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Review of Treatment and Complications in 79 Children With Rattlesnake Bite

Norberto Sotelo, MD

Introduction Envenomation by snakebite is a health problem in Mexico.

Objective To review the treatment and complications of rattlesnake bites in 79 children.

Materials and methods The variables studied were age, sex, season, hour, signs, symptoms, and complications during 1977 to 1996 (group I) and 1997 to 2006 (group II). Hospitalization time and antivenom type, including polyvalent equine antiviperin serum and a [F(ab')₂] antivenom (fabotherapeutic), were also studied. **Results.** Most incidents (35%) occurred within the perimeter of children's homes and 8.8% took place inside homes; 40.5% of the children were females; and

most snakebites occurred during the summer (70.8%). Members of groups I and II received polyvalent equine antiviperin serum and fabotherapy, respectively. Hospitalization time was less in group II members ($P < .0001$). The complications in group I members included hypoprothrombinemia and hypofibrinogenemia ($P < .0001$).

Conclusions Hospitalization time, complications, and treatment cost were less in patients undergoing fabotherapy.

Keywords: rattlesnake bite; envenoming; antiviperin serums; fabotherapy; hematologic complications

Introduction

In Mexico, 700 species and subspecies of reptiles have been identified. Of these, 120 are venomous; geographically, rattlesnakes (*Crotalus* spp.) are found in a large area in northern Mexico. In the state of Sonora, 16 species and subspecies of *Crotalus* genus have been identified; *C atrox* (Western diamondback rattlesnake) and *C cerastes* (sidewinder snake) are those that are involved in more snakebites.¹⁻³ Snakebites occur during spring and summer, generally in rural areas, and can occur in the countryside and within the perimeter of and even inside the house.^{4,5}

The venom is very complex; it contains, among other constituents, mixtures of proteins with enzymatic properties and low-molecular-weight polypeptides with

multiple receptor-variation capacity, favoring cardiotoxicity and neurotoxicity. The diverse components are responsible for edema, endothelial damage, cellular membrane changes, hematologic disorders, renal dysfunction, and neurologic effects.^{4,5-7} Signs and symptoms include localized pain, edema, ecchymotic lesions, local necrosis, blisters, somnolence, paresthesias, vomiting, and, in severe cases, hypotonia, oliguria, stupor, coma, and shock.^{4,8}

Serotherapy is the specific treatment currently, wherein 1 or multiple doses of a [F(ab')₂] antivenom (fabotherapeutic) are recommended according to grade. In this article, we report follow-up of 79 patients bitten by *Crotalus* spp treated with 2 different antivenoms as scheduled doses at a pediatric hospital in Northwestern Mexico.^{9,10}

Materials and Methods

The clinical files of patients with rattlesnake bite treated from 1977 through 2006 at the Hospital Infantil del Estado de Sonora in Hermosillo, the capital of state Sonora, were reviewed retrospectively and descriptively. Data obtained were age, sex,

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place of residence, time of incident (hour, season of the year), signs, symptoms, severity classification used, and edema grade.

Laboratory Test

Treatment was analyzed by establishing 2 groups: group I for patients treated between 1977 and 1996 with intravenous polyvalent equine serum and group II for patients treated with intravenous faboherapeutic from 1997 to 2006.

Hospitalization time and complications were compared between the 2 groups. Results in general are expressed in descriptive statistics; in addition, we conducted statistical tests such as the Pearson χ^2 test, the Fisher exact test, and the Welch and Levene tests using an SAS statistical software package (version 5, 2004).¹¹ As an additional exercise, treatment cost was calculated¹² at present-day prices according to socioeconomic level, taking into consideration the Mexican Ministry of Finance's high and low tariffs for the health system.^{13,14}

Results

The majority of patients (72, 91%) resided in a rural area; in 28 cases (35.4%), the bite occurred in the patio of the house, in 7 cases (8.8%) inside the house, and only in 7 cases in the open countryside. In 1 case, which occurred in the city, the patient boarded a pick-up vehicle containing firewood. Time of incident in 56 cases (70.8%) was between 2 and 7 PM, and in 11 cases (13.9%), the incident took place at night.

During the summer, 56 patients (70.8%) were seen in the hospital, whereas only 18 cases (22.7%) were seen in the autumn; of the 79 patients, 32 were females (40.5%) and 47 were males (50.5%). Ten patients were aged between 1 and 2 years (12.6%), 23 were aged between 3 and 5 years (29.2%), 17 were aged between 6 and 10 years (21.5%), and 29 patients were adolescents (36.7%). The most frequent wound site was legs and foot (in 60 patients; 75.9%); in one case, the cephalic vein pathway of the upper right limb was involved.

The time from the incident's occurrence to the initiation of patient care at the hospital was <1 hour in 21 children and between 1 and 3 hours in 33 (42.7%); 10 children received care between 3 hours and up to 24 hours after the snakebite, whereas 7 patients arrived for care after 24 hours and 2

patients after 48 hours. First aid and care prior to hospital admission included garlic and milk in 1 patient, anticrotalic serum (between 1 and 8 vials) in 45 patients (56.9%), incision and tourniquet in 10 (12%), incision and suction in 8 (8.8%), analgesics in 45 (56.9%), administration of aspirin in 2, and paracetamol, ketorolac, and metamizol in the remaining children. Two patients received ice applications and had multiple small incisions performed in the thigh and leg.

Predominantly, signs and symptoms included pain, edema, functional disability, ecchymoses, somnolence, paresthesias, and bleeding at the wound site. We considered the Christopher-Rodning classification¹⁴ for envenomation grade (Table 1).

Among laboratory parameters, prothrombin time was found prolonged in 46 patients (58.1%); in addition, 10 patients had alterations in activated partial thromboplastin time, and there were hemoglobin changes of <10 g/dL in 33 patients (41.7%). Of these, only 2 patients had reticulocytes of >5%; low fibrinogen was present in 17 (21.5%), platelets were <100,000 \times mm³ in 7 (8.8%), and glucose was >110 mg/dL in 9 (11.3%). There was altered urea, creatinine, and urine/plasma relationship in 4 patients; changed alanine aminotransferase and aspartate aminotransferase (AST) in 4; creatine phosphokinase of >200 to 400 U/L in 10; and amylase >1690 U/L in 1 case.

Support treatment consisted of the application of parenteral solutions, penicillin-type antibiotics, aminoglycosides, tetanus toxoid, hyperimmune antitetanic γ globulin, hydrocortisone, calcium gluconate, assisted ventilation with pressor amines (in 2 patients), peritoneal dialysis (in 1 case), and fasciotomy (in 5 cases), whereas 2 patients received no treatment and were solely under observation. In 25 patients (31.6%), support treatment consisted of cryoprecipitate transfusions, fresh plasma, and fresh whole blood; additionally, blood platelets were used. Seven patients (8.8%) received heparin, and 4 patients received dipyrindamole.

With regard to use of intravenous antiviperin serum and the treatment scheme used from 1977 through 1996, in the first 13 cases two patients required no treatment because their wounds were considered dry bites; among patients treated between 1977 and 1985, 11 received different modalities because no standardized treatment existed at that time. The serum doses applied varied between 1 and 6 vials of polyvalent antiviperin serum with serum-derived

Table 1. Signs, Symptoms, and Grade of Edema (n = 79)

Signs and Symptoms	Number of Cases	Percentage
Pain	79	100
Edema	76	96.2
Functional disability	74	93.6
Ecchymosis	33	41.7
Somnolence, paresthesia	21	26.5
Bleeding (wound site, blisters, ecchymosis, epitaxis ^a)	19	24.0
Vomiting	20	25.3
Local necrosis	13	16.4
Loss of consciousness	2	2.5
Shock	2	2.5
Hematuria	2	2.5

Grade	Edema Classification (Christopher–Rodning) ¹⁴	Number of Cases	Percentage
0	Bite prints without envenomation	3	3.7
I	Slight envenomation, pain, edema <10 cm	12	15.7
II	Moderate envenomation, greater pain, edema >10 cm	45	56.9
III	Severe envenomation, abdominal pain, nausea, petechiae, necrosis, bullae, paresthesia, oliguria	7	8.8
IV	Grave envenomation, renal insufficiency, disseminated intravascular coagulation, respiratory failure, multiple organ failure	3	3.7
	Not described	9	11.3

a. Epitaxis in 2 patients.

equine γ globulin, each vial containing >2 g of protein and 129 mg of albumin.⁴

Since 1986, we have modified the treatment scheme.^{9,15} Earlier, according to the grade of envenoming we administered the following: in patients with grade II or moderate poisoning, 4 vials in physiologic solution intravenous during the first hour and 3 to 4 additional vials during the following hour, where indicated. For the most severe poisonings (grades III and IV), 6 to 8 vials diluted with 250 mL of physiologic solution were used in the first hour, with 8 to 10 vials added during the following 3 hours, with a total of up to 15 vials recommended during the first 4 hours. This treatment scheme was used at the hospital until 1996, employing on average 10 vials per case; this treatment was modified in 1997, when the hospital began to employ a [F(ab')₂] antivenom (fabotherapeutic) according to grade of envenomation (as shown in Table 2).^{4,9,16}

With regard to fabotherapy, the maximum dose administered was 69 vials, the dose varying between 48 and 60 vials in gravely ill patients. In the 2 groups considered, no immediate or late allergic reactions were registered in the 8 weeks following the discharge of the patient from the hospital.

On comparing the 2 different periods based on number of hospitalization days for recuperation, 2 groups were established: group I (1977 to 1996), with 30 children who had initially received different treatment modalities and later a defined scheme^{5,9,15}; and group II (1997 to 2006), comprising 47 patients who received multiple fabotherapeutic doses.^{4,9,16} For unequal variances, *t* tests were applied, whereas the Welch test was performed for unequal variance analysis¹¹ ($4.17 < 10.36$), both resulting in a *P* value of <.0001; similarly, recuperation–time variability was less on applying the Levene test ($4.01 < 5.96$), with *P* = .0014.¹¹

On comparing the rate of hematologic and diverse complications between groups I and II, it was observed that these presented 26% more frequently in group I, with different proportions from those of the Fisher exact test (*P* = .029). On reviewing hematologic and diverse complications separately, hematologic complications were more frequent in group I (Pearson χ^2 test, *P* < .0001), whereas in group II, complications presented with the same frequency (Pearson χ^2 test, *P* = .2591) (Table 3).

Sequelae that presented in patients included the following: amputation of 1 patient's second

Table 2. Correlation Scale of Clinical Signs, Edema, and Modified Antivenom Dose in Children¹⁴

Grade	Signs and Symptoms	Impregnation Dose			Subsequent Doses
		Direct (intravenous; 1 mL/min), Number of Vials	First Hour (Dilute 100 mL Physiologic Solution), Number of Vials	Following 3 Hours on 250-mL Mixed Solution (Glucose- Physiologic Serum, 2:1)	
0	Punctiform prints, with envenomation (probable dry bite)	0	0	0	Maintenance (evaluate)
I	Slight envenomation, pain, edema >10 cm circumscribed to wound area	2-3	4	Evaluate 4 vials ^a	Evaluate clinical status
II	Moderate envenomation, intense pain, edema >15 cm of wound site, changes in skin, regional lymph nodes, nauseous state	5	10	Evaluate 6-8 vials ^a	Evaluate clinical status
III	Severe envenomation, edema of entire affected member, vomiting, vertigo, fever, more notable changes in skin (ecchymosis, bullae, petechiae-paresthesia, oliguria)	5	20	Evaluate 6-8 vials ^a	Evaluate 4-5 vials every 4 hours ^a
IV	Grave envenomation, bleeding in bite prints, extensive ecchymosis and petechiae, data of disseminated intravascular coagulation, acute renal insufficiency, respiratory difficulty, multiple organ failure	25	25	Evaluate 10 vials ^a	Evaluate 4-5 vials every 4 hours ^b

a. In dry bite (10% of cases), surveillance while patient is hospitalized during 12 hours, take laboratory parameters.

b. According to clinical status, hematologic changes, and renal function, more vials if necessary.

phalange, middle finger, and right hand; cheloid scars via fasciotomy in 3 cases; and necrosis-associated skin loss in 1 patient's middle finger of the right hand; another 4-year-old from group I had severe envenomation in addition to disseminated intravascular coagulation and died.

As an additional exercise in this study, it was considered prudent to know the actual treatment costs of using polyvalent antivenom fabotherapy in its multi-dose modality. A calculation was performed to find the present cost, taking into consideration the Mexican Health Sector Financial Recovery System¹³ classification (D and J); the cost included the cost for 1 bed day and a package that included, at a minimum, laboratory examinations (blood tests, coagulation test, creatine phosphokinase, antibiotics, penicillin, and

aminogluco-side), in addition to fabotherapy, including 15 vials on average for patients with moderate envenomation and 60 vials for severe cases.

We obtained costs expected for the 5-day treatment that a child with moderate envenomation required and for the 15-day treatment necessary for a gravely ill patient for recuperation. Subsequently, we calculated the cost that would be required for a patient with moderate-grade envenoming, such as that occurring in 72% of cases treated at the hospital according to average days obtained from real hospitalization days found in the treatment groups (I and II). We observed the following: for classification D (moderate envenoming), the cost for 5 days would be \$8100.00 MN (\$10 Mexican pesos [MN] = \$1US); for classification J, the cost would be \$11

Table 3. Group I and II Complications

	Complication	Number of Cases	Percentage
Group I (1997-1996), n = 32			
Hematologic ^a	Anemia, hemoglobin <10 g/dL	20	0.52
	Hypoprothrombinemia ^b	28	0.87
	Hypofibrinogenemia	11	0.34
Diverse	Wound-site infection	7	0.21
	Tissue-localized necrosis	7	0.21
	Paresthesia, somnolence ^c	8	0.25
	Acute renal insufficiency	1	0.03
Group II (1997-2006), n = 47			
Hematologic	Anemia, hemoglobin <10 g/dL	13	0.27
	Hypoprothrombinemia ^d	34	0.72
	Hypofibrinogenemia	6	0.12
Diverse	Wound-site infection	19	0.40
	Tissue-localized necrosis	14	0.08
	Somnolence, paresthesia	18	0.38
	Acute renal insufficiency	1	0.02

a. One patient developed disseminated intravascular coagulation and died.

b. Six patients had a thromboplastin alteration.

c. Two patients experienced loss of consciousness.

d. Two patients with thromboplastin.

987.00 MN. For a patient experiencing severe envenoming, for 15 hospitalization days in classification D the cost would be \$27 740.00 MN, whereas for classification J, the cost would be \$43 915.00 MN.

With respect to the cost for 10 treatment days for both socioeconomic levels (D and J), we obtained \$15 865.00 MN for classification D, whereas for classification J, the 10-day cost would be \$22 113.00 MN. For 4 days of treatment for classification D, the cost would be \$6728.00 MN, whereas for classification J, the cost would be \$9815.00 MN.¹²

Discussion

Rattlesnake-attack-related wounds by *C atrox* and *C cerastes* totaled 65% of the total wounds registered at the Hospital Infantil del Estado de Sonora. This corresponds to the area of influence of the institution at which we work, which comprises a semidesert zone near Hermosillo, the state capital of Sonora, where this variety of reptiles is found in great abundance.^{2-5,15}

It is well known that this type of snakebite occurs in adult males who work in the fields, in zoo workers, and in personnel in the herpetologic and toxicologic research areas. It is less frequent in children, predominating in

school-aged children and adolescents. In this series, there was a high proportion of children aged 5 years (41.7%), with practically no difference with regard to gender.

The snakebites occurred within the perimeter of the home in 35.5% of the cases and inside the dwelling itself in 8.8% of the cases.^{1-4,17,18} The time at which the snakebite occurred was noontime and during the afternoon hours in 70% of the cases during the summer, which coincided with the period of summer vacation. The most frequently injured anatomic areas were lower limbs.

It has been described that the degree of envenomation is more severe the lower the patient's age and weight, and the severity also depends on reptile size, reptile variety, and time of lesion. We observed that most patients affected were 5-year-olds, with a single adolescent included in this category.

Signs and symptoms consisted of those that are commonly reported in this type of envenomation, which should be clearly registered. These signs and symptoms are also very useful for classifying the grade of envenoming as administration of the specific serum is planned based on this classification.^{1,2,4,5,9,14,16}

At our Hermosillo-based hospital, we have had the opportunity of treating 79 patients in a period of nearly 30 years. This has afforded us the possibility of using the polyvalent equine antiviperin serum, employed until 1996, and fabotherapy, which we

have used after 1997. On comparing hospitalization times with each of the other modalities, these have been important reductions, from an average of 10 to an average of 4 days ($P < .0001$); in addition, variability in recuperation time was also less ($P = .00014$). As fasciotomy was not performed on any of the group II patients, this surgical procedure was required when inadequate antivenom doses have been applied.

Review of the venom's complex components and specific actions on different tissues, apparatuses, and systems does not fall within the purpose of this article; nonetheless, it is prudent to recall some of these, including histic wound production, endothelial capillary damage, cellular membrane destruction, inflammation, rhabdomyolysis, musculoskeletal necrosis, renal insufficiency, blood pressure changes, neurotoxicity, and cardiotoxicity. The most notorious effects are hematologic alterations produced by the complex interaction of the venom's diverse components; it is known that phospholipase A₂ provokes cytotoxicity, myonecrosis, and hemolysis. It also acts hydrolytically on lecithin, forming isolecithin; destroys erythrocytes; and leads to intravascular hemolysis. In addition, platelets are destroyed because of damage to the membranes of these cells.^{6,7,19}

Thromboserpentine, fibrinogenase, and kallikreins activate factor X, impeding fibrin cross-linked binding complex formation, presenting an abnormal thromboserpentine-related fibrin injury, and rendering an unstable clot. Thrombinoid enzymes favor the activation failure of factor XIII, which normally cross the fibrin chains, thus also provoking hypofibrinogenesis.^{4,6,7}

Inflammation mediators that are liberated, such as interleukin, α tumor necrosis factor, phosphatidases, and the proteolytic enzymes contained in the venom, favor the consumption of coagulation factors and can even lead to disseminated intravascular coagulation. This series of superficially described events is expressed among the diverse changes registered by means of laboratory examinations and those that are directly responsible for hematologic disturbances. In this work and on comparing complication rates between children treated during the first and second periods (groups I and II, respectively), complications were observed 26% more frequently in group I. On taking into account the number of events, hematologic events predominated in group I ($P < .0001$), noting that in group II there was a reduction in cases of hypofibrinogenemia.

Different from that referred in other works in which polyvalent anticrotalic ovine sera (Fab O) have been used and in which variable results have been obtained, we did not observe hematologic-alteration and toxicity-alteration recurrence phenomena.²⁰⁻²⁸

The cost of multiple-dose fabotherapy has been discussed (\$675.00 MN for each vial in private medical practice and \$260.00 MN per vial in the public sector). In this series, we were able to observe a very evident reduction in hospitalization time, which we attribute to the use of fabotherapy schemes that have allowed for resolution with rapid improvement in envenoming status. At pediatric ages, this acquires special importance because grave complications and fatal outcomes can be avoided, circumstances that unfortunately continue to exist in Mexico.^{29,30}

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