

The number of bothropic SBE involving children and teenagers is substantial, with 37 % of the accidents happening between 0 and 19 years old, according to an observation made by the Butantan Institute from 1982 to 1991 on Hospital Vital Brasil (Santiago et al., 2006). Nevertheless, the severity of the clinical manifestations and complications remains unclear. Thus, this study aimed to describe the epidemiological profile, clinical manifestations, and complications of snakebite accidents in children and teenagers.

MATERIAL AND METHODS

We collected and analyzed the clinical and epidemiological data from patients aged between 0 and 19 years old who were victims of snakebite accidents and treated at the Tropical Diseases Hospital (HDT) in Goiânia, Goiás, between January, 2018 and November, 2019. Patients were identified using the Epidemiological Surveillance Notification Local System, and their medical records were subsequently assessed.

Initially, the patients were categorized according to age: Groups 1 and 2 comprised patients aged 0-12 and 13-18, respectively. Next, the patients were regrouped according to clinical outcome: Groups A and B had favorable and unfavorable clinical evolution, respectively. The absence of complications was considered favorable clinical evolution.

The Ethical Committee Board of the Tropical Disease State Hospital Dr. Anuar Auad evaluated and approved the study under protocol number (CAE) 26164619.4.0000.0034. Patient consent was not required, considering the retrospective study design that used secondary data.

Data Analysis

Data collected from the hospital system were exported to a Microsoft Excel spreadsheet and analyzed using STATA software version 16.1 (StataCorp, Texas, USA). Distribution was verified using histograms. It was applied Qui-square or Fisher's exact test for association significance between groups and odds ratio with 95% confidence intervals for complications. P-values lower than 0.05 were considered significant.

RESULTS

We identified 325 individuals treated for SBE. Fifty-eight (17.8%) of these patients were aged under 19 years old. From these snake bites, 47 (81%) were attributed to snakes from the genus *Bothrops* and 11 (19%) from the genus *Crotalus*. From the 58 patients with a snakebite in this study, 40 (69%) were assigned to Group 1 and 18 (31%) to Group 2.

Snakebites occurred most frequently in rural areas (41 [69%] from the 58 cases). Most of the patients were males (74%, n = 43), and the lower limbs were the body parts most frequently involved in the accidents, with a total of 49 (84.5%) occurrences (Table 1).

All 58 patients presented local signs: 97% (57) pain, 85% (50) edema, 29% (17) ecchymosis, 12% (7) erythema, 12% (7) local bleeding, 7% (4) necrosis, and 5% (3) blister (Figure). Additionally, one 7-year-old child had cyanosis (2%), and one 18-year-old had dyspnea (2%).

There were 14 (13.8%) patients with compartment syndrome, 13 (92.5%) in Group 1 and only 1 in Group 2 (7.1%; aged 14 years old), leading to a significant association (p = 0.024).

Complications occurred in 62.1% (36/58) of the patients. From these patients, 27 (75%) had secondary infections, 14 (39%) had compartment syndrome, 3 (8%) had extensive necrosis, 13 (36%) had kidney damage, and 4 (11%) had bleeding. *Bothrops* accidents were statistically associated with secondary infections, demonstrating four times more chance for children under 12 years old to develop this complication. Also, compartment syndrome demonstrates an odds ratio of 9.6 (IC95% 1.1-435) and it should be explored more. Table 2 summarizes the complications on *Bothrops* between groups 1 and 2. Crotalic accidents were 11 cases and, the only complication was acute renal failure in 6 patients, 36% under 12 years old, and 2 (18%) with 13-18 years old. Although this analysis has double of children under 12 years old, the sample wasn't significant for this group of patients.

Table 1. 58 episodes of Snake Bite Envenomation´s characteristics according to the victim´s age group

	Group 1 ≤12 years old (n = 40)		Group 2 13-18 years old (n = 18)	
	n	%	n	%
Sex				
Male	30	75	13	72.2
Female	10	25	5	27.8
Time between bite and care				
0-1 hour	5	12.5	1	5.6
1-3 hours	2	5	8	44.4
3-6 hours	9	22.5	2	11.1
0-12 hours	8	20	3	16.7
1-24 hours	5	12.5	1	5.6
More than 24 hours	11	27.5	3	16.7
Snake genus				
Bothrops	32	80	15	83.3
Crotalus	8	20	3	16.7
Anatomic region				
Hand	7	17.5	2	11.1
Leg	10	25	6	33.3
Foot	23	57.5	10	55.6
Event occurrence zone				
Rural	28	70	12	66.7
Peri-urban	1	2.5	0	0
Urban	8	20	5	27.8
Severity				
Mild	11	27.5	9	50
Moderate	18	45	6	33.3
Severe	11	27.5	3	16.7
Case progression				
Cure	39	97.5	16	88.9
Self-discharge/transfer	1	2.5	2	11.1
Death	0	0	0	0

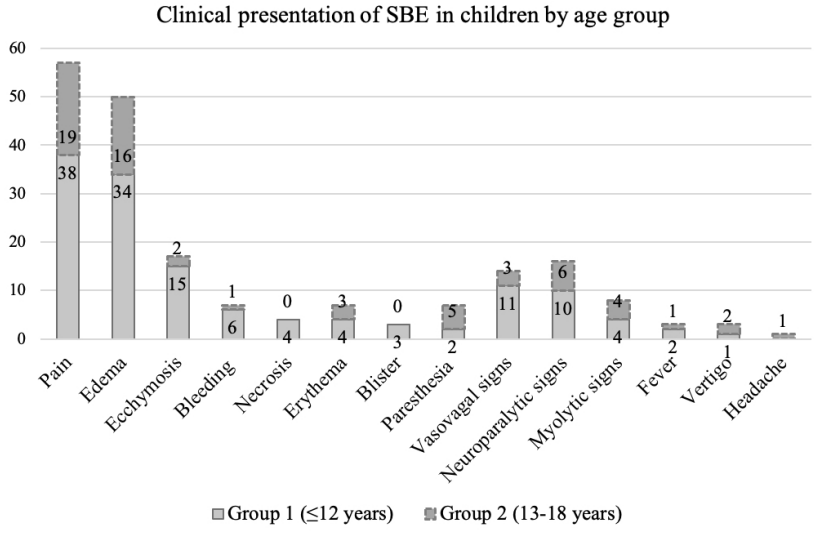

Figure. Clinical presentation and complications from Snakebite envenomation (SBE) in children by age group

Vasovagal signs: vomit, diarrhea; Neuroparalytic signs: eyelid ptosis, blurred vision; Myolitic signs: myalgia, anemia, dark urine

Table 2. Relationship between the complications of *Bothrops* Snakebite envenomation in children by age group

Local and Systemic Complications	*Bothrops* (n= 47)					
	Group 1 (n= 32)		Group 2 (n= 15)		Odds Ratio (IC95%)	p value
	n	%	n	%		
Local complications						
Secondary infection	22	68.8	5	33.3	4.4 (1- 20.5)	0.022
Compartment syndrome	13	40.6	1	6.7	9.6 (1.1- 435)	0.018
Extensive necrosis	2	6.3	1	6.7	0.93 (0.01- 58)	0.957
Systemic complications						
Kidney damage	5	15.6	2	13.3	1.2 (0.2- 14)	0.837
Hemorrhage	3	9.4	1	6.7	1.5 (0.1- 81)	0.756

Among the patients with an infection, 22 (81.5%) were in Group 1, and 5 (18.5%) were in Group 2. Sulfamethoxazole-trimethoprim (SMT-TMP) was the first-choice medication regimen for 15 (55.5%) patients, followed by amoxicillin with clavulanate for 12 (44.4%) patients, and cefepime for one 9-year-old patient (3.7%). Two patients from Group 1 required an antibiotic change from amoxicillin with clavulanate to SMT-TMP because of clinical failure using the first regimen.

There were a few cases of acute kidney injury, and 1 patient from Group 2 required hemodialysis for volemic control with the recovery of renal function during the same hospitalization.

No patients died during this study, with 95% cured. Three percent of patients were transferred to other hospital, and 2% were self-discharged against medical advice.

Table 3 describes the patients with favorable (Group A) and unfavorable (Group B) clinical evolution.

Table 3. Relationship between favorable (Group A) and unfavorable (Group B) clinical evolution from Snakebite envenomation in children

	Group A (n = 22)		Group B (n = 36)		p value
	n	%	n	%	
Age (in year old)					0.325
1 – 5	3	13.6	6	16.7	
6 – 9	6	27.3	13	36.1	
10 – 1	6	27.3	13	36.1	
15 – 18	7	31.8	4	11.1	
Sex					0.542
Male	16	72.7	27	75	
Female	6	27.3	9	25.0	
Accident classification					
Bothropic	17	77.3	30	83.3	0.725
Crotalic	5	22.7	6	16.7	0.535
Time between bite and care					0.010
< 6 hours	15	68.2	12	33.3	
≥ 6 hours	7	31.8	24	66.7	
Severity					0.000
Mild	14	63.6	6	16.7	
Moderate	8	36.3	16	44.4	
Severe	0	0	14	38.9	
Additional antivenom therapy					0.000
	0	0	14	38.9	

The time interval equal or greater than 6 hours between the bite and the patient care had a statistically significant association ($p = 0.010$) with unfavorable clinical evolution, as well as for the classification of the case as moderate or severe ($p < 0.000$).

All 58 patients received antivenom therapy. Initially, 45 (77.6%) patients received antibothropic serum (ABS), 10 (17.2%) received anticrotalic serum (ACS), and 3 (5%) received antibothropic-crotalic serum (ABCS) because they did not show classical clinical signs characteristic of crotalic or bothropic envenomation.

In 14 patients, additional antivenom therapy was necessary, which resulted in favorable clinical outcomes. From these children, 10 (71.4%) patients received ABS: 6 after their severity reclassification (5 were classified as having mild to moderate conditions, and 1 as having a moderate to severe condition), 2 due to clinical change, and 2 due to the permanence of coagulation disorder 24 hours after initial antivenom therapy. From the remaining 4 (28.6%) patients, 3 required ACS due to severity reclassification, and 1 required it due to clinical changes characterizing a crotalic accident.

DISCUSSION

Snakebite accidents in patients aged 18 years old or younger accounted for 19% of the total accidents in this study period, highlighting the importance of studying this event in the pediatric group. The high proportion of cases indicates the following: some snakebites occur far from labor activity in rural areas, snakes have predominantly nocturnal habits, and children and teenagers are not as protected as one might think (Williams et al., 2019; Ferreira et al., 2020; Santiago et al., 2006).

In Brazil, snakes of the genus *Bothrops* are responsible for 87% of snakebite accidents involving humans (Williams et al., 2019). The main local signs are pain, edema, and echymosis (Seifert et al., 2022). These signs are more frequent and intense in children than adults, especially in children aged under 12 years old. This phenomenon is probably due to the disproportion between the affected anatomical area and the amount of inoculated venom in children, contributing to local complications, such as abscess and compartment syndrome (FUNASA, 2001; Saborio et al., 1997). We observed an increased risk 4 times for infections and 9 times for compartment syndrome for children under 12 years old to develop these complications after a bothrops accident.

Recognizing compartment syndrome caused by snakebites, particularly in pediatric patients, is complex. There are several confounding factors, such as clinical signs caused by the direct action of the venom, pain and edema, markedly present in the subcutaneous tissue and not always in the compartmental space, in addition to the difficulties that children have in expressing symptoms and feelings (Wood et al., 2016; Hernandez et al., 2019). Thus, identifying predisposing

factors is relevant. Hernandez et al. (2019) identified the presence of tachycardia, leukocytosis, anemia, and period of time between bite and care longer than 24 hours as predictors for the development of compartment syndrome in this age group, favoring an early surgical approach.

This study demonstrates a statistical association between the time of the accident and patient care to unfavorable clinical evolution and complications. The first 6 hours after the accident are the most important ones to decrease morbidity and mortality because, during this time a high concentration of circulating venom can be found within the body and it can be neutralized by heterologous antivenom therapy (FUNASA, 2001; Marano et al., 2021). Our findings of crotalic complication was renal failure, as previously reported by FUNASA (2001).

Another relevant finding was that 40% (14/37) of the patients had unfavorable clinical evolution and they required additional antivenom therapy. From these, 57% (8/14) were due to reclassification of the accident type. The quantity of venom inoculated in a child is the same as in an adult. By contrast, the vascular volume of a child is lower than that of an adult, resulting in an increased concentration of circulating venom (Seifert et al.,2022). For this reason, children may require a higher dosage from specific antivenom (Seifert et al., 2022).

In addition, well-known protocols for ophidian accidents consider the same therapeutic approach for adults and for the pediatric population in Brazil (FUNASA, 2001) and in other countries (Marano et al., 2021). In this sense, studies that evaluate the prediction of severity based on laboratory tests are important and they can identify patients who require an increased amount of a specific antivenom. In the Boels et al. (2012) severity score adapted by Marano et al. (2014) for children who receive snakebites from members of the *Viperidae* family, information such as leukocyte counts greater than 11,000, neutrophils greater than 65%, and INR greater than 1.5 are severity criteria that help to guide the therapeutic approach related to heterologous antivenom therapy (Marano et al., 2021; Harry et al., 1999; Le Geyt et al., 2021).

Although this study is retrospective and it has a small sample size, its findings support the need for large studies to improve the understanding about complications presented by pediatric patients with snakebites.

Although the literature shows lower mortality from snakebites in children than adults, high morbidity remains in children, with those younger than 5 years old the most predisposed to develop complications (Sankar et al., 2013; Lahori et al., 1981). Some factors related to child morbidity have been identified and it can be modified. For example, the time between the accident and heterologous antivenom administration can be reduced through decentralized distribution in the health system. Another factor that can be improved is the administration of an increased antivenom dosage to neutralize the concentration of circulating venom (Harrison et al., 2009).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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