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ENVENOMING BY CORAL SNAKES (*Micrurus*) IN ARGENTINA DURING THE PERIOD BETWEEN 1979-2003

Adolfo Rafael de ROODT(1,2), Ernesto DE TITTO(3), Jorge Adrián DOLAB(4) & Jean-Philippe CHIPPAUX(5,6)

SUMMARY

Envenomation by coral snakes (*Micrurus* sp.) is one of the most dangerous injuries in America and it is considered as a serious medical emergency, however bites by these snakes appear to be rare. We analyzed epidemiological data, clinical signs and antivenom use in Argentina during the period between 1979-2003. During this period of study 46 non-fatal *Micrurus* bites were reported. The majority of cases were men from 31 to 40 years old. Bites occurred primarily in spring and summer. Most cases were reported from the northeast and northwest provinces of the country. The bites were mostly located on hands or feet and occurred mostly during agricultural activities and so mainly involved farmers. Only four cases occurred as a result of handling snakes. The median time it took for antivenom to be administrated was 60 minutes after the bite, and the median number of vials applied was 2. Local pain was mentioned and edema was reported in 41% of patients. All patients recovered without sequelae. This study showed a low incidence of *Micrurus* bites and low severity of envenomation. However, although no deaths have been reported during the last 30 years, given the toxicity of the venom of *Micrurus* snakes, the risk of severe envenomation should be considered.

KEYWORDS: Snakes; Envenoming; *Micrurus;* Epidemiology; Snakebite; Antivenom.

INTRODUCTION

Coral snakes are endemic in the Americas from the South of United States of America to the South of Argentina, in the Patagonian region. They represent a potential risk to human health throughout the continent.

Coral snakes belong to the Elapidae family which constitutes a taxonomic group of over 120 species and subspecies[7], represented by the genera *Micrurus*, *Micruroides* and *Leptomicrurus*. *Micrurus* is the main genus, containing more than 70 species[7], six of which can be observed in Argentina. The species described are *Micrurus* (*M.*) *altirostris, M. balyocoriphus, M. corallinus, M. frontalis, M. lemniscatus* and *M. pyrrhocryptus* [24].

Micrurus bites are less frequent than snakebites from Crotalinae in the Americas[5,10,14,23,24,25,33,42]. In Central America and Colombia less than 2% of all snakebites have been related to bites by *Micrurus* spp.[5,8], while in Brazil coral snakes accounted for 0.65% (486 out of 75,312) of bites by venomous snakes in the period between 2001-2004, with no recorded deaths[6]. In the United States of America, bites by coral snakes (principally by *M. fulvius*) represent 3.6% of accidents involving indigenous venomous snakes, based on records from the last 20 years (911 coral snake bites from a total of 25,551 bites by venomous snakes in the period between 1983-2003)[1], which equates to around 45 bites/year; while another report accounts for 1254 bites by *Micrurus* in the period between 1983-2007[41], leading to 50 ± 31 bites per year, this is in the same range as previous report.

Deaths occuring from *Micrurus* bites are uncommon. The fact that coral snake bites are rare is evidence of their reclusive nature, lack of aggressiveness, shyness and the low effectiveness of their venom delivery apparatus when compared to that of pit vipers[29].

Micrurus bites produce a neurotoxic envenoming, which can lead to peripheral paralysis of respiratory muscles in animals and humans[6,21,34]. The neurological symptoms may involve 1) a block of the postsynaptic cholinergic receptor by toxic peptides called α-neurotoxins, e.g. *M. frontalis frontalis*; 2) the inhibition of acetylcholine release related to presynaptic phospholipases A_2 (PLA_2) (called β-neurotoxins), in addition to postsynaptic blocking, e.g. *M. corallinus*; and/or 3) a combined action of α-neurotoxins and myotoxic PLA_2, e.g. *M. nigrocinctus* and *M. fulvius*[39,40].

In some experiments cardiovascular[15] and hemorrhagic activities were observed in a few coral snake venoms such as those of *M. fulvius*[37], *M. averyi*[3] and *M. frontalis frontalis*[17]. There are no reports of clotting

(1) Laboratorio de Toxinopatología, Centro de Patología Experimental y Aplicada, Facultad de Medicina, Universidad de Buenos Aires. Uriburu 950, 5º piso, CP 1114, CABA, Argentina.
(2) Área Investigación y Desarrollo, I.N.P.B.-A.N.L.I.S. "Dr. Carlos G. Malbrán", Ministerio de Salud. Av. Vélez Sarsfield 563, CP 1281, CABA, Argentina. Phone: +54 9 11 4147 4644. E-mail: aderoodt@gmail.com
(3) Dirección Nacional de Determinantes de Salud e Investigación. Av. 9 de Julio 1925 (C1073ABA) - Buenos Aires - República Argentina. Phone: + 54-11-4379-9000. E-mail: edetitto@msal.gov.ar
(4) Departamento Vacunas y Sueros, I.N.P.B.-A.N.L.I.S. "Dr. Carlos G. Malbrán", Ministerio de Salud.
(5) Institut de Recherche pour le Développement.
(6) Université Paris Descartes, Sorbonne Paris Cité, Faculté de Pharmacie, France. UMR 216, Mother and child facing tropical diseases, 08 BP 841, Cotonou, Bénin. Phone: +229 94345110. E-mail: jean-philippe.chippaux@ird.fr
Correspondence to: Adolfo Rafael de Roodt. E-mail: aderoodt@gmail.com

activity with plasma or fibrinogen in the venoms of South American coral snakes[17]. However, some South American *Micrurus* showed edema which induced inflammatory activity[3] and increased capillary permeability[36]. Although local lesions are uncommon, some *Micrurus* venoms have shown experimental myotoxic effects in mice[2,3,18].

While there are detailed clinical reports and summaries regarding envenoming by coral snakes (*M. fulvius*) in North America[1,21,23,30,31], such information does not exist in South America, although some case reports have been published in the last few decades[6,22,31]. Despite the important material regarding envenomings by *Micrurus* in South and Central America and the characteristics of their venoms and antivenoms, we are still lacking detailed descriptions of clinical or epidemiological characteristics of coral snake envenoming.

This is an account of data collected from epidemiological reports submitted to national health authorities, regarding patients bitten by coral snakes during the last 25 years in Argentina.

METHODS

This study is a retrospective analysis of available information from the former national program for snakebites (PNO = Programa Nacional de Ofidismo) from January 1979 to December 2003. All patients that were described as having been exposed to a coral snake bite were included.

Information was recorded in regular data sheets used by the PNO to report the use of antivenoms. Data took into account patient age, sex, location where the accident occurred, date and circumstance of the accident (inside or outside home, at work, etc.), anatomical site of the *Micrurus* bite, and signs and/or symptoms recorded at the time of medical examination. It also recorded the time elapsed between the bite and the treatment, the amount of antivenom given to the patient, and the clinical evolution of the case.

Specific incidences were calculated according to the provincial population of Argentinean provinces and the demographic distribution of ages in 1991[20]. The χ^2 test was used to compare the results where necessary.

RESULTS

A total of 46 coral snake bites have been reported during the 25 year period, i.e. an average of two bites per year. In 1995, eight bites were observed, the highest number of bites in a single year (Fig. 1). The seasonal distribution of *Micrurus* bites, showed the highest incidence from mid-spring (October) to autumn (April) (Fig. 2). As regards the geographical distribution, most of bites occurred in the Northwest Province while only one case was reported from Patagonia (Fig. 3). No deaths were recorded.

The age group most affected by snakebites was that of 31-40 years (34%), with males being most affected by snakebites (70%) (Fig. 4). The majority of bites occurred during working activities (44%) and in rural areas (55%). Only four illegitimate bites were related to snake handling.

Hands and feet were the most frequent anatomical site of the bites, accounting for 82% of all bites; with hands and forearms 45.6%, and feet and ankles 54.4%.

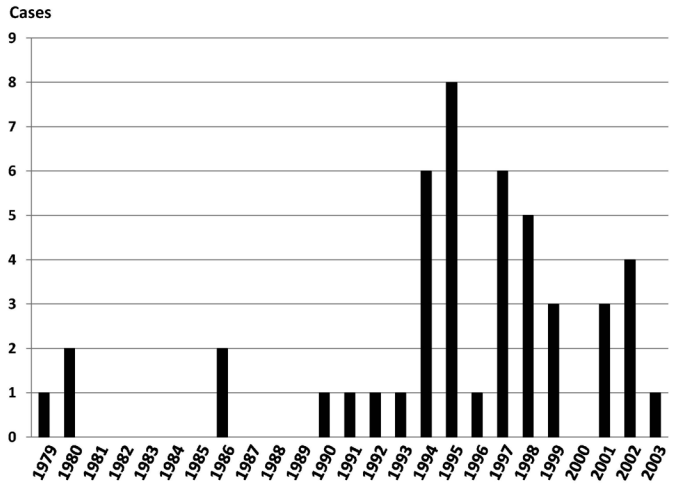

Fig. 1 - Annual occurrence of cases between 1979-2003.

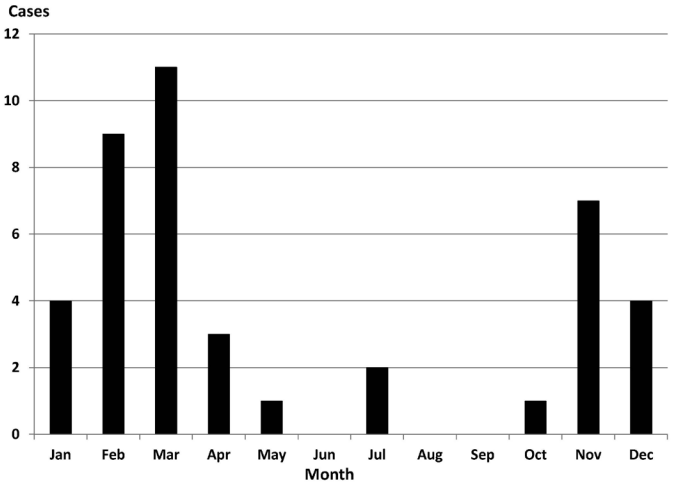

Fig. 2 - Seasonal occurrence of *Micrurus* bites in Argentina.

Interestingly, most patients presented local symptoms. Pain was present in 31 patients (68.9%) and edema was reported in 15 patients (33.3%). Other manifestations were rare: two patients reported burning (4.4%), while myalgia and arthralgia were reported in three (6.7%) and two (4.4%) cases respectively.

Systemic signs were described in few cases: dizziness, tachycardia, hypertension and sickness (one case each, 2.2%); paleness (two cases, 4.4%), tremors (four cases, 8.8%), while dispnoea and/or respiratory difficulty were reported in four cases (8.8%).

All patients received antivenom, which was a mandatory part of filling in the PNO report form. However, in nine cases the antivenom administered was not the specific one. In the 36 cases in which the specific antivenom was used, the median of injected vials was two (minimum one, maximum eight). The mean time for antivenom to be administrated after the bite was 194 min (from 15 min to 48 hours), while the median time between the bite and the treatment was 60 minutes.

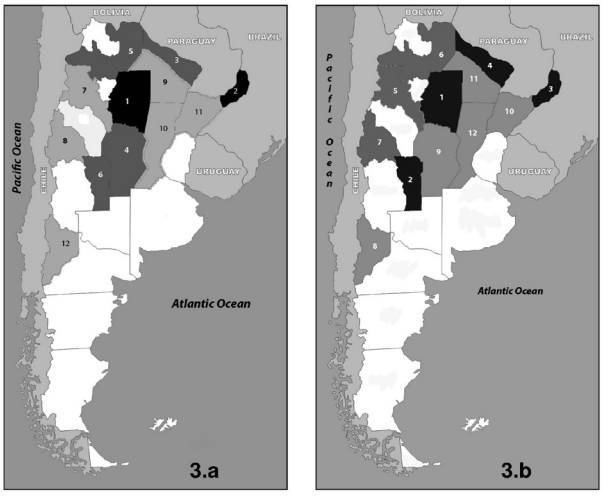

Fig. 3 - Geographical specific incidence according to Argentinean Provinces. **3.a.** Number of cases of accidents by *Micrurus* in each province. 1 - Santiago del Estero (11 cases), 2 - Misiones (10 cases), 3 - Formosa (five cases), 4 - Córdoba (five cases), 5 - Salta (four cases), 6 - San Luis (four cases), 7 - Catmarca (two cases), 8 - San Juan (two cases), 9 - Chaco, 10 - Santa Fe, 11 - Corrientes, 12 - Neuquén (one case in each province). **3.b.** Specific Incidence by province (cases/100,000 inhabitants). 1 - Santiago del Estero (1.63691), 2 - San Luis (1.39860), 3 - Misiones (1.26743), 4 - Formosa (1.25628), 5 - Catamarca (0.75758), 6 - Salta (0.46189), 7 - San Juan (0.37807), 8 - Neuquén (0.25707), 9 - Córdoba (0.18070), 10 - Corrientes (0.12563), 11 - Chaco (0.11905), 12 - Santa Fe (0.03579).

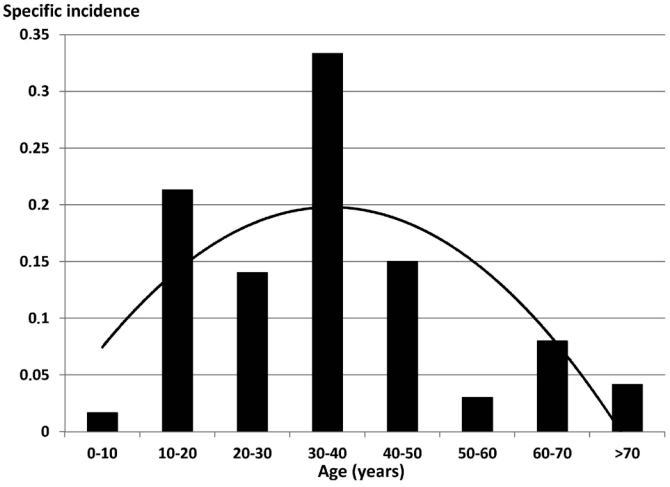

Fig. 4 - Specific incidence according to age distribution in the Argentinean population (the trend curve was based on a polynomial model).

In all cases the antivenom used for treatment was the Antiveneno *Micrurus* from the National Institute for Production of Biologicals of the National Administration of Laboratories and Institutes of Health, "Dr. Carlos G. Malbrán", depending of the National Ministry of Health. This was (and is) the only available antivenom for treatment of coral snakes in Argentina. The pharmaceutical is in liquid form, in 5 mL vials containing $F(ab')_2$ fragments of equine immunoglobulins. The neutralization is 1 mg or more of venom by mL of antivenom (which means at least 5 mg of venom neutralized per vial). The information on the antivenom used was included in the PNO sheets.

In some cases, antivenom was used in association with additional drugs: corticoids (32 cases, 71.1%), corticoids plus antihistamines (six cases, 13.3%), antitetanic toxoid (14 patients, 31.1%), antibiotics (seven patients, 15.6%) and analgesics in five cases (11.1%).

The duration of hospitalization ranged from one to four days. The outcome was good in all cases, without any sequels reported.

DISCUSSION

All *Micrurus* bites reported to the PNO in Argentina during the years 1979 to 2003 were analyzed except two of them that had been recorded twice. Since 2004, case reporting to PNO has been irregular and so it was not possible to continue the analysis.

The scarcity of cases reported before 1990, could be explained by an irregular distribution of antivenoms and/or, by a more parsimonious management of snakebites, but any possible reasons are difficult to determine retrospectively. Considering that the annual incidence of snakebites in Argentina is about 1,000 bites a year[12], the frequency of coral snake bites was very low, representing only 0.2% of total snakebites.

The geographical distribution was irregular and decreased from north to south, this variation was possibly due to the abundance of *Micrurus*, the human population density or, perhaps, human activities. The highest frequency of bites was recorded in four Northern provinces (Salta, Santiago del Estero, Formosa and Misiones), where 65% of accidents occurred. The risk gradually decreased going south to northern Patagonia, where only a single bite by *Micrurus* was reported in 25 years.

Taking into consideration the provinces where the accidents occurred, *M. pyrrhocryptus* was responsible for more than a half of the bites. However, no difference was observed in a clinical presentation of bites when *M. pyrrhocryptus* was involved compared to other species, even in the Misiones province where six different species of *Micrurus* are encountered ($\chi^2 = 0.8887$; $p = 0.62$).

Micrurus are not aggressive and often shy. Contrary to an erroneous reputation about *Micrurus* which states that they cannot bite because their mouth is too small and opens only slightly, coral snakes are able to bite and inoculate their venom. However, the amount of venom obtained from these snakes is low[9,15,16,19,34]. The yield of venom from Argentinean *Micrurus* is about 14 ± 6 mg per adult snake[11] ranging from 1 mg in small specimens to more than 40 mg in very large snakes (de ROODT unpublished results), as is the case for most South American *Micrurus*. In addition, the very short and fixed fangs and the absence of a closed duct to inject the venom, reduce the effectiveness of venom inoculation in comparison to vipers. As a consequence, not all bites result in envenoming. Significant clinical symptoms are recorded in approximately 40% of *Micrurus* bites reflecting venom inoculation[30,32,33], which seems to be slightly lower than elapid envenomings reported from other continents where the incidence of clinical disorders is estimated at 50-60% in humans[7,9]. However, it is well known that even a venomous snake may inflict a dry bite[6,35]. It is also possible that the rapid management of patients, half of which are treated within one hour after the bite, could explain the absence of death and severe envenoming among patients of Argentina. Most of them did not show any systemic disorder. Only four patients presented respiratory symptoms that quickly disappeared after

antivenom administration. In contrast, 70% of them showed local signs, which is consistent with observations published elsewhere[28].

In this study, no deaths were observed. However, nearly 10% of patients had respiratory symptoms that could have lead to severe complications. The venom of the Argentinean *Micrurus* is as toxic as the venom of *Micrurus* that causes death in other countries[13,19,26,34,38]. In Brazil, a country with very similar characteristics regarding the fauna and snakebite epidemiology, *Micrurus* bites are also uncommon[4,14,25,27,31] and usually mild[6,9] representing about 0.4% of total snakebites with 0.36% mortality[25], which is very consistent with our results.

During the period of study the treatment with antivenom was highly variable, ranging between 1-8 vials. However, recent official recommendations from the national authorities suggest the application of 10 vials[24], as recommended by the Ministry of Health of Brazil[25]. No clinical trial has been conducted in Argentina so far and so until this is possible the recommended doses are those suggested in Brazil, because of their experience of such accidents. Although the population of *Micrurus* snakes is not identical, all the *Micrurus* species that inhabit Argentina can be found in the South of Brazil[7,9,24,25]. The number of vials recommended is the same, nevertheless, the neutralizing potency of Argentinean antivenom by vial could be lower than the Brazilian one, since the neutralization capacity of Argentinean antivenom during the period of study was of 5-10 mg per 5 mL vial (DOLAB J.A., unpublished data) versus 15 mg per 10 mL vial (at least 1.5 mg/mL) of the Soro Antielapídico produced by the Butantan Institute (Sao Paulo, Brazil). However, it is difficult to compare the potencies because of the different methods used for determining the neutralization of these antivenoms in both countries (i.e. type and characteristic of the venoms used for determination, challenge doses of venom, inoculation route of the experimental animals used for the assay, among others). Clinical trials are necessary in order to establish the optimal dose of the antivenom in Argentina.

Our data were collected through the "Programa Nacional de Ofidismo". This program relied upon cases being reported by health care professionals. As a routine passive surveillance system, an under-registration of snake bite reports can be expected for many reasons. Among the potential reasons are: a lack of antivenom that leads to people doubting the usefulness of the surveillance system, a lack of health professionals for operational issues, or patients being unable to access a health center for antivenom therapy.

Although this type of system has several weaknesses, because all cases of *Micrurus* bites hold potential for severe envenoming in this country, these accidents are always reported and given precedence over the lack of antidote, the provincial and national sanitary authorities are required to treat the case. Therefore the antivenom (there is only one producer in the country) is sent via sites of the Ministry of Health and after treatment, the surveillance sheets are completed and sent.

One issue that is impossible to solve is when patients do not access the health center for the antivenom treatment. This is possibly the key weakness in this notification system.

Another problem regarding the notification system, based on patient reports, is a possible over registration of cases where it is only a suspected *Micrurus* bite and not a confirmed diagnosis. We discarded all cases where there was evidently some doubt concerning the clinical data or where another type of snakebite was indicated. Nevertheless, false coral snake bites may be a cause of misdiagnosis. In Argentina there are several species of false coral snakes, such as the species of *Lystrophis, Oxyrrhopus* and *Erythrolampus*. The lack of experience and familiarity of health professionals regarding red, white and black color pattern combinations placed in rings, could cause a misdiagnosis or mistaking a colubrid snake as a coral "dry bite". Although this is certainly a possibility, professionals in health centers where snakebites are common receive instructions regarding the identification of true coral snake or false coral snake, which would theoretically diminish diagnostical errors. However, although bites misdiagnosed as false coral snake bites could be present among the cases considered in our study, the regions and centers where cases occurred and cases were attended indicate to us a high likelihood that the diagnosis of coral snake bites can be relied upon.

Despite the aforementioned, the key symptoms described in coral snake envenoming are due to the main venom action, which is neurotoxicity. However, symptoms such as myasthenia, palpebral ptosis, diplopia, or blurred vision were not described in data sheets recorded. This could be attributed to the physicians attending the emergency room not completely filling the spaces for recording specific clinical symptoms (due to work overload) and only noting down the most obvious symptoms. Finally, the other possibility is that there was only a very slight envenomation by coral snake bite due to a low injection of venom in the cases reported.

We are currently using new systems of collecting data on accidents involving venomous animals, and modified epidemiological sheets. It is possible that these changes along with the improvement of communication systems from the peripheral centers (where the snakebites occur) and the central levels (which collect and analyze data), will improve our knowledge regarding the envenomation by venomous animals in general and by coral snakes in particular.

In Argentina, *Micrurus* bites are rare and cause very few severe envenomings. This may be due to a small amount of venom injected, or the small size of the animal, or because the venom apparatus and the limited ability of the venom glands do not allow an effective inoculation of venom. However, although no deaths have been recorded over the past 30 years, the toxicity of the venom is high and the risk of severe envenoming should be considered. The specific antivenom is available throughout the country and should be administered early in all patients suffering from envenoming after *Micrurus* bites.

RESUMO

Envenenamento por cobras corais na Argentina durante o período 1979-2003

O envenenamento por corais (*Micrurus* sp.) é um dos mais perigosos na América e considerado uma emergência médica grave ainda que acidentes por estas serpentes pareçam raros. Analisamos dados epidemiológicos e clínicos e o uso de soro antiofídico, durante o período de 1979-2003. As comunicações indicam 46 acidentes por *Micrurus*, aproximadamente dois casos anuais, sem registro. A maioria

dos casos ocorreu em homens de idade entre 31 e 40 anos, principalmente no período de primavera e verão e provenientes do noroeste e nordeste do país. Os acidentes na sua maioria ocorreram em mãos e pés, durante atividades agrícolas envolvendo trabalhadores rurais. Apenas quatro acidentes foram relacionados a manejo dos animais. Em todos os casos analisados houve descrição de dor local e em 41% dos pacientes houve edema. Por paciente foram administradas, em média, duas ampolas. O tempo médio de aplicação do soro foi de 60 minutos. Em todos os casos a recuperação foi favorável sem presença de sequelas. Neste estudo foi possível observar uma baixa incidência de acidentes e baixa severidade nos envenenamentos. Apesar de que não aconteceram mortes nos últimos 30 anos, dado a toxicidade do veneno das cobras corais, o risco de envenenamento severo deveria ser considerado.

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