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Envenoming by the rattlesnake *Crotalus durissus ruruima* in the state of roraima, Brazil

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ABSTRACT

The aim of this study was to evaluate the clinical-epidemiological factors associated with victims of rattlesnake envenoming in the state of Roraima, Brazil. In this location, rattlesnake accidents are caused by the subspecies *Crotalus durissus ruruima*. This is a prospective observational study carried out at the General Hospital of Roraima from april 2017 until july 2018. A total of 37 alleged rattlesnake victims had their medical records evaluated. However only one of them proved to be by *C. d. ruruima*. All individuals were residents from the savannas (lavrados) of Roraima. The town of Bonfim on the border between Brazil and Guyana had the highest occurrence of rattlesnake bites. The most affected group were males aged 13–20 years and farmers. The highest number of incidents occurred during daytime and lower limbs (feet) were the most major affected part of the body. Tourniquets were used as first aid after snake envenoming in 32.4% of victims. Out of 37 patients, 16.2% were classified as severe cases of snakebite envenoming and in 5.4% dry bites seem to have occurred. Among the symptomatic patients, 100% presented local manifestations and 70.3% presented systemic manifestations. The clinical setting showed local effects such as pain and edema while the systemic effects were blurred vision, myalgias, myasthenic facies, palpebral ptosis, muscle weakness and headache. Laboratory results of aspartate aminotransferase (62.2%), creatine phosphokinase (51.3%), lactic dehydrogenase (37.8%), urea level (32.4%) and serum creatinine (29.7%) were increased significantly in relation to the reference standards. In 16.2% of the cases, the victims presented acute kidney injury. Patients were treated with anticrotalic serum in 70.3% of the cases and antibotropic + anticrotalic serum in 24.3%. The victims of *C. d. ruruima* in Roraima showed a local symptomatology similar to *Bothrops* envenoming, while systemic symptoms and laboratory analysis proved kidney and muscular injuries, similar to envenoming by *Crotalus d. terrificus* in Brazil.

1. Introduction

Snakebite envenoming is a public health problem in many parts of the world and is considered a neglected disease (WHO, 2017). In Latin America, there are four genera of venomous snakes that are clinically relevant: *Lachesis*, *Micrurus*, *Bothrops* and *Crotalus*, the last two are the snakes mainly responsible for the accidents in Brazil (Brasil, 2001).

The snakes of *Crotalus* genus (family Viperidae) originated in North America and subsequently spread across Central and South America. The *Crotalus durissus* species is restricted to South America and has a discontinuous and wide geographical distribution from Colombia to Argentina (Wüster et al., 2005).

The *C. durissus* subspecies have shown great biochemical and pharmacological venom variations, which is related to their geographical

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distribution (Calvete et al., 2010). According Costa and Bérnils (2018) there are four recognized subspecies of *C. durissus* in Brazil: subspecies of *Crotalus d. durissus* in Amapá; *C. d. terrificus* in Minas Gerais, São Paulo, Santa Catarina, Paraná, Rio Grande do Sul and Mato Grosso do Sul; *C. d. marajoensis* in open areas of Marajó Island in Pará and *C. d. ruruima* in the savanna (lavrado) of Roraima.

Venoms are a complex mixture of distinct proteins and peptides with diverse biological activity. The venom of *C. d. terrificus* is composed of the toxins such as convulxin (Prado-Franceschi and Vital-Brazil, 1981), gyroxine (Barrabin et al., 1978), crotoxin (Slotta and Fraenkel-Conrat, 1938) and crotamine (Radis-Baptista and Kerkis, 2011).

Brazilian *Crotalus durissus* envenomings cause neurotoxic, myotoxic and coagulant actions (Gutiérrez, 2002). They are responsible for symptoms at the site of the bite, such as pain, edema, paresthesia and erythema. In most cases, only paresthesias and bite marks occur. Erythema and edema are rare, and when they occur they are discrete, usually close to the affected site, being ascending edema unusually observed. In addition to local manifestations, other systemic symptoms characterize the effect of envenoming like myasthenic facies, prostration, drowsiness, myalgia, urine alterations (reddish or dark), kidney failure, bleeding among others (Bucaretchi et al., 2002; Pardal et al., 2007; Faro et al., 2020). These clinical manifestations are accompanied by increased serum levels of the enzymes aspartate aminotransferase (AST), creatine phosphophokinase (CPK), lactate dehydrogenase (LDH), myoglobin, urea and creatinine in blood (Azevedo-Marques et al., 1985, 1987bib_Azevedo_Marques_et_al_1985bib_Azevedo_-Marques_et_al_1987; Cupo et al., 1991; Bucaretchi et al., 2002). The severity of the envenoming depends on the volume of the venom injected, the bite site and symptom intensity. In Brazil, crotalic envenomings may be classified based on clinical manifestations as mild, moderate and severe. This classification is used as therapeutic and prognostic guidance for choosing the specific antivenom for the treatment of snakebite patients (Brasil, 2001).

In Roraima, snake envenoming is an important public health problem (Nascimento, 2000); nevertheless, only one fatal case of rattlesnake envenoming has been registered in this region Northern Amazonia (Medeiros et al., 2020). The venom of *Crotalus durissus ruruima* can present a yellow or white coloration (Dos-Santos et al., 1993a). The white venom shows biological activity similar to the *C. d. terrificus*, with a lethal, coagulant, myotoxic, edematogenic and hemolytic activity (Dos-Santos et al., 1993a). The yellow variety causes hemorrhagic, necrotic, caseinolytic activities and has the toxin crotamine in its venom composition (Dos-Santos et al., 1993a,b). In order to fill in the lack of information concerning the envenoming by *C.d. ruruima*, the purpose of this work is to determine the clinical, laboratory and epidemiological profile of victims of *C. d. ruruima* snakes assisted at the General Hospital of Roraima. These victims (or their companions) incriminated and reported during medical care that they had been bitten by a rattlesnake, accusing that the snake presented a rattle on the tip of their tail.

2. Methods

This is a prospective observational study carried out at the General Hospital of Roraima from april 2017 until July 2018, and included patients who claimed to have been bitten by a rattlesnake. All of the victims were admitted to the General Hospital of Roraima (HGR) which is a reference for the treatment of snake envenoming.

The State of Roraima is located in the northernmost portion of Brazil, with natural vegetation in a mosaic of landscapes that range from savannas (northeast) to forests (south and west), and different types of oligotrophic (nutrient-poor) systems such as campos (grasslands), campinas and campinaranas (low woodlands on white-sand soils) in the center-south portion of the state and has fifteen municipalities along the borders with Pará, Amazonas (Brazil), Venezuela and Guyana.

All patient's information was collected during medical care in HGR, using forms developed by the authors. The forms contained the following data: (i) epidemiological characteristics (gender, age, profession, municipality, month of the year and time of the day when the bite occurred, bite site, time of treatment, use of tourniquet, symptom's severity and antivenom used; (ii) clinical manifestations: local and systemic; and (iii) serum laboratory tests performed, to evaluate possible muscle and renal lesions.

Concerning the clinical diagnosis of the victims, to validate the snake genera responsible for the accident, the following criteria were established: (i) presentation of the offending animal and/or (ii) presence of neurotoxic manifestation and/or (iii) alterations in laboratory tests of renal function and muscle enzymes and/or (iv) the spontaneous information given by the victims themselves or by their companions of the presence of a tail rattle in the offending snake.

Tests such as urinary myoglobin to detect myoglobinuria and partial thromboplastin time to determine clotting were unavailable and therefore not performed.

The envenoming severity was classified as mild, moderate or severe according to the criteria established by the Brazilian Ministry of Health (Brasil, 2001) based on the diagnostic manual and treatment of envenomings. Cases were considered mild when patients presented only local pain and edema, without neurological manifestations. The moderate envenoming cases showed discrete or evident myasthenic facies, mild myalgia and no change in color and urinary volume. Severe cases were the ones presenting evident and intense neurotoxic signs and symptomes, generalized myalgia, dark urine, possibly presenting oliguria or anuria. Envenoming cases were classified as dry bite when they did not present local or systemic clinical manifestations and had normal laboratory tests.

Symptomatic patients received crotalic polyspecific antivenom (AV) or a combination of crotalic (AC) with botropic antivenom (AB) on suspicion of *Bothrops* envenoming. Each 10 ml ampoule of anticrotalic serum contains heterologous, F(ab')2 fragment of immunoglobulin, that neutralizes 1.5 mg of *C d. terrificus* venom per mL. Each 10 mL ampoule of antibotropic serum contains heterologous F(ab')2 fragment of immunoglobulin, that neutralizes 5.0 mg of venom of *Bothrops jararaca* per mL of antivenom. The antivenoms were produced by the Butantan Institute of São Paulo and Ezequiel Dias Foundation in Belo-Horizonte, Minas Gerais State, Brazil.

3. Results

All victims of the study are from the state of Roraima, Brazil, where an area of native open vegetation called lavrado (Fig. 1).

According to reports of the injured patients admitted to the HGR and their companions, the snakebite they suffered was caused by a rattlesnake; however, only one patient brought in the snake which was identified as *C. d. ruruima* (Fig. 2).

Regarding the annual frequency of envenoming, a higher occurrence was observed in 2017, with 24 cases (64.9%), when compared to 2018, with 13 cases (35.1%). The higher accident frequency happened mainly in the period from January to June (54.1%). However, most of them occurred in June when 21.6% was recorded (data not shown).

Table 1 presents the epidemiologic characteristics of the envenomed patients. Results show that there is a higher frequency of accidents in males, age group from 13 to 20 years, farmers, from the municipality of Bonfim, during daytime, and the most affected corporal segment were the feet. Concerning the time elapsed between the accident and the patient's medical care; most of the cases received treatment up to 6 h after the accident and were classified as mild. Concerning the rattlesnakebite treatment, the anticrotalic antivenom was the therapeutical most used followed by antibotropic (AB) + anticrotalic (AC) antivenom. Monovalent antivenom (AC) was used when victims presented neurotoxicity symptoms, typical of crotalic accidents, and were capable of describing rattlesnakes' characteristics. AB antivenom was the treatment of choice when only generic symptoms such as pain and edema were observed, and no particular snake characteristics were initially

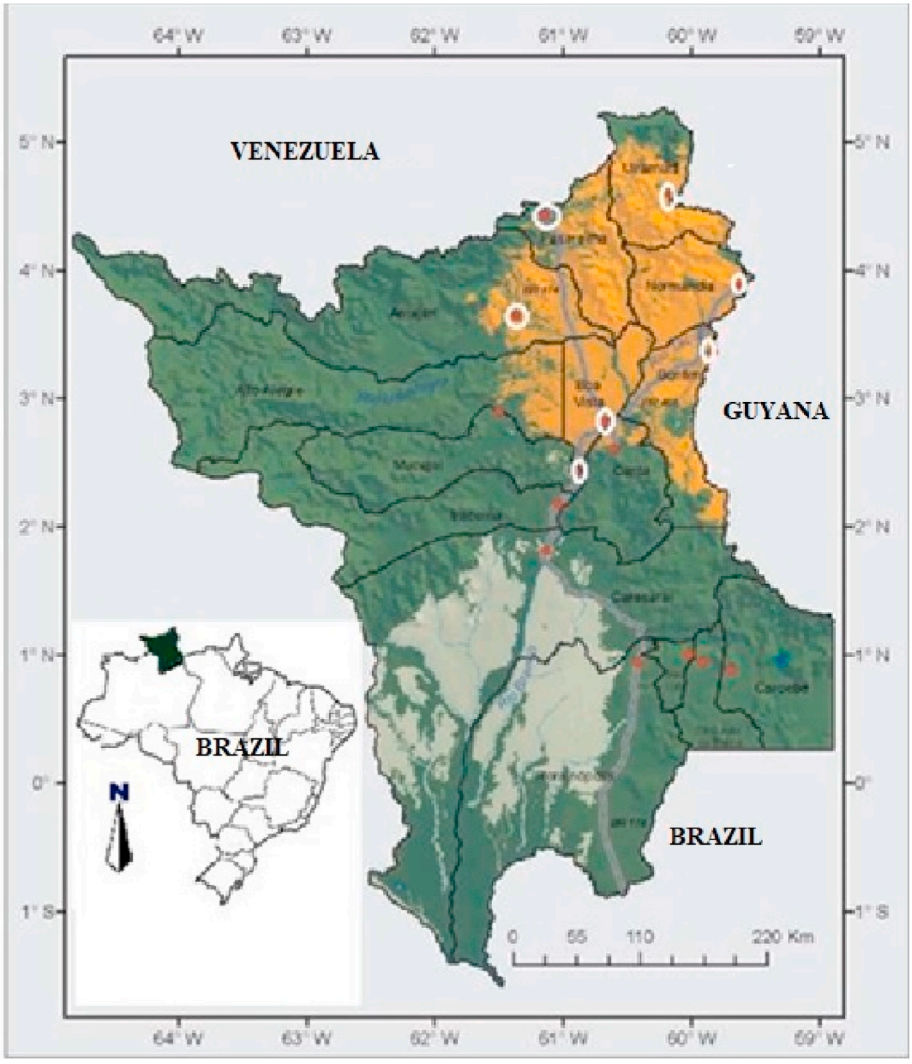

Fig. 1. Map of Roraima, Brazil, adapted from Barbosa and Bacelar-Lima (2008), the highlighting in white and yellow indicate the municipalities with snakebite case recorded in the savanna (lavrado).

Fig. 2. The *Crotalus durissus ruruima* snake responsible for envenoming of a victim.

described.

In relation to the clinical manifestations, 5.4% of the injured patients did not present symptoms (dry bite). 100% of the patients of the symptomatic group present local manifestations and 70.3% systemic manifestations. The most common signs and symptoms were pain (91.9%) and edema (73.0%), that were classified from mild (48,1%) to moderate (51,9%). In 10.8% of the cases edema became ascendant (Fig. 3A), therefore, three patients had edema extending over more than one segment of the bitten limb and the other in two segments. Table 2 shows that the most frequent systemic manifestations were dark vision (35.2%), myalgias (27.0%), muscle weakness (24.3%), myasthenic facies (24.3%) (Fig. 3B) and headache (24.3%).

When analyzing, through Fischer's exact test, the relationship between local edema and the service time of patients treated up to 6 h and between 7 and 24 h, the test showed $p = 0.681$ and, between local edema with the severity of the envenomings, the victims classified as

Table 1
Frequency distribution of the epidemiologic characteristics in the patients envenomed by *Crotalus durissus ruruim* at General Hospital in Roraima, Brazil.

Variable	n.	%
Gender		
Male	29	78.4
Female	8	21.6
Age group (years)		
13–20	13	35.2
21–30	4	10.8
31–40	7	18.9
41–50	8	21.6
51–60	4	10.8
61–70	1	2.7
Employment status		
Farmer	18	48.7
Student	8	21.6
Domestic	3	8.1
Teacher	2	5.4
Others	6	16.2
Municipality		
Bonfim	15	40.6
Uiramutá	6	16.2
Boa Vista	4	10.8
Amajarí	4	10.8
Pacaraima	4	10.8
Normandia	3	8.1
Mucajaí	1	2.7
Time to treatment (hours)		
<3	9	24.4
4 to 6	12	32.4
7 to 12	7	18.9
13 to 18	3	8.1
19 to 24	6	16.2

Parameters	n.	%
Time of day		
Morning	11	29.8
Afternoon	18	48.6
Evening	8	21.6
Snakebite site		
Hand	6	16.2
Leg	2	5.4
Foot	29	78.4
Tourniquet		
Yes	12	32.4
No	25	67.6
Severity		
Dry bite	2	5.4
Mild	16	43.2
Moderate	13	35.2
Severe	6	16.2
Antivenom		
None	2	5.4
Crotalic	26	70.3
Bothropic + Crotalic	9	24.3

mild severity, 12 had local edema and four without edema; among the moderate, 12 with edema and one without edema and among the severe, five with edema and one without edema ($p = 0.3432$). However, when we analyzed the edema in relation to the use of the tourniquet, the observed result was $p = 0.0010$, suggesting that there may have been a worsening of the local edema.

Results of the laboratory tests on the snakebite victims' serum (Table 3) show an increase in AST levels (59.4%), above the reference range, and the average level and standard deviation obtained was 332.26 ± 561.55U/L). An increase in CPK (51.4%) and in LDH (43.24%) levels were also observed. The averages and standard deviation for.

CPK and LDH were respectively 4652.77 ± 4575.04U/L and 1063.59 ± 772.05U/L. Therefore, these results suggest different degrees of skeletal muscle injury. The levels of serum urea increased 32.43%, with an average and standard deviation of 62.91 ± 32.99 mg/dl. The increase in serum creatinine was of 13.51%, and this evaluates kidney function. According to the guidelines of the Brazilian Medical

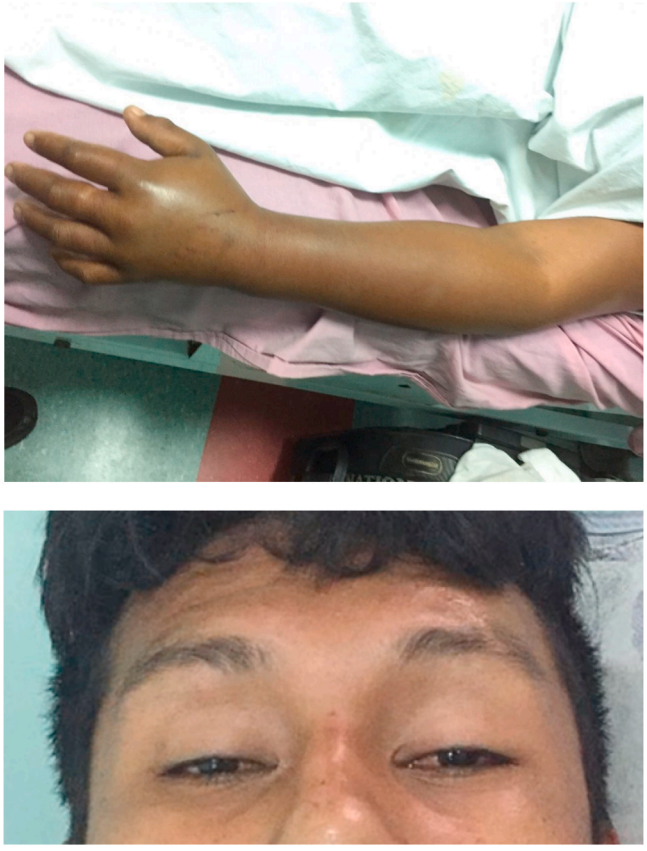

Fig. 3. Envenomings by*Crotalus durissus ruruima*in Roraima, Brazil. **A**-snake bite on the left hand with local and ascending edema. **B**- myasthenic facies showing bilateral palpebral ptosis.

Table 2
Frequency distribution of clinical manifestation of *Crotalus durissus ruruima* envenoming at General Hospital of Roraima, Brazil.

Symptom/Sign[a]	n.	%
Bite site		
Asymptomatic	2	5.4
Pain	34	91.9
Heat	11	29.8
Erythema	4	10.8
Local edema	27	73.0
Ascending edema	4	10.8
Paresthesia	6	16.2
Bleeding	9	24.3
Equimose	1	2.7
Systemic manifestations		
Asymptomatic	10	27.0
Myasthenic facies	9	24.3
Palpebral ptosis	9	24.3
Dark vision	13	35.2
Double vision	8	21.6
Dizziness	4	10.8
Headache	9	24.3
Nausea	8	21.6
Vomiting	3	8.1
Abdominal pain	3	8.1
Myalgias	10	27.0
Urine reddish or dark	5	13.5
Oliguria	2	5.4
Muscle weakness	9	24.3
Dificulty of walking	2	5.4
Fevers	3	8.1

[a] Some envenoming patients had more than one sign or symptom.

Table 3
Laboratory exams of serum to evaluate the muscle and renal injury frequency distribution by *Crotalus durissus ruruima* at the General Hospital of Roraima, Brazil.

Exams	n.	%	Range	Mean/standard deviation
AST				
<40U/L	11	29.72		
>40U/L	22	59.45	41.20 to 2704,01	332.26 ± 561.55
Not done	4	10.81		
CPK				
<200U/L	3	8.1		
>200U/L	19	51.4	212.65 to 12627.33	4652.77 ± 4575.04
Not done	15	40.6		
LDH				
<190U/L	0	0		
>190U/L	16	43.24	320.0 to 2684.71	1063.59 ± 772.05
Not done	21	56.75		
Urea				
<40 mg/dl	25	67.56		
>40 mg/dl	12	32.43	41.26 to 156.79	62.91 ± 32.99
Not done	1	2.70		
Creatinine				
<1.2 mg/dl	26	70.27		
>1.3 a 1.4 mg/dl	5	13.51		
>1.5 mg/dl[a]	5	13.51	1.67 to 9.96	3.52 ± 3.61
Not done	1	2.70		

[a] Guidelines of the Brazilian Medical Association and Brazilian Nephrology Society (Yu et al., 2007).

Association and the Brazilian Society of Nephrology (Yu et al., 2007), acute kidney failure is characterized by increased creatinine levels higher than 1.5 mg/dl. In the present report serum creatinine level was higher than the reference range in 13.51% of cases, and the average and standard deviation obtained was 3.52 ± 3.61 mg/dl.

In relation to patients bitten by snakes who had clinical manifestations compatible with the botropic accident, in which AB was initially administered, Table 4 shows the nine clinical cases, the time between the bite and the medical assistance, severity, local and systemic symptoms and the results of muscle enzymes. Of the nine patients, 88.8% had mild manifestations, with pain and local edema being the most frequent symptoms and without manifestations of systemic neurotoxicity. Regarding muscle enzymes, there was an increase in AST levels of 66.6%, in CPK of 77.7% and in LDH of 55.5%, with their respective means and standard deviation of 149.41 ± 135.76U/L, 2835.11 ± 3953.59U/L and 522.64 ± 287.46U/L.

4. Discussion

In this study, patients were selected based on their claims to have been bitten by rattlesnakes or by proving the identity of the snake responsible for the accident. In addition, patient selection was also based on the clinical history of envenoming and the snake description according to information provided by the victims and/or companions, who said that there was a rattle located at the end of the snake's tail, which is an important characteristic of this snake. All injured patients were from the State of Roraima, where *C. d. ruruima* subspecies is endemic (Hoge and Romano, 1972).

In Brazil, according to the Ministry of Health (Brasil, 2019), 57,414 snake envenoming cases were recorded from 2017 to 2018. Among the Brazilian regions, the North contributed with 18,448 cases. In the State of Roraima, 1038 envenoming cases were recorded during the same period. The cases notified were assigned to snakes from Elapidae, *Micrurus* genus (7 cases, 0.67%) and from the Viperidae family, the genera *Bothrops* (742 cases, 71.48%), *Crotalus* (159 cases, 15.31%) and *Lachesis* (37 cases, 3.56%). To non-venomous snakes were attributed 25 (2.4%), and to unidentified snakes 68 (6.55%) cases.

A higher incidence of envenomings occurred in Amazonas State during the months with a higher rainfall index. In Acre (Moreno et al., 2005) and Amapá States (Lima et al., 2009), the rainy season period occurs from january to april while in the state of Roraima it is from march to june (Araújo et al., 2001), which corroborate with our findings that showed a correlation between the higher rainfall period and the highest incidence of rattlesnake bites recorded in June. This is probably due to the increase of river and lake's water levels during the rainy season which consequently tends to concentrate snakes in dry places thus increasing their encounters with humans.

Regarding the gender, there was a prevalence of accidents in males, farmers, and the age group between 13 and 20 years. The highest number of accidents happened during the daytime and they can be related to work in the rural area or leisure activities. Previous works showed similar results as Nascimento (2000) in the savanna of Roraima State as well as Lima et al. (2009) in the State of Amapá and Moreno et al. (2005) in the State of Acre.

The victims involved in this study came from the rural area of several municipal districts: Boa Vista, Uiramutá, Amajarí, Pacaraima, Normandia and Bonfim. All of these areas are located in a native open vegetation area called lavrado (Barbosa and Barcelar-Lima, 2008) that is the habitat of *C. d. ruruima* in Roraima. The highest records of envenomings were in the municipality of Bonfim in the northeast of the State at the border with Guyana. Some victims looked for medical care in the municipality of Lethan in Guyana. However, Guyanese health services did not have the specific antivenom, and because of that, the victims were sent back to Roraima, to the HGR in Boa Vista for medical

Table 4
Distribution of the frequency of clinical manifestations and muscle enzymes in nine patients envenomed by of *Crotalus durissus ruruima* and treated at Hospital Geral de Roraima, Brazil.

Cases	Time for help	Gravity	Local syntoms	Systemic syntoms	AST	CPK	LDH
1	8	Moderate	Pain, edema, ascending edema, Paresthesia, Heat	Nausea, Vomiting, myalgia	21	219.62	338.25
7	7	Mild	Pain	Dizziness	111	4190.66	–
27	5	Mild	Pain, edema, paresthesia	Headache. myalgia	–	67.12	460.54
32	6	Mild	Pain, edema	-	46.4	383.90	–
33	1,30	Mild	–	-	48.01	–	330.26
34	6	Mild	Pain, paresthesia, bleeding	-	47.56	372.62	459.82
35	22	Mild	Pain, edema, heat, bleeding	-	–	–	–
36	24	Mild	Pain, edema	-	321.77	10300.69	1024.36
37	4	Mild	Pain, edema	-	321.77	1543.19	–

assistance. According to Nascimento (2000), the highest incidence of *C. d. ruruima* in Roraima occurs in open areas of the municipalities of Normandia, Boa Vista and Bonfim.

In relation to the time elapsed between the accident and medical care, all patients received treatment from 6 to 24 h after the bite. The most common is about 6 h. These results are similar to those obtained by Rebouças Santos (2019) in the Amazon. But they differ from other Brazilian regions: in Amapá and Ceará the medical treatment is normally received after more than 12 h (Lima et al., 2009) while in São Paulo and Paraíba this time is reduced to 3 h (Bucaretchi et al., 2002; Oliveira et al., 2013).

Regarding the clinical data, Brazilian literature (Bucaretchi et al., 2002; Oliveira et al., 2013; Rebouças Santos et al., 2019) shows that the most affected corporal segments in snakebite are the lower limbs. Feet are especially affected due to non-use of protective equipment during daily activities.

According to the here-obtained data, tourniquets were used as first aid in 12 cases (32.4%) to limit the spread of the venom in the body, with the appearance of edema at the bite site in 11 patiens (5 mild and 6 moderate) and one with ascending edema of moderate intensity. However, this practice is not recommended. Indeed, besides its ineffectiveness, the tourniquet applied in the field can increase the severity of *Crotalus durissus* envenoming, consequently leading to complications (Amaral et al., 1998).

According to Cupo et al. (1991) and Bucaretchi et al. (2002) in São Paulo, the subspecies *C. d. terrificus* was responsible respectively for moderate (23.8% and 29.0%) and severe (76.2% and 58.6%) envenomings. In the present studies with *C. d. ruruima* in Roraima the severity was classified as moderate (35.2%) and severe (16.2%).

A small percentage (5.4%) of injured people falls into the category of “dry bite”. These victims had no local or systemic features. Some studies including the incidence of dry bite by *Crotalus* were reported in the literature by Bucaretchi et al. (2002) and Naik (2017).

It is observed in the medical reports from the symptomatic patients that all of them had local symptoms and 73.0% systemic symptoms. Among the local manifestations, the most frequent were pain (91.9%), edema (73.0%), heat (29.7%) and bleeding (24.3%), all at the bite site, of mild intensity and without blood coagulation assessment measured, which are similar to envenoming by *Bothrops atrox* (Pardal et al., 2004). These findings differ from those reported by Cupo et al. (1991) and Bucaretchi et al. (2002) who observed a lower frequency of pain (38.1% and 48.3%, respectively) and edema (71.4% and 64.5%), similar in envenoming by *C. d. terrificus*.

In this study, the pain intensity and local edema ranges from mild to moderate, and edema spreading to other segments besides the affected limb were also observed (10.8%). These results are in disagreement to other reports of envenoming by C. *d. terrificus* in Brazil, where pain (Cupo et al., 1991) and edema (Bucaretchi et al., 2002) were discreet without ascending edema. In North and Central America, rattlesnake envenomings often present with pain, edema, equimoses, blisters and necrosis, at the bite site as well as the whole affected limb (Russell et al., 1997; Corbett and Clark, 2017). In the report from the HGR, no blisters or necrosis were observed at the affected site.

There was no statistical significance between the relationship between local edema and hospital service time, as well as between local edema and the severity of the envenomoing, however, significant between the use of the tourniquet and local edema. Suggesting that the application of a tourniquet may worsen local edema. According to Amaral et al. (1998) the application of a tourniquet is ineffective in reducing the severity of envenomig by *Crotalus durissus*.

Regarding symptoms, there was no systemic manifestation of *C. d. ruruima* envenoming in 27%, differently from what was observed by the study of Cupo et al. (1991), where all the victims presented systemic manifestations. The most frequent neurological manifestations in the systemic symptomatic victims are: myasthenic facies, palpebral ptosis, muscle weakness, headache, dark and double vision. The symptoms observed by Pardal et al. (2007) and Faro et al. (2020) were drowsiness, myasthenic facies, bipalpebral ptose, ophthalmology and dark vision impairment in victims of *C. d. marajoensis* envenoming on Marajó Island, Brazil. In the State of São Paulo, Bucaretchi et al. (2002) and Cupo et al. (2003), describe the envenoming by *C. d. terrificus*. The symptoms observed are myasthenic facies, diplopia, myalgia, drowsiness, muscle weakness, palpebral ptosis, prostration and mydriasis. Neurological manifestations are rare in envenoming by *Crotalus durissus* in Central and North America (Russell et al., 1997; Bush and Siedenburg, 1999), where predominate manifestations are mainly cytotoxic and hemotoxic venom components (Corbett and Clark, 2017), while the Brazilian *C. d. terrificus* venom induces myotoxic, neurotoxic and coagulation actions (Azevedo-Marques et al., 1985, 1987bib_Azevedo_Marques_et_al_1985bib_Azevedo_Marques_et_al_1987; Bucaretchi et al., 2002; Cavalcante et al., 2017), and the rattlesnake venom from Roraima according Medeiros et al. (2020), it induced neurotoxicity, myotoxicity without alteration in coagulation.

Table 2 shows other systemic manifestations as myalgia and urine reddish or dark, which were also reported among rattlesnake victims in South America by Jorge and Ribeiro (1992) and Bucaretchi et al. (2002). According to Azevedo-Marques et al. (1985, 1987) myalgia occurs with rhabdomyolysis, which is commonly associated with myoglobinuria and myoglobinemia and is responsible for urine reddish or dark and acute kidney injury. Urinary myoglobin tests could prove muscle injury. However, they were not performed due to no reagent availability for the assay.

The envenoming symptoms found in this study can be explained by individual venom variability in *C. d. ruruima* snakes. The biological activities of the yellow and white venoms of *Crotalus durissus ruruima* have been studied and compared with the *Crotalus durissus terrificus* venom (Dos-Santos et al., 2005). The white venom is found to be the most lethal, coagulant, myotoxic, edematogenic and hemolytic, similar to the poison of *C. d. terrificus* (Dos-Santos et al., 1993a). Yellow venom of *C. d. ruruima* shows hemorrhagic, necrotic, caseinolytic and crotamine activities (Dos-Santos et al., 1993a,b). The caseinolytic activity of the yellow venom of *C. d. ruruima* is three-fold higher than the white venom of *C. d. terrificus* or *C. d. ruruima*. On the other hand, Cavalcante and Ponce-Soto (2015) showed that the venom of *C. d. ruruima* and *C. d. . cumanensis* displays neurotoxic activity due to crotoxin activity, and crotoxin from *C. d. cumanensis* was more potent than that from *C. d. ruruima* venom. Intraspecific variation in venoms and activity are present among the American rattlesnakes.*Crotalus durissus* from North and Central America presents a high cytotoxic and hemotoxic activity, but low neurotoxicity (Gutiérrez 2002; Russell et al., 1997; Corbett and Clark, 2017). The rattlesnakes from South America show low local intensity activity and strong neurotoxic activity, like *Crotalus durissus* from the South of Brazil and Argentina which presents primarily neurotoxic activity (Brazil, 1972).

South American rattlesnake venom causes structural damage to the muscle. In the present study we observed an elevation in CPK, LDH and AST activity. This suggests the occurrence of rhabdomyolysis. Dos--Santos et al. (1993a) demonstrate by histopathological experimental study that the white venom of *C. d. ruruima* is more toxic than yellow to muscle fibers.

Azevedo-Marques et al. (1985) described for the first time that the elevation in CPK, LDH and AST enzymes and the presence of urinary myoglobin produced by crotalic envenoming confirm muscle injury. Magalhães et al. (1986) also observed rhabdomyolysis following the South American rattlesnake *Crotalus durissus terrificus* venomation, and other Brazilian authors corroborated these findings Bucaretchi et al. (2002), Cupo et al. (2003), Pardal et al. (2007). Studies show that myonecrotic activity of snake venom is caused by both the action of phospholipase A2 (PLA2) and crotoxin, although PLA2 has less potent activity than crotoxin (Gutiérrez et al., 2008).

Kidney function evaluation was performed with serum urea and creatinine dosage, but urinary bladder volume was not measured.

According to the Guidelines of the Brazilian Society of Nephrology (Yu et al., 2007), acute kidney failure (AKI) is based on serum creatinine dosage and urinary bladder volume. In this research, creatinine presents an average level of 3.1 mg/dl, suggesting kidney injury. Indeed, creatinine is the most reliable and commonly used marker for assessment of glomerular function. This renal complication is caused if the venom contains crotoxin, gyrotoxin and phospholipase A2, which are found in rattlesnake venoms (Monteiro et al., 2001; Martins et al., 2002). AKI is reported after snakebite envenomings by *Crotalus durissus* in Brazil, by Azevedo-Marques et al. (1985), Jorge and Ribeiro (1992), Bucaretchi et al. (2002) and Naik (2017), therefore corroborating the findings of this report.

All patients included in the study were hospitalized due to the rattlesnake bite; however only one snake was brought in by the patient to prove that the accident was caused by *C. d. ruruima*. This patient, while working in an agriculture field, was bitten by the snake on his right foot. The medical care was provided in an interval of 7 h after the bite, and the victim reported mild local pain and dizziness without other complaints. Laboratory assessment revealed an elevated AST (111 U/L) and CPK (4190.6 U/L). The LDH test was not performed. The serum urea and creatinine were within normal levels. The envenoming was classified as mild intensity, after being administrated five ampoules of crotalic antivenom. The cured patient was discharged from the HGR.

When evaluating the nine patients suspected of envenoming by *Bothrops*, it is observed that local pain and edema were the most frequent clinical manifestations. These symptoms are absent in the accident by *C. d. marajoensis* (Faro et al., 2020) and less frequently in acidentes caused by *C. d. terrificus* (Cupo et al., 1991; Bucaretchi et al., 2002), however, frequent in accidents by *Bothrops* (Pardal et al., 2004), which led to the suspicion of botropic envenoming and induced doctors to use AB. However, after a new assessment of the cases, with information from the companion and the results of changes in muscle enzymes in laboratory tests, even without systemic neurotoxic manifestations, led to the assumption that it was rattlesnake envenomig and that the specific AC was administered. Bucaretchi et al. (2002) and Faro et al. (2020), show that the increased of muscle enzymes are suggestive of rattlesnake envenomings in Brazil.

Rattlesnake envenoming treatment protocol is established according to the Brazilian Ministry of Health criteria for the diagnosis and treatment of ophidian accidents. The treatment takes into account the intensity of local and/or systemic manifestations. It establishes crotalic polyspecific antivenom, applied intravenously, in dosages according to the severity of envenoming (Brasil, 2001). In this study, all symptomatic patients received crotalic alone or combination of bothropic (AB) + crotalic (AC) antivenom. Antibotropic was applied on suspicion of envenoming being caused by *Bothrops*. However, after patients and/or companions affirmed and described the snake as a rattlesnake, the anticrotalic was applied. The administration of bothropic antivenom was applied similarly to the protocol for *Bothrops* envenoming according to the local symptomatology of the victims (Moreno et al., 2005). The patients evolved without complication and received discharge from the HGR.

In conclusion: the present work has some limitations, such as the lack of an unequivocal identification of the offending snake by the majority of the evaluated patients and the unavailability of some laboratorial tests. Nevertheless, this report describes the clinical and epidemiological manifestations of victims of venomous snakes admitted to the General Hospital of Roraima, Brazil, who claimed to have been bitten in the savannas (lavrados) of Roraima presumably by *Crotalus durissus ruruim*a. However only one of them proved the accident was caused by *C. d. ruruima*. The local symptoms observed were similar to envenoming provoked by *Bothrops* snakes, predominating pain and edema with a lower frequency of ascending edema. Neurological systemic symptoms/signs and laboratory tests demonstrated kidney and muscular injuries, similar to envenoming by *Crotalus d. terrificus* in Brazil. However, the acidentes reported here showed to be less severe when compared to other reports in other Brazilian regions. All of these patients received crotalic antivenom or combined crotalic + bothropic antivenom and evaluated to cure without any sequelae.

Author contributions

MSA, RCCC, MACG, CMM and PPOP designed the study; MSA, RCCC, AGM collected the data; CDCO, MACG and PPOP analyzed the data; RCCC and MSA performed the figures. All authors read, revised and approved the manuscript.

Ethical aspects

This research was approved by the Brazilian Medical Ethics Research Committee (Institutional Review Board, Plataforma Brasil) of the University of Pará (UFPA) approval number (CAAE: 69320917.1.0000.0017).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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