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Bites by the colubrid snake *Philodryas patagoniensis*: A clinical and epidemiological study of 297 cases

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ABSTRACT

We retrospectively analyzed 297 proven cases of *Philodryas patagoniensis* bites admitted to Hospital Vital Brazil (HVB), Butantan Institute, São Paulo, Brazil, between 1959 and 2008. Only cases in which the causative animal was brought and identified were included. Part of the snakes brought by the patients was still preserved in the collection maintained by the Laboratory of Herpetology. Of the 297 cases, in 199 it was possible to describe the gender of the snake, and seventy three (61.3%) of them were female. The length of snakes (snout-vent length) ranged from 160 to 1080 mm. In 117 snakes their state of preservation enabled the dissection and examination of their stomach contents. The stomach was empty in 106 snakes (89.1%). Most bites occurred in the seasons of spring and summer ($n = 196$, 66.0%) and during warmer periods of the day. The mean age of the victims was 24.1 ± 15.1 years old and 206 (69.4%) patients were men. Around 92% of the patients sought medical care within 6 h after the bite. Both lower ($n = 188$, 63.3%) and upper limbs ($n = 102$, 34.3%) were most frequently bitten, especially the feet and hands ($n = 205$, 69.0%). The local clinical manifestations were pain ($n = 151$, 50.8%), transitory bleeding ($n = 106$, 35.7%), erythema ($n = 47$, 15.8%) and edema ($n = 39$, 13.1%). Ecchymosis was not observed. Only 7 (2.4%) patients reported systemic symptoms characterized by mild dizziness and 88 patients (29.6%) showed no evidence of envenoming. The whole blood clotting time was performed in 76 (25.6%) patients on admission and all of them had coagulable blood. Supportive treatment was offered to only 13.4% of patients, namely administration of antihistamines ($n = 19$, 6.4%) and analgesics ($n = 12$, 4.1%). Eight patients (2.7%) were mistreated with *Bothrops* antivenom before their admission to HVB. No sequels or relevant complications were observed in patients, and the prognostic was benign. Therefore, although *P. patagoniensis* accidents can cause mild local symptomatology, it is very important that health professionals know how to make the correct diagnosis to avoid unnecessary use of antivenom.

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1. Introduction

In Brazil, approximately 26,000 snakebites were reported in 2008 and most of these (~73%) were caused by *Bothrops*-like species and only 3% caused by non-venomous snakes (SINAN, 2009), including colubrids. Since in many cases the offending species was not identified and the diagnosis was established by clinical findings, it is possible that some of these unidentified bites have been caused by colubrids (Nishioka and Silveira, 1994; Ribeiro et al., 1994; Prado-Francheschi and Hyslop, 2002; Salomão et al., 2003).

Despite the biological relevance and abundance of colubrid snakes in the world, little information is known about the composition and biological activities of their venoms. The *Philodryas* genus, belonging to the Dipsadidae family (Zaher et al., 2009), is widespread in all South America with 17 species, 10 of which can be found in Brazil. These are considered of minor clinical significance to humans and, therefore, have received little attention from the clinical point of view. However, they are able to produce secretions from Duvernoy's gland, currently synonymized by Fry et al. (2003) as the venom glands, which are toxic enough to produce lesions at the bite's site. Several species of *Philodryas* cause accidents with clinical significance (Prado-Francheschi and Hyslop, 2002): *Philodryas aestivus* (Fowler and Salomão, 1994), *Philodryas baroni* (Kuch and Jesberger, 1993), *Philodryas chamissonis* (Otero et al., 2007), *Philodryas olfersii* (Nickerson and Henderson, 1976; Silva and Buononato, 1983/84, Fowler and Salomão, 1994; Ribeiro et al., 1999) and *P. patagoniensis* (Martins, 1916; Fowler and Salomão, 1994; Nishioka and Silveira, 1994; Araújo and Santos, 1997).

P. patagoniensis is an opistoglyphous snake that has diurnal habits, being semi-arboreal, predominantly terrestrial (Marques et al., 2001; Sazima and Haddad, 1992; Fowler and Salomão, 1994; Hartmann and Marques, 2005), occupying open environments such as fields and savannas (Lema, 1973; Thomas, 1976). Fig. 1 shows the species distribution in South America. They are 0.5 to approximately 1 m long, weighing between 100 and 250 g (Fig. 2). In the few cases of human accidents described in the literature, only local symptoms, such as edema, pain, itching, and slight increase in temperature at the site of the bite, have been described (Martins, 1916; Nishioka and Silveira, 1994; Araújo and Santos, 1997). In all these cases no systemic symptoms or coagulopathy were reported.

In 1916, Naur Martins conducted the first studies with this venom, noting proteolytic and hemolytic actions without coagulant activity, pain, swelling and hemorrhage in animal models (Martins, 1916). Over eighty years later, neuromuscular activity of this venom in mice was demonstrated (Souza-Filho et al., 2000). Recently, biochemical and biological characterization of this venom and the study of the mechanisms of local action such as pain and edema have been reported (Acosta et al., 2003; Peichoto et al., 2004, 2005, 2006, 2007, 2009; Rocha and Furtado, 2007; Zelanis et al., 2010).

While these experimental studies suggest a potential severity of these bites (and the possibility misidentification of *P. patagoniensis* bites as *Bothrops* bites), there is, apparently, an absence of significant symptoms in the few cases described in the literature. Therefore, we decided to study the epidemiological and clinical aspects of the *P. patagoniensis* accidents.

2. Material and methods

2.1. Study design and population

A retrospective study was conducted by reviewing the records of patients admitted to Hospital Vital Brazil (HVB), Butantan Institute, São Paulo, Brazil, between January, 1959 and December, 2008, with diagnosis of snakebite by *P. patagoniensis*. Only proven cases, in which the causative animal was brought and identified, were included. The taxonomical identification of the snakes involved in envenomations was carried out at the Herpetology Laboratory of Butantan Institute, which still preserves most of the snakes brought since 1959. *P. patagoniensis* preserved in this collection were dissected and the following data was collected: reproductive status, gender, genital tract, stomach or intestine contents, and snout-vent-length (SVL). The critical values of SVL between immature and adult *P. patagoniensis* males and females are 42 cm and 47 cm respectively (Fowler and Salomão, 1995). Physicians through the use of a standardized form reviewed the records. The following variables were analyzed: gender and age of patients, month and time of the accident, circumstance and site of the bite, use of tourniquet, variables related to the snake, clinical manifestations, whole blood clotting time (WBCT), when carried out, and treatments. The study maintained the privacy of the patients' data, with approval of the Ethics Committee (Protocol number: 5502).

2.2. Statistical analysis

To ascertain whether the values were normally distributed, the Kolmogorov–Smirnov test was used. The chi-square test was applied for the analysis of the significance of data obtained. When at least one cell of the 2×2 contingency tables presented an expected frequency of less than 5, Fisher's exact test was used. Mann–Whitney test for independent samples was used to study the association between clinical manifestations and time between the bite and the admittance to the hospital, and the association between clinical manifestations and the length of snakes. Values of $p < 0.05$ were considered statistically significant.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows (version 15.0, 2006; Statistical Products and Service Solutions Inc., Chicago, IL, USA).

3. Results

Two hundred ninety seven medical records were analyzed, with 5.9 accidents per year. All cases occurred in the city of São Paulo and surrounding areas with predominance of accidents in rural areas. Of the 297 patients, 206 were men (69.4%) and 91 were women (30.6%) distributed according to age as shown in Table 1. The mean age of the patients was 24.1 ± 15.1 years old, and the median age was 22.0 years old (interquartile range 11.0–36.0). Although

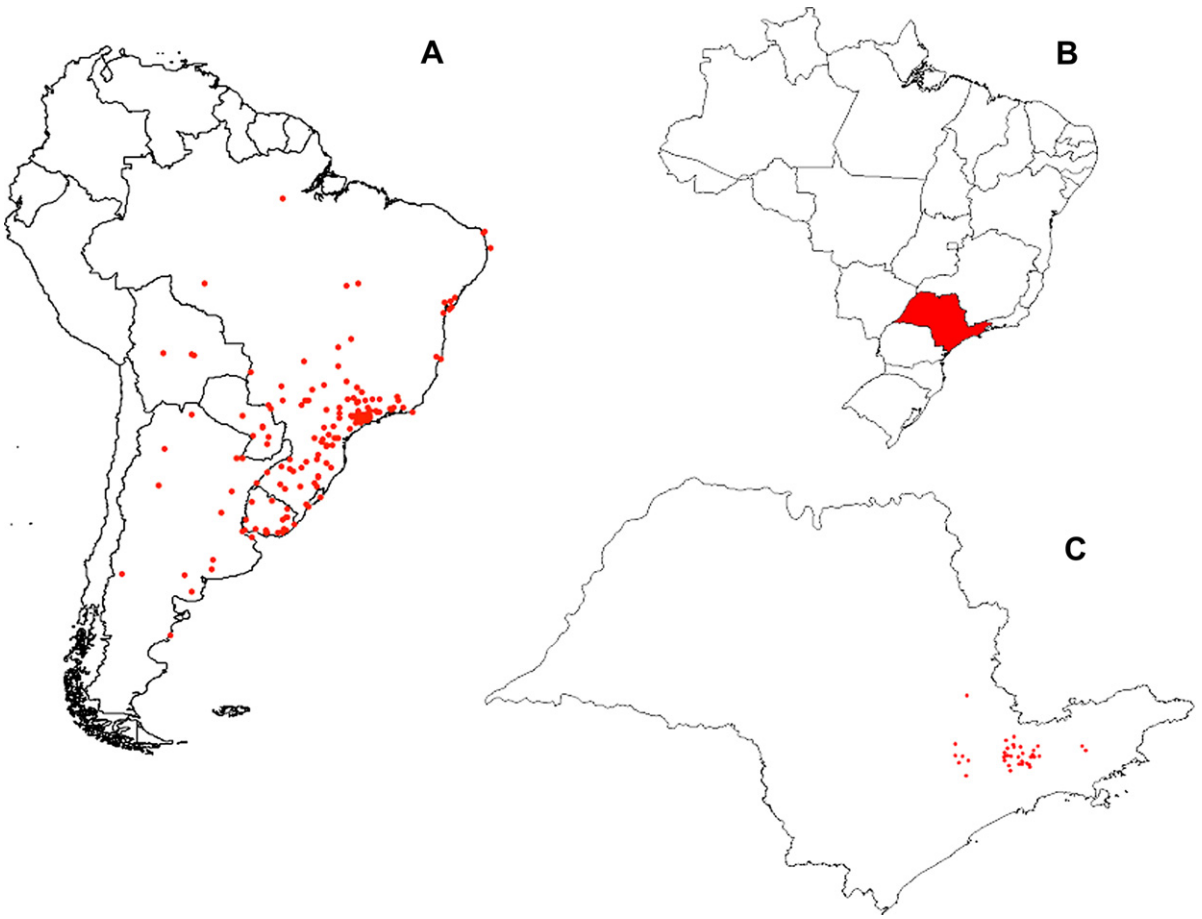

Fig. 1. Distribution of *Philodryas patagoniensis* in the South America (A) and in São Paulo State, Brazil (B). Origin of cases of *P. patagoniensis* bites admitted to the HVB in São Paulo State (C).

most patients were younger than 29 years (195 patients, 65.7%, $X^2 = 29.1$, $p < 0.001$) and were predominantly men ($X^2 = 44.5$, $p < 0.001$), no statistically significant differences were found for the distribution of accidents by age group according to gender ($X^2 = 7.8$, $p = 0.164$).

Of the 297 patients bitten, in 199 it was possible to describe the gender of the snake. Seventy three (61.3%) were female. The stomach contents were evaluated in 119 snakes and were empty in 106 of them (89,1%). Only in 117 snakes did the preservation status allow them to be measured. The SVL ranged from 16 to 108 cm. Sixty (51.3%) were immature and 57 (48.7%) adult.

The number of *P. patagoniensis* bites occurring during the spring and summer (October–March) seasons was 196 (66.0%) and during autumn and winter (April–September) seasons it was 101 (34.0%). Therefore, a higher frequency of accidents was noticed during the spring and summer seasons ($X^2 = 30.4$, $p < 0.001$). Most cases occurred between 10 a.m. and 1 p.m. ($n = 118$, 39.7%), and 1 p.m. and 4 p.m. ($n = 105$, 35.4%) ($X^2 = 165.4$, $p < 0.001$). Female snakes were responsible for the majority of the accidents ($X^2 = 4.442$, $p = 0.035$).

The lower limbs were the sites where bites occurred most frequently ($n = 188$, 63.3%), followed by the upper limbs ($n = 102$, 34.3%) ($X^2 = 165.7$, $p < 0.001$). The feet ($n = 114$, 38.4%) and the hands ($n = 91$, 30.6%) were the anatomical regions most frequently bitten (Table 2). The time between the bite and the admittance to the hospital was usually less than 6 h ($n = 271$, 91.6%). A tourniquet had been applied proximal to the bite in 30 cases (10.1%).

As shown in Table 3, local clinical manifestations included pain ($n = 151$, 50.8%), transitory bleeding ($n = 106$, 35.7%), erythema ($n = 47$, 15.8%) and edema ($n = 39$, 13.1%) (Fig. 3). Ecchymosis was not observed. Only 7 (2.4%) patients reported systemic symptoms characterized by mild dizziness. Eighty eight patients (29.6%) showed no evidence of envenoming, although presenting signs of the bite. But it is likely that the real percentage of dry bites could be more expressive, since several of these manifestations (edema, pain, dizziness, erythema, and hemorrhage) could be explained by another causes than envenoming.

The WBCT was performed in 76 (25.6%) patients on admission and all of them had coagulable blood (mean = 6.4 ± 2.1 min, median = 6.0, interquartile range 5.0–8.0 min).

Table 4 shows that 40 patients (13.4%) received supportive therapy, namely antihistamines ($n = 19$, 6.4%)

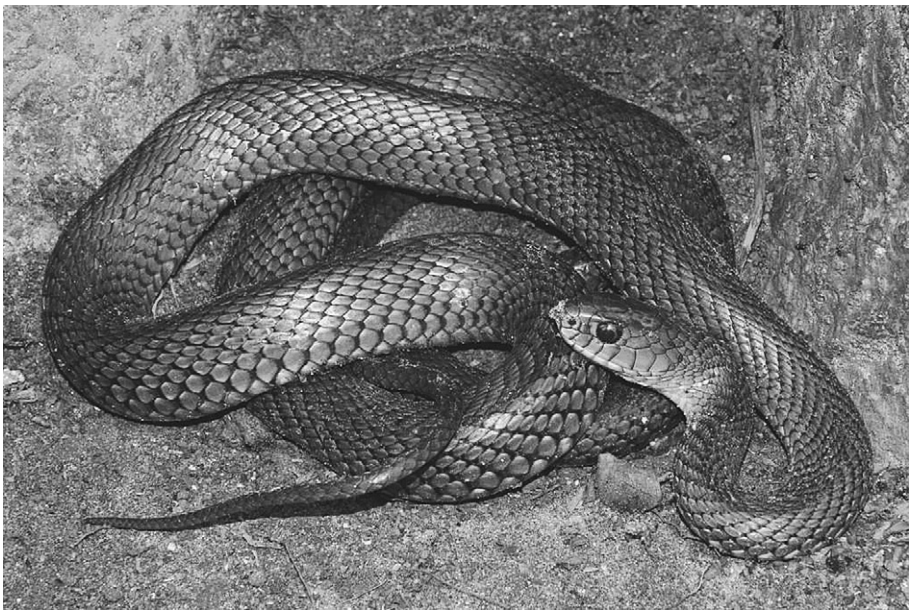

Fig. 2. *Philodryas patagoniensis* (adult) from São Roque City, São Paulo State, Brazil. Total length not recorded.

and analgesics ($n = 12$, 4.1%). Eight patients (2.7%) were treated with *Bothrops* antivenom before their admission to HVB.

There was no significant association between the age of the snake (immature or adult) and clinical manifestations including local pain ($X^2 = 0.24$, $p = 0.62$), edema ($X^2 = 0.81$, $p = 0.36$), transient local bleeding ($X^2 = 0.14$, $p = 0.70$) and local erythema ($X^2 = 0.18$, $p = 0.66$).

There was no significant association between SVL and local clinical manifestations including pain ($p = 0.363$), transitory bleeding ($p = 0.235$), erythema ($p = 0.752$) and edema ($p = 0.732$) using Mann–Whitney test for independent samples.

In addition, no significant association between the presence of stomach contents and local clinical manifestations including pain ($p = 0.436$), transitory bleeding ($p = 0.753$), erythema ($p = 0.450$) and edema ($p = 0.508$) was found.

Moreover, there was no significant association between snake gender and local clinical manifestations including pain ($p = 0.471$), transitory bleeding ($p = 0.875$), erythema ($p = 0.651$) and edema ($p = 0.648$).

There was a positive association between the use of tourniquet and local edema ($p < 0.001$) (Table 5).

In addition, no significant association between local edema and time between the bite and the admittance to hospital was found using Mann–Whitney test for independent samples ($p = 0.441$).

Secondary infection was observed in 3 subjects (1.0%) with no sequels during the follow-up of patients, and the prognostics were benign.

4. Discussion

Most accidents occurred in young adults males and involved the lower limbs. We have observed the same results in other venomous snakebites (genera *Bothrops*, *Crotalus* and *Lachesis*) in Brazil (Brasil, 1998).

The distribution of *P. patagoniensis* bites by month (spring and summer) and time of day was similar to those caused by *Bothrops* and *Crotalus* spp (Ribeiro and Jorge, 1990; Jorge and Ribeiro, 1992), probably reflecting the seasonal variation of human activities, often occupational-related (Warrell, 1992). However, some biological

Table 1
Distribution of *P. patagoniensis* bites according to age and sex of patients, HVB, Butantan Institute, São Paulo, Brazil, from 1959 to 2008.

Age (Years)	Sex		Total *n* (%)
	Females *n* (%)	Males *n* (%)	
0–9	25 (8.4)	35 (11.8)	60 (20.2)
10–19	20 (6.7)	49 (16.5)	69 (23.2)
20–29	15 (5.0)	51 (17.2)	66 (22.2)
30–39	11 (3.7)	37 (12.5)	48 (16.2)
40–49	13 (4.4)	22 (7.4)	35 (11.8)
50 and +	7 (2.4)	12 (4.0)	19 (6.4)
Total	91 (30.6)	206 (69.4)	297 (100.0)

Table 2
Distribution of *P. patagoniensis* accidents according to the site of the bite, HVB, Butantan Institute, São Paulo, Brazil, from 1959 to 2008.

Site of the sting	*n* (%)
Hands	91 (30.6)
Arms	11 (3.7)
Feet	114 (38.4)
Legs	74 (24.9)
Others	3 (1.0)
Not informed	4 (1.4)
Total	297 (100.0)

Table 3
Main symptoms manifested by patients after *P. patagoniensis* bite, HVB, Butantan Institute, São Paulo, Brazil, from 1959 to 2008.

Symptom	*n* (%)
Local pain	151 (50.8)
Local Hemorrhage	106 (35.7)
Local erythema	47 (15.8)
Edema	39 (13.1)
Ecchymosis	–
Systemic symptoms (only mild dizziness)	7 (2.4)
Asymptomatic	88 (29.6)

characteristics and behavior of these animals could also explain these findings.

The reproduction in *P. patagoniensis* is seasonal, restricted to spring, and egg laying and hatching in midsummer (Fowler et al., 1998), which coincides with the main peaks of accidents observed herein. The majority of accidents in these seasons was caused by female snakes ($X^2 = 4.4$, $p = 0.035$), which could be explained by an increment of activity related to the higher reproductive cost and, therefore, a greater energy required by this gender (Shine, 1980; Albolea et al., 1999; Madsen and Shine, 2000).

The majority of the accidents occurred in the hottest periods of the day, which is in accordance with the diurnal habits and the thermoregulation periods of the snake (Gibson and Falls, 1979; Sazima and Haddad, 1992), increasing the chances of encountering the animal (Aldridge and Brown, 1995). This same profile was found in other epidemiological studies such as Albolea et al. (1999) for the species *P. olfersii*, *P. patagoniensis* and *Liophis miliaris*.

Similarly to Albolea et al. (1999), our results showed that bites by specimens of *Philodryas* occur most often in hands and feet. Accidents with these snakes usually occur when a person steps into the animal without seeing it or after trying to manipulate it. This explains the higher number of bites on the feet and hands (Warrell, 1992). The tendency to consider these snakes as harmless, which in turn leads to greater handling of this species and less regard for the possibility of envenomation (Prado-Francheschi and Hyslop, 2002) could also explain these findings.

The fact that the use of tourniquet was more frequent in patients with edema could be due to the limitation of venous return instead of having been caused by the direct action of venom.

The major local clinical manifestations reported were pain, transient bleeding, erythema and edema. Such events are consistent with some cases previously published (Martins, 1916; Nishioka and Silveira, 1994; Araújo and Santos, 1997). In spite of the fact that some experimental envenoming studies *in vivo* have showed edematogenic, nociceptive and high haemorrhagic activity (Peichoto et al., 2004, 2005; Rocha and Furtado, 2007), none of the patients showed spontaneous systemic hemorrhage. Peichoto et al. (2007) showed α-fibrinogenolytic and haemorrhagic activities, but our patients only presented transitory local bleeding from the bite wound without ecchymosis. This is an example of a clear dissociation between animal model and human accident. Probably the transient bleeding observed in some patients was caused only by the mechanical action of the fangs.

The pathogenesis of venom-induced local effects is rather complex, mainly involving the action of metalloproteinases (Acosta et al., 2003; Peichoto et al., 2004). However, the combined action of metalloproteinases and other venom components cannot be ruled out, as well as the release of various endogenous inflammatory mediators, as it has been described for *Bothrops* venoms (Trebien and Calixto, 1989; Teixeira et al., 1994; Moura-da-Silva et al., 1996; Chacur et al., 2002).

Peichoto et al. (2006) showed that when this venom was administered i.v. it induced histopathological modifications

Fig. 3. Edema caused by a *Philodryas patagoniensis* bite a few hours after the accident. Tourniquet was not used.

Table 4
Therapies used for patients bitten by *P. patagoniensis*, HVB, Butantan Institute, São Paulo, Brazil, from 1959 to 2008.

Therapy	*n* (%)
Antihistaminic	19 (6.4)
Analgesic	12 (4.1)
Cortisone	2 (0.7)
Antihistaminic and analgesic	3 (1.0)
Others	4 (1.3)
Total	40 (13.5)

Table 5
Association between the use of tourniquet and local edema.

Local edema	Use of tourniquet		Total
	No	Yes	
No	238	16	254
Yes	24	13	37
Total	262	29	291

in vital organs of mice, e.g. multifocal hemorrhage in cerebellum, brain and lung sections, severe peritubular capillary congestion in kidney sections and degeneration in liver sections. However, mild dizziness was the only systemic manifestation observed in our patients (2.4% of all patients) and, as discussed above, it could have been caused only by patient anxiety or hyperventilation.

Even though all these venom activities have been described, surprisingly, we did not observe severe envenomation. It is possible that this venom does not have the same effects in humans. It may be that the amount of venom injected is minimal in most accidents due to the anatomy of the inoculating teeth (located in the posterior region of the maxilla) of these serpents (rear-fanged snakes) and, therefore, the difficulty to inject their venom. This would also explain why 29.6% of these accidents were dry bites.

The WBCT was performed in 76 patients on admission and all of them had coagulable blood. Peichoto et al. (2005) showed no clotting activity in the *P. patagoniensis* venom, neither thrombin-like activity that converts fibrinogen to fibrin nor procoagulant enzymes that produce thrombin.

Forty (13.5%) patients received supportive therapy, namely antihistamines and analgesics.

Eight patients (2.7%) were mistreated with *Bothrops* antivenom before their admission to HVB, apparently without having presented any adverse reaction. Nishioka and Silveira (1994) reported a case of biting by *P. patagoniensis* in a 5-year-old child, who was wrongly diagnosed and treated as a bothropic accident, receiving 10 ampoules of serum; however, the authors do not describe the evolution of the patient after having received the serum. Although Rocha et al. (2006) showed that the lethal action of the venom was neutralized by the *Bothrops* antivenom in rats, there is no evidence in the literature that this antivenom has any significance to treat human accidents.

We observed three (1.0%) patients with secondary infection. Of course, this could be a result of injuries caused by the fangs of the snake in the cutaneous surface associated with the local inflammatory activities of the venom.

There are few papers that evaluate variables related to the venomous snakes with clinical picture (Ribeiro and Jorge, 1989; Jorge et al., 1999; Oliveira et al., 2003). In *Bothrops jararaca* accidents it was demonstrated that blood incoagulability was more frequent in young snakes compared to adult snakes (Ribeiro and Jorge, 1989; Oliveira et al., 2003). Jorge et al. (1999) demonstrated that patients bitten by *Bothrops*-like snakes with more than 60 cm in length required amputation more frequently than the other patients. However, there was no association between local clinical picture and variables related to the snakes (such as SVL, age, gender and stomach contents of the snakes involved in the accidents).

In terms of treatment, as initial steps after the accident it is recommended to wash the site with clean water and soap, as well as to use local antiseptics (Puorto and França, 2003). Of course, the use of tourniquet, suction, incisions, or any domestic actions should be discouraged. The treatment of local manifestations should be symptomatic.

The use of antibothropic antivenom is strongly not recommended (Prado-Franceschi and Hyslop, 2002). Firstly, there is no evidence that it can neutralize toxins from the *P. patagoniensis* venom. Secondly, as we have observed, the vast majority of accidents are mild, or they do not even present any relevant clinical manifestations at all. All this makes it unacceptable to expose patients to the risk of a adverse reaction to the antivenom.

In conclusion, although *P. patagoniensis* accidents can cause mild local symptomatology, it is very important that physicians know very well this kind of accident in order to provide the correct treatment to victims, avoiding unnecessary distress to the patient, and over prescription of antivenom, which may eventually cause severe untoward effects.

Conflict of interest statement

None declared.

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