

Snakebites by *Bothrops* spp in children in Campinas, São Paulo, Brazil

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SUMMARY

From January, 1984 to March, 1999, 73 children under 15 y old (ages 1-14 y, median 9 y) were admitted after being bitten by snakes of the genus *Bothrops*. Twenty-six percent of the children were classified as mild envenoming, 50.7% as moderate envenoming and 20.6% as severe envenoming. Two patients (2.7%) showed no signs of envenoming. Most of the patients presented local manifestations, mainly edema (94.5%), pain (94.5%) ecchymosis (73.9%) and blisters (11%). Local and/or systemic bleeding was observed in 28.8% of the patients. Before antivenom (AV) administration, blood coagulation disorders were observed in 60.7% (incoagulable blood in 39.3%) of the 56 children that received AV only in our hospital. AV early reactions, most of which were considered mild, were observed in 44.6% of these cases (in 15/30 patients not pretreated and in 10/26 patients pretreated with hydrocortisone and histamine H₁ and H₂ antagonists). The main clinical complications observed were local infection (15.1%), compartment syndrome (4.1%), gangrene (1.4%) and acute renal failure (1.4%). No deaths were recorded. There were no significant differences with regard to severity of envenoming versus the frequency of blood coagulation disorders among the three categories of envenoming ($p = 0.75$) or in the frequency of patients with AV early reactions between the groups that were and were not pretreated ($p = 0.55$). The frequency of local infection was significantly greater in severe cases ($p < 0.001$). Patients admitted more than 6 h after the bite had a higher risk of developing severe envenoming ($p = 0.04$).

KEYWORDS: *Bothrops* spp; Snakebites; Children; Antivenom; Early reactions

INTRODUCTION

According to the Brazilian Ministry of Health, snakes of the genus *Bothrops* are the most important cause of snakebites in this country³. From 1990 to 1993, bites by *Bothrops* spp accounted for 90.5% of the 65,911 accidents involving snakes in which the genus was known or suspected, with a lethality rate of 0.31%³. Acute renal failure, shock, acute respiratory failure and sepsis have been reported as the main causes of death in these accidents^{1,3,19}.

Bothrops venoms contain many biologically active peptides and proteins that can cause local inflammatory cell responses, local muscle lesions and hemostatic disturbances^{3,5,11-13,22}. *Bothrops* venoms may activate coagulation factor X and prothrombin and lyses fibrinogen, causing hypofibrinogenemia or complete fibrinogen consumption which can result in partial or complete blood incoagulability¹¹⁻¹³. These venoms may also alter platelet function and show hemorrhagic activity (hemorrhagins) as a result of the degradation of the basement membrane of the blood vessel wall^{11-13,22}.

Twenty-one percent of snakebites in Brazil occur in patients under 15 years old². However, a search of the literature (Pub Med, 1965-2000 and LILACS, 1981-2000) revealed that no study has specifically described the clinical aspects of *Bothrops* snakebites in a case series of

children in Brazil. This report describes the clinical aspects and outcome of bites caused by *Bothrops* spp snakes in children less than 15 y old admitted to the University Hospital of the State University of Campinas, São Paulo (UNICAMP).

PATIENTS AND METHODS

The hospital records of 73 patients was prospectively collected over a 16-year period (January, 1984 - March, 1999). The diagnosis was based on the envenoming syndrome and/or snake identification.

In all cases, information on the time, day and month of bite, as well as the patient's age, sex and geographic residence were recorded. The place where the bite occurred, as well as the anatomical site of the bite, the application of first aid, the time elapsed between the bite and medical treatment, the local and systemic signs and symptoms observed, the severity of envenoming, the treatment administered upon admission [including medication prior to antivenom (AV) infusion], the number of vials of AV and associated any reaction to AV and the subsequent outcome of the cases were noted.

Following posterior review, the accidents were classified according to the Brazilian Ministry of Health recommendations³: *mild*- little or no edema at the bite site with or without pain and ecchymosis; *moderate*-

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local edema was evident, indurate and spread from the bite site, generally associated with pain and ecchymosis, with or without local and/or mild systemic bleeding; *severe*- massive swelling generally affecting the whole limb and associated with ecchymosis, pain and occasionally with blisters. Independent of the intensity of the local lesion, extensive hemorrhaging, acute renal failure and shock also characterized severe envenoming. According to this classification, there is no correlation between blood coagulation disorders and the severity of envenoming. Indeed, coagulopathy may occur in mild cases without any other change. The accidents were also classified as *dry-bites* when the children did not present local or systemic clinical manifestations and showed normal blood coagulation tests.

The whole blood clotting time³ and/or prothrombin, thrombin and activated partial thromboplastin times (using commercial reagents kits) were determined. A whole blood clotting time between 10 and 30 min was considered prolonged, whereas a time greater than 30 min represented incoagulable blood³.

When required, the patients received polyspecific, hyperimmune equine bothropic AV, 10 ml/vial (produced by Instituto Butantan, São Paulo; Fundação Ezequiel Dias, Minas Gerais and Instituto Vital Brazil, Rio de Janeiro, Brazil) i.v. over 20 - 30 min. One milliliter of this AV, which consists mainly of the F(ab')₂ fragment of immunoglobulins, neutralizes 5 mg of *B. jararaca* reference venom in mice. From January, 1989, to March, 1999, 26 among 28 patients who received bothropic AV only at UNICAMP were pretreated with histamine H₁ and H₂ antagonists such as chlorpheniramine (0.05 mg/kg), cimetidine (10 mg/kg) or ranitidine (3 mg/kg) i.v. or i.m. and hydrocortisone i.v. (10 mg/kg) at least 15 min before AV infusion.

These data were analyzed using the software program Epi-Info version 6.02 produced by the Centers for Disease Control (Atlanta, GA, USA). Differences between the frequencies of some variables were compared using the χ^2 and Fisher's exact probability tests. A p value < 0.05 was considered to indicate significance.

RESULTS

The offending snake was brought for identification to the level of genus in 37% of the 73 cases, and was a young animal (< 40 cm in length) in 8 cases. The species was identified in 13 cases (*B. jararaca*, N = 11; *B. alternatus*, N = 1 and *B. neuwiedi*, N = 1).

The patients' age ranged from 1 y to 14 y (median = 9 y, mean \pm SD = 8.1 \pm 3.7 y). Most accidents involved male victims (66.6%) and occurred between 13:00 and 19:00 h (47.9%), from October to March (68.5%), in rural areas, including around the home.

Lower limbs were the most commonly bitten (84.9%), with 39.7% involving the feet and 28.8% the ankles. A tourniquet was used in 17.8% of the cases.

Table 1 summarizes the main features in this case series. Most of the patients presented local manifestations, mainly edema (94.5%), pain (94.5%) and ecchymosis (73.9%). Local and/or systemic bleeding was observed in 21 patients (28.8%). Two patients showed no signs of envenoming and did not receive AV.

Local infection (15.1%), compartment syndrome (4.1%), gangrene (1.4%) and acute renal failure (1.4%) were the main clinical complications observed, mainly in severe cases (Table 1). The bacteria isolated from the purulent exudates collected from abscesses (N = 4) and blisters in two patients with cellulitis included *Streptococcus* group D non *Enterococcus* (2 cases), *Bacillus* sp (2 cases), *Enterobacter cloacae* (1 case), *Providencia rettgeri* (1 case), *Morganella morganii* (1 case), *Klebsiella pneumoniae* (1 case), *Streptococcus* group A (1 case) and *Staphylococcus aureus* (1 case). The frequency of local infection was significantly greater in severe cases (N = 7/15) compared to mild and moderate cases (N = 4/56) (Fisher's exact test, p < 0.001, Table 1).

Blood coagulation disorders were observed in 60.7% (incoagulable blood in 39.3%) of the 56 children who received AV only at UNICAMP. There were no significant differences in the severity of envenoming and the frequency of blood coagulation disorders among the three categories of envenoming (χ^2 , p = 0.75, Table 2). Most (76.8%) of these children received AV less than 6 h after the bite. Patients admitted more than 6 h after the bite showed a higher risk of developing severe envenoming (Fisher's exact test, p = 0.04, Table 2).

AV early reactions were observed in 44.6% of the 56 children who received AV only at UNICAMP, and there were no significant differences in the frequency of AV early reactions between the groups that were and were not pretreated with histamine H₁ and H₂ antagonists and hydrocortisone (χ^2 , p = 0.55, Table 2). A higher frequency of AV early reactions per individual was observed in non pretreated children (Table 3). Most of these reactions were considered mild in both groups. Only one patient (not pretreated) developed an acute severe early reaction with dyspnea and shock (Table 3). No late AV reactions were observed.

Two children developed fibular nerve palsy after compartment syndrome and one required amputation of the second foot finger because of gangrene. No deaths were recorded.

DISCUSSION

In most of the cases reported here, diagnosis was based on the anamnesis plus the clinical manifestations and blood coagulation tests which suggested envenoming by *Bothrops* spp. Diagnosis by ELISA to detect venom at the bite site and in the blood stream²⁴ is not yet routinely available at our service.

That accidents were more common from October to March generally reflected the influence of seasonal factors such as an increase in temperature and humidity (rain season) and in human activity in rural areas^{3,19,23}. *B. jararaca* snakes are also more active in this season and during the evening²³.

There were no significant differences in the severity of envenoming and the frequency of blood coagulation disorders among the three categories of envenoming. Five patients with bleeding had normal blood coagulation tests (Table 1). It has been shown that the bleeding observed in patients bitten by *B. jararaca* may be independent of the alterations in the coagulation system. Other cofactors are required for spontaneous hemorrhage such as direct vascular damage by hemorrhagins, platelet function disturbs and thrombocytopenia^{11-13,22}. Of the eight children bitten by young *Bothrops* snakes, one showed no signs of envenoming, seven

Table 1
The main features of bites according to the severity of the envenoming in 73 children bitten by *Bothrops* spp.

| Features | Dry-bite N = 2 | Mild N = 19 | Moderate N = 37 | Severe N = 15 | Total N = 73 | % |
|---------------------------------|-------------------|----------------|--------------------|------------------|-----------------|---------|
| Bite site | | | | | | |
| Edema | 0 | 17 | 37 | 15 | 69 | 94.5% |
| (massive swelling) | 0 | (0) | (0) | (13) | (13) | (17.8%) |
| Pain | 1 | 17 | 36 | 15 | 69 | 94.5% |
| Ecchymosis | 0 | 8 | 31 | 15 | 54 | 73.9% |
| Blisters | 0 | 0 | 1 | 7 | 8 | 11.0% |
| Necrosis | 0 | 0 | 0 | 1 | 1 | 1.4% |
| Blood coagulation | | | | | | |
| Normal | 2 | 9 | 15 | 4 | 30 | 41.1% |
| Altered | 0 | 10 | 22 | 11 | 43 | 58.9% |
| (incoagulable) | | (7) | (16) | (4) | (27) | (37.0%) |
| Bleeding | 0 | 2 | 12 | 7 | 21 | 28.8% |
| Local | 0 | 2 | 5 | 5 | 12 | 16.4% |
| Gingival | 0 | 0 | 3 | 1 | 4 | 5.5% |
| Local + gingival | 0 | 0 | 2 | 0 | 2 | 2.7% |
| Local + epistaxis + hematemesis | 0 | 0 | 0 | 1 | 1 | 1.4% |
| Local + otorrhagia | 0 | 0 | 1 | 0 | 1 | 1.4% |
| Gingival + epistaxis | 0 | 0 | 1 | 0 | 1 | 1.4% |
| With altered coagulation | 0 | 2 | 8 | 6 | 16 | 21.9% |
| With normal coagulation | 0 | 0 | 4 | 1 | 5 | 6.9% |
| AV* before UNICAMP | 0 | 0 | 3 | 4 | 7 | 9.6% |
| AV before and at UNICAMP | 0 | 1 | 6 | 1 | 8 | 11.0% |
| AV only at UNICAMP | 0 | 18 | 28 | 10 | 56 | 76.7% |
| Complications | | | | | | |
| Local infection | 0 | 1 | 3 | 7 | 11 | 15.1% |
| Cellulitis | 0 | 1 | 1 | 4 | 6 | 8.2% |
| Cellulitis + gangrene | 0 | 0 | 0 | 1 | 1 | 1.4% |
| Abscess | 0 | 0 | 2 | 2 | 4 | 5.5% |
| Compartment syndrome | 0 | 0 | 1 | 2 | 3 | 4.2% |
| Acute renal failure | 0 | 0 | 0 | 1 | 1 | 1.4% |

* AV = antivenom

Table 2
The interval between bite and hospital admission and the frequency of blood coagulation disorders and antivenom early reactions (with and without pretreatment) according to the severity of envenoming, in 56 children bitten by *Bothrops* snakes who received antivenom only at UNICAMP

| Features | Mild N = 18 | Moderate N = 28 | Severe N = 10 | Total N = 56 | % |
|--------------------------|----------------|--------------------|------------------|-----------------|---------|
| Admission (h after bite) | | | | | |
| < 3 h | 11 | 13 | 3 | 27 | 48.2% |
| 3 – 6 h | 7 | 7 | 2 | 16 | 28.6% |
| > 6 h | 0 | 8 | 5 | 13 | 23.2% |
| Coagulation | | | | | |
| Normal | 8 | 11 | 3 | 22 | 39.3% |
| Altered | 10 | 17 | 7 | 34 | 60.7% |
| (incoagulable) | (7) | (12) | (3) | (22) | (39.3%) |
| Bothropic AV* (ml) | 20-80 | 20-120 | 60-120 | | |
| Median (ml) | 40 | 70 | 100 | 60 | |
| Early reactions | 6/18 | 15/28 | 4/10 | 25/56 | 44.6% |
| (with pretreatment) † | (4/11) | (4/9) | (2/6) | (10/26) | 38.5% |
| (without pretreatment) | (2/7) | (11/19) | (2/4) | (15/30) | 50.0% |

* AV = antivenom; † = Pretreatment with histamine H₁ and H₂ antagonists and hydrocortisone.

Table 3

Antivenom early reactions in 25 children bitten by *Bothrops* snakes who received antivenom only at UNICAMP. Ten patients were pretreated with histamine H₁ and H₂ antagonists and hydrocortisone

| Early reaction | Pretreated N = 10 | Not pretreated N = 15 | Total N = 25 | % |
|---------------------------|----------------------|--------------------------|-----------------|-------|
| Urticaria | 4 | 7 | 11 | 44.0% |
| Cough | 4 | 3 | 7 | 28.0% |
| Flushing | 3 | 3 | 6 | 24.0% |
| Tremors | 0 | 6 | 6 | 24.0% |
| Vomiting | 0 | 5 | 5 | 20.0% |
| Morbiliform rash | 2 | 0 | 2 | 8.0% |
| Tachycardia | 0 | 2 | 2 | 8.0% |
| Agitation | 0 | 2 | 2 | 8.0% |
| Dyspnea | 1 | 1 | 2 | 8.0% |
| Abdominal pain | 1 | 1 | 2 | 8.0% |
| Wheezes | 0 | 1 | 1 | 4.0% |
| Facial edema | 0 | 1 | 1 | 4.0% |
| Itching | 0 | 1 | 1 | 4.0% |
| Shock | 0 | 1 | 1 | 4.0% |
| Others | 3 | 5 | 8 | 32.0% |
| TOTAL | 18 | 39 | 57 | |
| ER* per individual | 1.8 | 2.6 | 2.3 | |

* ER = early reaction (mean)

were classified as mild cases and five had incoagulable blood upon hospital admission. A greater frequency of blood coagulation disorders has been found in accidents caused by young *B. jararaca* compared to adult animals¹⁷. On the other hand, accidents caused by adult *Bothrops* snakes have been associated with more severe envenoming and a higher risk of abscess, necrosis and amputation^{10,18,21}.

Enterobacteriaceae, *Streptococcus* group D, *Aeromonas hydrophyla* and anaerobic bacteria are the main germs isolated from purulent exudates in soft-tissue infections after *Bothrops* snakebites^{8-9,15}. With the exception of anaerobic bacteria, which were not screened in the present study, our microbiological results agrees with the foregoing studies. In a recent severe case with compartment syndrome (not included in the present series), we identified *A. hydrophyla* in cultures of debrided tissue. Most patients in this series who had a local infection were treated with chloramphenicol (N = 10), either alone (N = 5) or in association with other antibiotics (N = 5), with good results. Chloramphenicol is apparently a good alternative for the empirical treatment of local infections which may complicate bites by *Bothrops* spp, particularly since it is inexpensive and is active against most aerobic and anaerobic bacteria found in local infections caused by these snakes⁸⁻⁹.

Since skin sensitivity tests before AV infusion have low sensitivity and predictive values^{6,14}, several pretreatment schemes, mostly based on non-controlled studies, have been proposed and used to prevent AV early reactions^{3-4,6-7,16,24}. Although a higher frequency of AV early reactions was observed in patients not pretreated with histamine H₁ and H₂ antagonists and hydrocortisone, statistical analysis suggested that such treatment was not efficient. However, the present study is not a

randomized, placebo controlled trial, with methodological limitations to conclude about the real efficacy of this pretreatment scheme. Recent randomized, double-blind clinical studies have shown a significant reduction in AV early reactions in patients pretreated with adrenaline s.c. in Sri-Lanka¹⁶, and inability of promethazine i.m. in preventing AV early reactions in patients who received bothropic AV⁷.

Except for the higher frequency of ecchymosis and bleeding and the lower frequency of local necrosis in this case series, our data are very similar to those reported by RIBEIRO & JORGE (1997) for 3,139 accidents caused by *Bothrops* snakes, in which *B. jararaca* was identified as the most important species¹⁸.

In conclusion, the prognosis for snakebites especially involving *B. jararaca* can be good as long as the children receive prompt medical care, including an adequate AV prescription and correct treatment for the main complications. In contrast, for other *Bothrops* species such as *B. asper*, the envenoming in children may be more severe than that seen here, with a greater frequency of acute renal failure and deaths²¹.

RESUMO

Acidentes por serpentes do gênero *Bothrops* em crianças em Campinas, São Paulo, Brasil

De janeiro de 1984 a março de 1999, 73 crianças com menos de 15 anos de idade (1 a 14 anos, mediana = 9 anos) foram admitidas após terem sido picadas por serpentes do gênero *Bothrops*. 26,0% das crianças foram classificadas como acidente leve, 50,7% como moderado e 20,6% como grave. Dois pacientes (2,7%) não apresentaram sinais de envenenamento. A maioria dos pacientes apresentou manifestações locais, principalmente edema (94,5%), dor (94,5%), equimoses (73,9%) e bolhas (11,0%). Sangramento local e/ou sistêmico foi constatado em 28,8% das crianças. Alterações da coagulação, antes da administração da soroterapia antiveneno (SAV), foram observadas em 60,7% (sangue incoagulável em 39,3%) das 56 crianças que receberam a SAV exclusivamente em nosso hospital. Reações precoces à SAV foram observadas em 44,6% destes 56 casos, sendo 15 em 30 pacientes não pré-tratados e 10 dentre 26 pré-tratados com antagonistas H₁ e H₂ da histamina e hidrocortisona, a maioria das quais foi considerada leve. As principais complicações observadas foram a infecção local (15,1%), a síndrome de compartimento (4,1%), gangrena (1,4%) e insuficiência renal aguda (1,4%). Nenhum óbito foi registrado. Não foram constatadas diferenças estatísticas significativas comparando-se a frequência de distúrbios da coagulação de acordo com a gravidade (p = 0,75), bem como na frequência de reações precoces à SAV entre os grupos que receberam ou não o pré-tratamento (p = 0,55). A frequência de infecção local foi significativamente maior nos casos graves (p < 0,001). Pacientes atendidos mais de 6 horas após o acidente apresentaram um maior risco quanto à evolução para casos graves (p = 0,04).

ACKNOWLEDGEMENTS

Silvia R. F. Herrera was the recipient of a PIBIC/CNPq-PRP-UNICAMP (1999-2000) scholarship. The authors thank Maria Teresa de Oliveira (CCI-UNICAMP) for her technical assistance.

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Received: 4 July 2001

Accepted: 5 October 2001