

ORIGINAL ARTICLE

Antivenom for Critically Ill Children with Neurotoxicity from Scorpion Stings

Leslie V. Boyer, M.D., Andreas A. Theodorou, M.D., Robert A. Berg, M.D., and Joanne Mallie, R.N., for the Arizona Envenomation Investigators,* Ariana Chávez-Méndez, B.S., Walter García-Ubbelohde, M.D., Stephen Hardiman, Ph.D., and Alejandro Alagón, M.D., Ph.D.

ABSTRACT

BACKGROUND

Clinically significant scorpion envenomation by *Centruroides sculpturatus* produces a dramatic neuromotor syndrome and respiratory insufficiency that often necessitate intensive supportive care. We hypothesized that a scorpion-specific F(ab')₂ antivenom would promptly resolve clinical symptoms in children with this syndrome.

METHODS

In a randomized, double-blind study, the efficacy of scorpion-specific F(ab')₂ antivenom, as compared with placebo, was assessed in 15 children 6 months to 18 years of age who were admitted to a pediatric intensive care unit with clinically significant signs of scorpion envenomation. The primary end point was the resolution of the clinical syndrome within 4 hours after administration of the study drug. Secondary end points included the total dose of concomitant midazolam for sedation and quantitative plasma venom levels, before and after treatment.

RESULTS

The clinical syndrome resolved more rapidly among recipients of the antivenom than among recipients of placebo, with a resolution of symptoms in all eight antivenom recipients versus one of seven placebo recipients within 4 hours after treatment (P=0.001). More midazolam was administered in the placebo recipients than in the antivenom recipients (mean cumulative dose, 4.61 vs. 0.07 mg per kilogram of body weight; P=0.01). Plasma venom concentrations were undetectable in all eight antivenom recipients but in only one placebo recipient 1 hour after treatment (P=0.001).

CONCLUSIONS

Among critically ill children with neurotoxic effects of scorpion envenomation, intravenous administration of scorpion-specific F(ab')₂ antivenom resolved the clinical syndrome within 4 hours, reduced the need for concomitant sedation with midazolam, and reduced the levels of circulating unbound venom. (ClinicalTrials.gov number, NCT00685230.)

From the University of Arizona Health Sciences Center, Tucson (L.V.B., A.A.T., J.M.); Children's Hospital of Philadelphia, Philadelphia (R.A.B.); Instituto de Biotecnología, Universidad Nacional Autónoma de México, Cuernavaca, Morelos (A.C.-M., A.A.); Instituto Bioclon, México Distrito Federal, Mexico (W.G.-U.); and Stephen Hardiman Statistics, Hackettstown, NJ (S.H.). Address reprint requests to Dr. Boyer at the VIPER Institute, University of Arizona Health Sciences Center, 1295 N. Martin Ave., Tucson, AZ 85721-0202, or at boyer@pharmacy.arizona.edu.

*The investigators who participated in this clinical study as members of the Arizona Envenomation Investigators are listed in the Appendix.

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IN NORTH AMERICA, ENVENOMATION BY neurotoxic scorpions affects more than a quarter of a million people annually, mostly in Mexico.^{1,2} The sting produces a syndrome that ranges in severity from a simple sting mark to a life-threatening illness. Mild envenomation, which is more common in adults than in children and consists mainly of local pain, resolves without specific treatment over the course of hours or days. Severe envenomation, which is more common in small children, affects approximately 200 patients annually in Arizona, on the basis of our consultation records. The clinical syndrome includes uncoordinated neuromotor hyperactivity, oculomotor and visual abnormalities (see video), and respiratory compromise due to abundant respiratory secretions, airway obstruction, aberrant ventilatory effort, and occasional noncardiogenic pulmonary edema.³⁻⁵ The clinical pattern is a consequence of specific ion-channel toxins in the scorpion venom, which stimulate or potentiate action potentials throughout the peripheral nervous system.⁶ All North American scorpions whose venom has medical consequences fall within one genus, *Centruroides*, which is represented in the United States by several varieties that do not have medical consequences and a single neurotoxic species, *Centruroides sculpturatus*,⁷ formerly synonymous with *C. exilicauda*.⁸

In severe cases that are treated without antivenom, intensive supportive care is necessary for the management of violent neuromotor hyperactivity and respiratory compromise. During hospitalization, patients commonly receive extremely high doses of benzodiazepines for sedation.⁴ The mean duration of the stay in the intensive care unit (ICU) with this approach is 16 hours, but intensive care may be required for up to several days. Intubation and ventilation are occasionally necessary.^{4,5,9}

Although there is no federally approved therapy in the United States for the treatment of scorpion envenomation, uncontrolled observations in Mexico and in Arizona suggest that scorpion antivenoms can successfully resolve the systemic toxicity of scorpion envenomation within 1 to 4 hours after treatment.^{3,9-11} We hypothesized that, as compared with patients treated with supportive care only, a greater proportion of patients who received the antivenom would have resolution of the clinical syndrome within 4 hours, with decreased use of benzodiazepine sedation and lower

plasma venom levels. To test this hypothesis, we conducted a double-blind, placebo-controlled trial of an F(ab')₂ scorpion antivenom in children admitted to a pediatric ICU because of systemic scorpion envenomation.

METHODS

PATIENTS

Eligible patients were children 6 months to 18 years of age in whom systemic neurotoxic symptoms developed as a result of scorpion envenomation and who were admitted to a pediatric ICU within 5 hours after being stung by a scorpion. The systemic toxic effects included one or more of the following: characteristic neuromotor agitation with wild flailing of extremities, oculomotor manifestations, and respiratory compromise. Patients were not included in the study if they had a baseline medical condition involving neuromotor hyperactivity or if they were allergic to horse serum. Recruitment took place from May 2004 through October 2005, and patients were followed for 2 weeks after enrollment. Race or ethnic group was determined by the study nurse in consultation with the patients' parents.

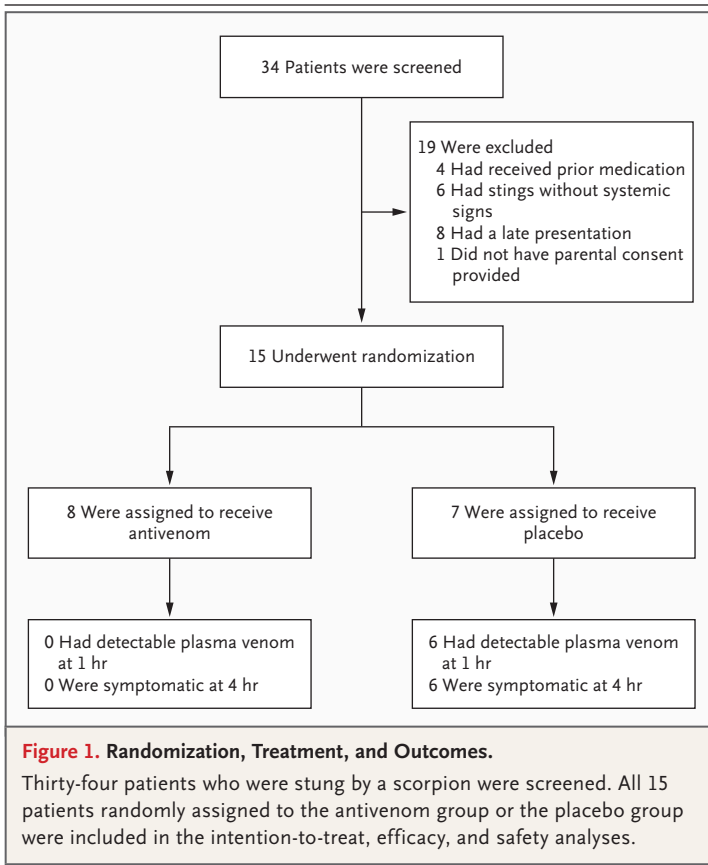
STUDY DESIGN

This was a prospective, randomized, double-blind study, conducted at two hospitals in Arizona, in which we compared scorpion-specific F(ab')₂ antivenom (Anascorp, *Centruroides* [scorpion] immune F(ab)₂ intravenous [equine], Instituto Bioclon) with placebo. The institutional review board at each site approved the study protocol. Written informed consent was obtained from the parents or guardians of the children.

Patients who met eligibility requirements were randomly assigned in a 1:1 ratio to receive intravenous antivenom (3 vials) or placebo (inactive excipient, 3 vials) dissolved in 50 ml of saline and administered immediately after the baseline assessment. This antivenom is commercially available in Mexico but is available in the United States only through an investigational new drug (IND) application. It is produced with the use of scorpions from several southern Mexican species in the same genus as the Arizona variety (*C. limpidus limpidus*, *C.l. tecomanus*, *C. noxius*, and *C. suffusus suffusus*). The binding affinity of the antivenom to *C. sculpturatus* venom is similar to that for the venoms used as immunogens.¹² For this study,



A video showing oculomotor abnormalities after scorpion sting is available at NEJM.org



the manufacturer produced coded study kits, with inactive excipient placebo that was visually indistinguishable from the active product. Randomization between the two products was performed in permuted blocks of 4. A master list containing unblinded identifiers was sealed and retained in the pharmacy for emergency use only. After informed consent had been obtained, patients received the product contained in the next available sequentially coded kit. The participants, the investigators, the pharmacists, the IND sponsor, and the study monitors were unaware of the specific group assignments until completion of the study.

Concomitant sedation in all cases was provided with the use of intravenous midazolam, administered in bolus doses of 0.05 to 0.2 mg per kilogram of body weight, with frequent increases in the dose of the infusion in increments of 0.05 mg per kilogram per hour, in order to minimize the patient's physical agitation while avoiding excessive sedation. Other than midazolam, no sedative drugs were administered to patients in either group during the observation period.

The antivenom and placebo were provided by Instituto Bioclon, the sponsor of the IND application for the scorpion antivenom. The study was monitored by the sponsor. The academic authors designed the study, collected and analyzed the data, wrote the manuscript, and vouch for the accuracy and completeness of the reported analyses.

STUDY ASSESSMENTS

Patients were evaluated at baseline and 1, 2, and 4 hours after infusion of the study drug. The primary end point was the resolution of the clinical syndrome within 4 hours after infusion of the study drug. Secondary end points included the cumulative dose of midazolam for control of agitation and plasma venom levels at 1 and 4 hours.

In the absence of a previously validated grading scale for measuring the severity of envenomation, we established a descriptive definition of the neurotoxic effects of scorpion envenomation. The primary end point was the resolution of the clinical syndrome within 4 hours after administration of the study drug. The clinical syndrome included pathologic agitation and respiratory compromise. Pathologic agitation was defined by abnormal eye movements, thrashing of limbs, loss of ability to ambulate, or the presence of muscle fasciculations. Respiratory compromise was defined by pulmonary edema, abnormal ventilatory effort, upper-airway compromise, hypoxemia (less than 90% oxygen saturation while breathing enriched oxygen mixtures), or any other sign of respiratory compromise.

A trained study coordinator recorded physical observations, which were confirmed by a physician-investigator who had clinical experience in the assessment of scorpion envenomation. The study coordinator and physician-investigator were unaware of the group assignments of the patients. For assessments that were made during infusion of the sedative, study personnel noted whether agitation indicative of neurotoxicity was evident at any point within 15 minutes after the recorded observations, to minimize misleading results due to transient suppression of the clinical syndrome. Concomitant sedation was recorded at each time point and at discharge from the hospital. A physician-investigator determined at each time point whether there was resolution of the syndrome.

Data collected for the calculation of the cumulative dose of midazolam required for sedation, one of the secondary end points, included the bolus doses and the rate (or rates) and duration of

infusion. The total dose of midazolam was calculated separately during the pre-enrollment period (to establish comparability of groups) and thereafter (as a secondary end point).

Adverse events were recorded and categorized according to severity and apparent cause. Because a type I immune reaction (acute hypersensitivity) and a type III immune reaction (serum sickness) are potential adverse events associated with the intravenous administration of serum derivatives, we specifically looked for signs of these events, using a predefined checklist. Patients were followed for 2 weeks after their enrollment in the study.

MEASUREMENT OF ANTIGENS OF *C. SCULPTURATUS* VENOM

An enzyme-linked immunosorbent assay for the measurement of antigens to *centruroides* scorpion venom in human plasma samples has been developed and validated.¹³ A detailed description of the immunoassay method can be found in the Supplementary Appendix (available with the full text of this article at NEJM.org).

STATISTICAL ANALYSIS

A preliminary chart review at the participating centers showed that approximately 10 patients per year would be eligible for enrollment. We estimated that with a minimum sample size of 14 patients, the study would have 80% power to show a success rate of 95% for the antivenom group as compared with 20% for the placebo group, based on Fisher's exact test and a two-sided type I error of 5%.

For the primary clinical efficacy end point (resolution of medically important signs of scorpion envenomation), significance was determined with the use of a two-tailed Fisher's exact test. For the midazolam dose, the study groups were compared with the use of the Wilcoxon rank-sum test. Average venom levels were compared with the use of the Wilcoxon rank-sum test, and the presence or absence of detectable venom with the use of a two-tailed Fisher's exact test, at baseline, 1 hour, and 4 hours. All reported P values are two-sided and have not been adjusted for multiple testing.

RESULTS

PATIENTS

A total of 15 patients were enrolled in the study; 8 patients were assigned to the antivenom group

Table 1. Demographic and Baseline Characteristics of the Patients.*

Variable	Antivenom (N=8)	Placebo (N=7)
Age — yr		
Mean	2±2	4±3
Median	1.0	4.3
Range	1–6	1–10
Weight — kg		
Mean	11.9±4.0	16.0±11.7
Median	10.3	18.8
Range	8.7–20.0	8.2–42.0
Female sex — no. (%)	4 (50)	3 (43)
Race or ethnic group — no. (%)†		
White	3 (38)	4 (57)
Hispanic	3 (38)	1 (14)
Black	1 (12)	1 (14)
Native American	1 (12)	1 (14)
Midazolam dose before enrollment — mg/kg		
Mean	0.20±0.1	0.27±0.7
Median	0.25	0.5
Range	0.1–0.4	0.1–2.0

* Plus-minus values are means ±SD.

† Race or ethnic group was determined by the study nurse in consultation with the patients' parents.

and 7 to the placebo group (Fig. 1). The characteristics of the patients are summarized in Table 1. Although the patients in the placebo group tended to be slightly older and to weigh correspondingly more than the patients in the antivenom group, these differences were primarily due to outliers for one patient, who, at 10 years of age and 42 kg, was 4 years older and 17 kg heavier than any other child in the study. No patients had received antivenom previously.

The median dose of midazolam that was administered for sedation before study enrollment was similar in the two groups. Other sedatives administered during the period before enrollment included lorazepam and codeine in two patients who received antivenom and diazepam, lorazepam, and meperidine in three patients who received placebo. Use of midazolam in the hour immediately before infusion of the study drug was similar in the two groups, and the dose in all cases was 0.3 mg per kilogram or less. All patients were discharged between 4 and 48 hours after enrollment in the study, when the effects of

envenomation and sedation had resolved. None required readmission for recurrent effects.

EFFICACY

Neuromotor abnormalities were present in all patients at baseline, and respiratory distress was present in 20%. Beginning 2 hours after treatment, resolution of the clinical syndrome differed significantly in patients treated with antivenom as compared with those who received placebo. Over-

all, within 4 hours after the infusion, the clinical syndrome had resolved in 100% (all eight) of the antivenom recipients, as compared with only 14% (one of seven) of the placebo recipients ($P=0.001$) (Table 2 and Fig. 2). The one placebo recipient in whom there was spontaneous resolution of the syndrome was the oldest and heaviest child in the study.

The use of midazolam was significantly greater among placebo recipients than among antivenom

Table 2. Clinical Signs of Neurotoxic Effects, Cumulative Midazolam Dose, Venom Levels, and Adverse Events.*

Variable	Antivenom (N=8)	Placebo (N=7)	P Value
Any sign of neurotoxic effects — no. (%) [†]			
At baseline	8 (100)	7 (100)	
At 1 hour	4 (50)	7 (100)	0.08
At 2 hours	1 (12)	6 (86)	0.01
At 4 hours	0 (0)	6 (86)	0.001
Abnormal eye movements — no. (%) [‡]			
At baseline	8 (100)	7 (100)	
At 1 hour	2 (25)	6 (86)	
At 2 hours	1 (12)	5 (71)	
At 4 hours	0 (0)	4 (57)	
Limb thrashing — no. (%) [§]			
At baseline	8 (100)	7 (100)	
At 1 hour	3 (38)	5 (71)	
At 2 hours	2 (25)	6 (86)	
At 4 hours	0 (0)	4 (57)	
Respiratory compromise — no. (%)			
At baseline	2 (25)	1 (14)	
At 1 hour	1 (12)	1 (14)	
At 2 hours	0 (0)	0 (0)	
At 4 hours	0 (0)	0 (0)	
Cumulative midazolam dose — mg/kg [¶]			
At 1 hour			
Mean	0.07±0.10	0.32±0.44	0.27
Range	0.0–0.2	0.0–1.1	
At 2 hours			
Mean	0.07±0.10	0.66±0.74	0.02
Range	0.0–0.2	0.1–2.1	
At 4 hours			
Mean	0.07±0.10	1.77±1.58	0.01
Range	0.0–0.2	0.1–4.4	
At discharge			
Mean	0.07±0.10	4.61±5.76	0.01
Range	0.0–0.2	0.1–16.7	

Table 2. (Continued.)

Variable	Antivenom (N=8)	Placebo (N=7)	P Value
Plasma venom			
At baseline			
Patients with detectable venom — no./total no.	7/8	5/6	1.00
Venom level — ng/ml			
Mean	7.1±4.6	6.6±10.2	0.38
Range	0.0–12.9	0.0–26.8	
At 1 hour			
Patients with detectable venom — no./total no.	0/8	6/7	0.001
Venom level — ng/ml			
Mean	0.0±0.0	2.7±3.0	0.005
Range	0–0	0.0–8.6	
At 4 hours			
Patients with detectable venom — no./total no.	0/7	4/6	0.02
Venom level — ng/ml			
Mean	0.0±0.0	1.8±1.9	0.03
Range	0–0	0.0–5.0	
Adverse events — no. (%)**			
Anaphylaxis or serum sickness	0	0	
Any adverse event	2 (25)	1 (14)	
Serious adverse event	0	0	

* Plus-minus values are means ±SD.

† Any sign of neurotoxic effects refers to the composite primary study end point, defined as the presence or absence of pathologic agitation (including abnormal eye movements, thrashing of limbs, loss of ability to ambulate, or presence of muscle fasciculations) and respiratory compromise (pulmonary edema, abnormal ventilatory effort, upper airway compromise, hypoxemia [less than 90% oxygen saturation], or any other respiratory compromise).

‡ Erratic, but nearly conjugate, rotatory and saccadic eye movements are characteristic of the clinical syndrome of envenomation.

§ Limb thrashing was judged to be present if purposeless, sudden movements were observed by investigators.

¶ Midazolam was administered with the use of a standardized dosing regimen. Specimens were unavailable for analysis in the case of one patient at baseline and one patient at 4 hours in the placebo group and in the case of one patient at 4 hours in the antivenom group.

|| Plasma venom levels were measured with the use of a scorpion-specific enzyme-linked immunosorbent assay. Specimens were unavailable for analysis in the case of one patient at baseline and one patient at 4 hours in the placebo group and in the case of one patient at 4 hours in the antivenom group.

** Safety measures were assessed for 2 weeks after administration of the study drug and included predefined questions related to symptoms of serum sickness.

recipients ($P=0.01$) (Table 2 and Fig. 3). Although all patients received at least some midazolam before enrollment or during the first hour, no antivenom recipient received midazolam after the first hour of treatment. The mean cumulative dose from enrollment to discharge was increased by a factor of 65 in the placebo group as compared with the dose in the antivenom group (4.61 vs. 0.07 mg per kilogram). No patient in either group received sedating agents other than midazolam after enrollment in the study.

Mean plasma venom concentrations were sim-

ilar at presentation in the two groups (Table 2 and Fig. 4). By 1 hour after infusion of the study drug, none of the eight patients receiving antivenom had detectable levels of venom in plasma; in contrast, six of the seven patients in the placebo group had detectable venom levels ($P=0.001$).

ADVERSE EVENTS

There was a similar number of adverse events in the two groups, and all adverse events were mild. One placebo recipient was lost to follow-up, but all the other children were followed up at 2 weeks.

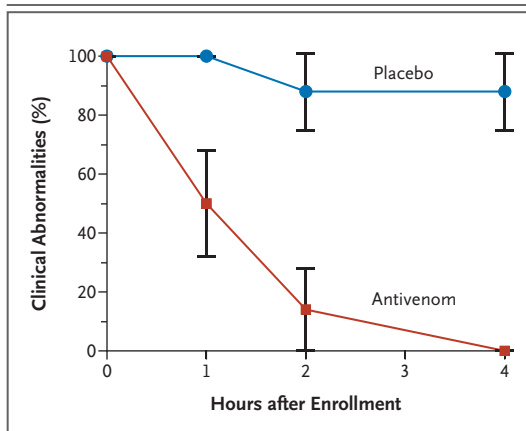


Figure 2. Clinically Important Signs of Envenomation (Primary Efficacy End Point).

Overall, within 4 hours after treatment, clinically important signs of scorpion envenomation had resolved in all eight patients treated with antivenom but in only one of seven patients who were given a placebo. I bars indicate 95% confidence intervals.

No cases of acute serum reactions or delayed serum sickness were observed. Minor vomiting and diarrhea were reported in one antivenom recipient several days after treatment, and a second antivenom recipient had an episode of emesis 6 days after treatment (Table 2).

DISCUSSION

Our randomized, double-blind, placebo-controlled study shows that treatment with a specific F(ab')₂ antivenom can effectively resolve the clinical neurotoxic syndrome associated with envenomation by the *centruroides* scorpion. The primary end point — cessation of the syndrome within 4 hours — occurred in 100% of antivenom recipients, suggesting that administration of antivenom in the emergency room might obviate the need for intensive care altogether. This outcome is particularly important with respect to small children who are stung in rural settings, where long-distance transport to urban ICUs is associated with additional costs and risks. In addition, plasma venom concentrations were not detectable in any of the antivenom recipients within 1 hour after administration of the antivenom, and the patients treated with antivenom received substantially less midazolam than the patients treated with placebo.

There has never been an approved, marketed

therapy in the United States for the treatment of scorpion envenomation. Nevertheless, our results are consistent with previous case reports and uncontrolled studies describing an apparent clinical response to several antivenoms for this indication.^{3,11,14}

The only previously available scorpion antivenom in the United States, a goat-derived whole-IgG preparation that was introduced in 1965 by Arizona State University,¹⁴ has not been produced since 1999. Use of this product was the source of controversy for decades¹⁵; some physicians reported satisfaction with its efficacy,¹⁶ whereas others preferred to provide intensive supportive care^{4,5} rather than risk serum reactions with an unregulated product. Given these circumstances, ethical study design proved to be an unusual challenge: physicians in rural Arizona and in Mexico, where the use of antivenom was firmly established as the standard of care, would not administer a placebo to children for whom respiratory failure and death were seen as potential consequences. Physicians at the two sites whose institutional review boards accepted our protocol argued that antivenom was unnecessary in the intensive care setting and was potentially harmful owing to the risk of serum reactions.

During the years 2004 and 2005, while this study was ongoing, hospital pharmacies in the United States used up their remaining stores of whole-IgG scorpion antivenom, and public demand for a safe alternative to intubation and transport of critically ill children resulted in a legislative appropriation in Arizona mandating the distribution of the antivenom used in our study to rural Arizona hospitals. Our simple binary primary end point — the presence or absence of the neurotoxic syndrome 4 hours after administration of the study drug, which was chosen to distinguish as completely as possible between the findings in the two study groups — reflected the need to prove, with the smallest possible number of critically ill children as subjects, whether the antivenom was, in fact, effective and to accomplish this goal quickly enough to respond to the unusual legislative mandate.

The secondary end point of the total midazolam dose also had important clinical implications: all antivenom recipients received total doses that were low enough that the children could be safely discharged from the hospital soon after treatment

with the antivenom. In contrast, the control patients received total midazolam doses as high as 16.7 mg per kilogram, and they therefore needed a longer period of observation in the ICU before it was deemed safe to discharge them from the hospital.

Plasma venom levels have not been used routinely as end points in studies of envenomation in humans, but controversy regarding the clinical significance of a pharmacokinetic–toxicokinetic mismatch between antivenom and venom suggests that better markers of disease severity and persistence may be useful both for a basic understanding of the disease process and for the development of antivenom.¹⁵ The findings in this study suggest that measurement of venom levels may be valuable for monitoring the suppression of venom antigenemia and for developing correlations with ongoing venom toxicity. In addition, the presence of detectable venom at baseline served as a confirmation of the validity of the clinical diagnosis of the syndrome, and its disappearance after treatment with the antivenom supports the expectation that antivenom works by binding venom, eliminating its ability to interact with biologic targets.¹⁷

In the past, administration of whole-immunoglobulin antivenoms was associated with both acute hypersensitivity reactions and delayed serum sickness, affecting 61% of the recipients of scorpion antivenom in Arizona.¹⁶ In theory, $F(ab')_2$ products should be associated with a much lower risk of these adverse events, but there are few published clinical data on these relatively new agents. The most important limitation of this study is that the small sample size precludes an adequate demonstration of safety. In addition, the risk of immune reactions increases the second time an antivenom is administered — a risk that we did not test in this study. The lack of serum reactions in this study tends to support the contention that the $F(ab')_2$ product has a better safety profile than the whole-immunoglobulin antivenoms, but larger studies are needed to confirm this.

Generalizability of these results is limited by the age distribution of the study subjects, the use of inactive placebo rather than nonspecific $F(ab')_2$ as a control, and the potential for geographic variation in scorpion venom. However, our findings are consistent with findings from uncon-

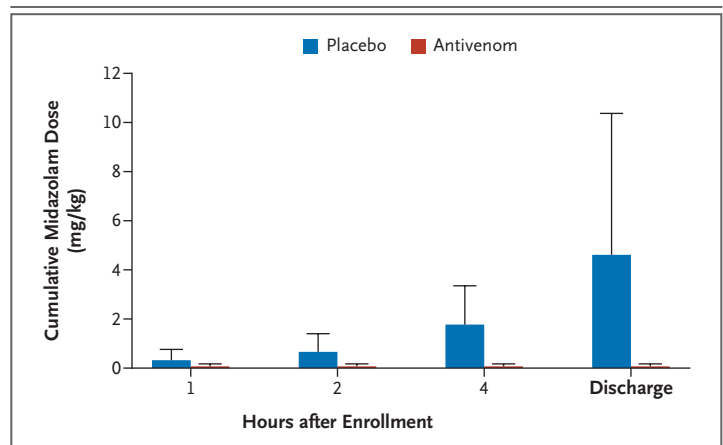


Figure 3. Sedation with Midazolam.

Recipients of antivenom received an average of 0.07 mg of midazolam per kilogram of body weight during the first hour after administration of the study drug, but in no case was sedation continued beyond the first hour of observation. In contrast, placebo recipients received an average of 0.32 mg of midazolam per kilogram during the first hour and continued to receive up to 1.8 mg per kilogram (median, 1.2 mg per kilogram) during the 4-hour observation period, for a mean total dose of 4.61 mg per kilogram (median, 3.44 mg per kilogram) between enrollment in the study and discharge from the hospital. The average time from baseline until the last dose of midazolam was 22.5 minutes for patients who received antivenom and 534 minutes (8.9 hours) for patients who received placebo. T bars indicate standard deviations.

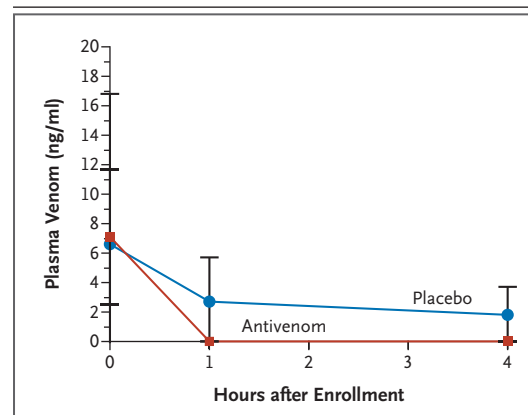


Figure 4. Plasma Venom Levels.

Venom was detected in plasma in all patients except for one placebo recipient and one antivenom recipient. Levels in the seven other antivenom recipients became undetectable within an hour after treatment, a finding that is consistent with binding by antivenom. Levels in the six other placebo recipients dropped more slowly and were still detectable at the end of the 4-hour observation period, a finding that is consistent with the ongoing clinical effects of envenomation in this group. T bars indicate standard deviations.

trolled studies that showed the efficacy of antivenom in adults and children in Mexico.²

Development of new pharmaceutical agents for rare conditions, particularly those that present as emergencies, and most particularly those that involve intensive care of young children, is a daunting task in the regulatory and economic environment in the United States. With a carefully designed study performed in the only two hospitals in the disease's natural range in which a double-blind, placebo-controlled study was permitted, and despite the extremely low incidence of the disease, we found that a novel antivenom was effective. Our findings suggest that this F(ab')₂ antivenom effectively resolved the toxic effects of scorpion venom within 4 hours after administration of the antivenom.

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Dr. Boyer reports receiving grant support for other studies from Instituto Bioclon and Rare Disease Therapeutics and serving as an expert witness for Wyeth; Ms. Mallie, receiving salary support through grants from Instituto Bioclon and Rare Disease Therapeutics; Dr. Garcia, being a full-time employee of Instituto Bioclon, which is the holder of the investigational new drug application for the study drug; and Dr. Alagon, receiving grant support from Instituto Bioclon and Laboratorios Silanes, holding patents on and receiving royalties for two other antivenom agents, through contracts between Instituto Bioclon and Universidad Nacional Autónoma de México, and serving as a scientific adviser to Instituto Bioclon on antivenom development. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

In addition to the authors, the following members of the Arizona Envenomation Investigators participated in this study: M.D. Berg, P.B. Chase, L. Esparza, J. Gutierrez, R.J. Meyer, M. Karadsheh, and J.T. McNally — all from the University of Arizona, Tucson.

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