

A large single-center experience with treatment of patients with crotalid envenomations: outcomes with and evolution of antivenin therapy

Michael G. Corneille, M.D.*, Scott Larson, Ph.D., Ronald M. Stewart, M.D.,
Daniel Dent, M.D., John G. Myers, M.D., Peter P. Lopez, M.D.,
Marilyn J. McFarland, M.S., Stephen M. Cohn, M.D.

Division of Trauma and Emergency Surgery, Department of Surgery, University of Texas Health Science Center San Antonio, San Antonio, TX, USA

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Abstract

Background: Antivenin (crotalid) polyvalent (ACP; Antivenin Crotalidae Polyvalent; Wyeth, Melville, NY) is associated with frequent allergic reactions. Allergic reactions are fewer with ovine Fab antivenin (FabAV). This study describes the management of crotalid envenomations in patients treated with FabAV or ACP, and without antivenin.

Methods: We performed a retrospective chart review of crotalid envenomations over 10 years. Demographic data, hematologic profiles, details of antivenin administration, and in-hospital morbidity and mortality were collected.

Results: There were no mortalities and a single amputation. Fewer fasciotomies were performed in the FabAV (9%) group versus the ACP group (24%). Mean hospital stay was 3.4 days. No allergic reactions were associated with FabAV. Fourteen of 211 reactions were associated with ACP ($P < .001$). Coagulopathy was frequent.

Conclusions: FabAV represents an improvement in management of crotalid envenomations because of reduced allergic reactions. Serious morbidity and mortality is rare. Coagulopathy is frequent but bleeding is not. Limb salvage is high. Surgical debridement and ACP are contraindicated when FabAV is available. © 2006 Excerpta Medica Inc. All rights reserved.

Keywords: Crotalid; Antivenin; FabAV; Pit viper; Snakebite

There are approximately 8000 pit viper envenomations annually in the United States, with the majority resulting from the *Crotalus* genus and most occurring in the southwest [1–3]. Treatment of snakebites remains controversial. Prior to the introduction of antivenin (Antivenin Crotalidae Polyvalent [ACP]) by Wyeth (Melville, NY) in 1954, there was no specific therapy for the treatment of crotalid envenomation. The ability of ACP to neutralize crotalid venom has been demonstrated in animal models as well as in human subjects [4–6]. Effective surgical management of snakebites was also demonstrated in the 1970s by several authors,

who described excision of envenomated tissue for the purpose of reducing venom burden [7–15]. Patients treated with surgery only showed high rates of survival and animal models showed that radiolabeled venom was effectively excised following surgical debridement [5]. Although both medical and surgical therapies have proven efficacious, they also have been associated with significant morbidity.

The original antivenin, ACP, was isolated immunoglobulins from horse serum following exposure to venom from 4 species of pit viper: *Crotalus atrox*, *Crotalus adamanteus*, *Crotalus durissus terrificus*, and *Bothrops atrox* [16]. Because this immunoglobulin was derived from horse serum, it was associated with allergic reactions in up to 56% of patients. These allergic reactions varied from mild hypersensitivity reactions, including rash, itching, hives, and serum sickness, to anaphylaxis and, on rare occasions, death [16]. This morbidity associated with treatment of pit viper

* Corresponding author. Division of Trauma and Emergency Surgery, Department of Surgery, University of Texas Health Science Center San Antonio, 7703 Floyd Curl Dr.–MC 7840, San Antonio, TX 78229-3900. Tel.: +1-210-567 3623; fax: +1-210-567-0003.

E-mail address: Corneille@uthscsa.edu

Table 1
Demographic characteristics

Characteristic	None (N = 55)	Crofab (N = 75)	Equine (N = 74)	P value
Gender, n(%)				.08*
Male	37 (67%)	48 (64%)	59 (80%)	
Female	18 (33%)	27 (36%)	15 (20%)	
Age (y)	55	75	74	.9†
Mean (SD)	33 (22)	31.7 (22)	31.3 (19)	
Range	2–88	2–84	2–78	

* Fisher exact test.

† Analysis of variance.

envenomations necessitated establishment of a safer therapy. Antivenin obtained from sheep serum minimizes the potential for allergic reactions seen with equine-derived antivenin. Additionally, during the manufacturing process, the Fc fragment of immunoglobulin, which carries most of the antigenicity, is cleaved. This leaves the active Fab portion, which binds venom proteins [17]. FabAV (Crofab, Savage Laboratories, Melville, NY) was released in 2001 and has been shown in animal studies, phase III trials, and aftermarket surveys to be 5 times more potent and to have significantly fewer allergic reactions compared to ACP [18]. While the safety and efficacy of FabAV have been established, it has never been prospectively compared to other treatments for pit viper envenomation, including ACP or observation alone. This retrospective review represents the first large series comparing the results of treatment with FabAV versus ACP or observation only. We hypothesized that due to the improved safety profile of FabAV and the abandonment of ACP, we would observe a change in treatment patterns and fewer complications.

Methods

After obtaining institutional review board approval, a retrospective chart review was performed for all patients

presenting with a diagnosis of snakebite to our institution from 1995 to 2005. Coral and nonvenomous snakebites were excluded. Three groups of patients were identified based on antivenin treatment: those treated with ACP, those treated with FabAV, and those treated with expectant management, without antivenin. Patients who received both ACP and FabAV antivenins were included in the overall analysis but were excluded from the comparisons between groups. No patients were treated with surgical debridement alone, although some patients who were treated without antivenin underwent fasciotomy for suspected compartment syndrome. Demographic information; date, time, and location of the bite; dates of admission and discharge; length of stay in the hospital and intensive care unit; and associated symptoms were collected. Antivenin data including time of initial dose, total dose, and associated reactions were recorded. Hematologic data, including hemoglobin, platelet count, international normalized ratio, and fibrinogen were also recorded. SAS version 9.1 (Cary, NC) was used for all analyses. All statistical testing was 2-sided with a significance level of 5%.

Results

Demographics

A total of 211 patients were treated for snakebites over the 10-year period. The majority of bites (196/211, 93%) occurred from March to October. There were 144 (68%) males, with an average age of 31.9 years, and 31 patients were under age 18. All bites, except 1 to the face, were to the extremities. Additional demographics are presented in Table 1 and length of stay data are presented in Table 2.

Antivenin administration

Seventy-four patients were treated with ACP alone, with the last dose of ACP being given in August 2002. The first dose of FabAV administered at University Hospital was in April 2001; a total of 75 patients in this series were treated with FabAV. During the transition period from April 2001

Table 2
Allergic reactions

	Age	Gender	Length of stay (d)	Treatment group	Total antivenin vials	Severity of reaction	Symptoms
1	39	M	1	ACP	20	Mild/mod	Rash
2	33	M	17	ACP	4	Mild/mod	Rash
3	53	F	2	ACP	10	Mild/mod	Hives
4	13	M	2	ACP	5	Mild/mod	Rash
5	3	F	2	ACP	1	Mild/mod	Hives
6	45	M	3	ACP	5	Mild/mod	Rash
7	45	M	3	None	0†	Mild/mod	Rash
8	47	F	4	ACP	10	Mild/mod	Hives
9	54	M	4	ACP	10	Mild/mod	Rash*
10	55	F	3	ACP	10	Mild/mod	Rash
11	87	F	6	None	0†	Mild/mod	Rash
12	54	M	5	ACP	3	Severe	Anaphylactic shock
13	50	M	2	FabAV	4‡	Mild/mod	Rash
14	18	M	17	ACP	8	Mild/mod	Rash
15	10	M	3	FabAV	18‡	Severe	Anaphylactic shock

* May be related to plasma transfusion.

† Reaction to test dose of ACP.

‡ These patients were treated with full dose of FabAV after allergic reaction to ACP skin test.

Table 3
Fasciotomy, allergy, and length of stay

	None (N = 55)	Crofab (N = 75)	Equine (N = 74)	P-value
Fasciotomy, N (%)	4 (7)	10 (13)	18 (24)	
P values				
Compared to none		.391	.02 ¹	
Crofab vs. equine			.1 ¹	
Between groups				.03 ¹
Allergy, N (%)	2 (3.7)*	2 (2.7)†	10 (14.9)	
P values				
Compared to none		1 ¹	.04 ¹	
Crofab vs. equine			.009 ¹	
Between groups				.01 ¹
Length of stay (d)	55	75	74	
Mean (SD)	2.3 (1.6)	3.5 (2.9)	4.2 (4.8)	
Range	0–6	1–16	1–35	
P values				
Compared to none		.01 ²	<.001 ²	
Crofab vs. equine			.18 ²	
Between groups				<.001 ³

* Reaction to test dose of ACP.

† These patients were treated with full dose of FabAV after allergic reaction to ACP skin test.

¹ Fisher exact test.

² Wilcoxon rank-sum test.

³ Kruskal-Wallis test.

to August 2002, 7 patients were treated with both ACP and FabAV. Six of these patients were initially treated at the transferring hospital with ACP and were subsequently converted to FabAV at an outside facility; 1 patient was initially treated at the transferring hospital with FabAV and was subsequently converted to ACP. In those patients receiving a single antivenin, an average of 12 vials of ACP antivenin and 10 vials of FabAV were used. Antivenin was administered within 6 hours of envenomation in 143 of 157 (91.1%) patients. The 55 (26%) patients managed without antivenin were treated with elevation, immobilization, and analgesia.

With regard to the cost of antivenin treatment, data were available for analysis in 64 of 75 patients treated with FabAV. The average hospital charge was \$34,066, with the antivenin accounting for \$24,875, representing 73% of the total hospital charges. The acquisition cost to the hospital

per vial of FabAV was \$1,063 and the patient charge was \$2,416.

Complications

There were no deaths and only 1 amputation at the thumb interphalangeal joint, occurring in a patient in the ACP treatment group. Allergic reactions were identified in 15 of 211 patients, all following exposure to ACP. Ten patients in the ACP group experienced allergic reactions. Anaphylactic shock occurred in 2 patients. Four patients reacted to test doses of ACP at outside hospitals, 2 were subsequently treated with FabAV and 2 were managed without further antivenin. One patient developed rash and itching 48 hours after ACP administration, which was attributed to plasma infusion. No patients experienced allergic reactions after FabAV exposure. There were no airway or pulmonary manifestations requiring intubation. All allergic reactions were treated with a combination of diphenhydramine, corticosteroids, and subcutaneous epinephrine. Details regarding the type and severity of reaction are available in Table 2.

Fasciotomies were performed for suspicion of compartment syndrome in 33 of 211 (15.6%) patients: 19 (58%) on the upper extremity and 14 (42%) on the lower extremity. Fasciotomies were performed only when compartment syndrome was suspected by clinical examination and/or elevated compartment pressures (Table 3).

Derangements of coagulation occurred in 88 of 211 (42%) patients. An INR greater than 1.5 was present in 46 (22%) patients and greater than 2.0 in 14 (6.6%). Thrombocytopenia, defined as platelets less than 100,000/mL, occurred in 42 (19.9%) patients, and hypofibrinogenemia, defined as less than 200,000/mL occurred in 57 (27%) (Table 4). There were no differences among the 3 groups in the incidence of laboratory evidence of coagulopathy. There were no bleeding complications associated with coagulopathy in any group; however, 17 of 211 (8.1%) patients received blood component transfusions (Table 4).

Comments

Crotalid envenomation continues to represent a treatment dilemma due to the variable risks and benefits of antivenin administration, the subjective nature of determining the severity of envenomation, and the difficulty in determining the need for surgical intervention. In addition, the antivenin cost must be considered despite the demonstration of its

Table 4
Incidence of coagulopathy and transfusion

	Total	FabAV	ACP	None	Both
Coagulopathy	88/211 (42%)				
Thrombocytopenia (platelets <100,000/mL)	42/211 (20%)	15 (20%)	19 (26%)	5 (9%)	2 (29%)
Hypofibrinogenemia, fibrinogen <200 mg/dL	57/211 (27%)	22 (29%)	21 (28%)	8 (15%)	6 (86%)
INR >1.5	46/211 (22%)	24 (32%)	12 (16%)	8 (15%)	2 (29%)
INR >2.0	14/211 (7%)	8 (11%)	3 (4%)	3 (5%)	0 (0%)
Blood component transfusion	17/211 (8.1%)	7/75 (9%)	7/74 (10%)	3/55 (6%)	0 (0%)
Plasma transfusion (FFP or Cryo)	11/211 (6%)	6/75 (8%)	4/74 (5%)	1/55 (2%)	0 (0%)
Platelet transfusion	12/211 (6%)	4/75 (5%)	6/74 (8%)	2/55 (4%)	0 (0%)
RBC transfusion	4/211 (2%)	1/75 (1%)	3/74 (4%)	0/55 (0%)	0 (0%)

INR = international normalized ratio; FFP = fresh frozen plasma; Cryo = ; RBC = red blood cells.

efficacy, as the majority of hospital charges following admission for snakebite are for antivenin [18].

Antivenin therapy was frequently withheld in the past due to the associated morbidity. Evolution in the management of crotalid envenomation has resulted in the development of a treatment with fewer immunogenic sequelae. Our data show a significant reduction in the incidence of allergic reactions associated with ovine FabAV antivenin compared to horse serum-derived ACP. The rate of allergic reaction we report is consistent with previously reported rates: 0% to 14.3% for FabAV and 23% to 56% for ACP [17,19,20]. While anaphylactic shock associated with antivenin remains a considerable concern, only 2 of 14 patients manifested hypotension, which resolved promptly with treatment. The remaining allergic reactions were all considered to be mild to moderate. Our incidence of serum sickness cannot be determined as presentation usually occurs in a delayed fashion and follow up data for patients in this series were largely unavailable. Although no patients developed symptoms while hospitalized, serum sickness has been reported in up to 56% of patients receiving equine-derived antivenin [21].

Benefits of treatment for mild envenomation are frequently debated. Several authors have made a case for supportive treatment of snakebites without antivenin therapy citing the complications associated with antivenin [20]. These conclusions are based on the horse serum-derived antivenin, which was associated with anaphylaxis, serum sickness, and death. Unfortunately, the long-term sequelae of supportive treatment alone without antivenin are not known. Determining the degree of envenomation is often subjective and discerning a mild rattlesnake envenomation from a severe non-rattlesnake envenomation is often not possible. Animal data are compelling regarding administration of antivenin as close to the time of bite as possible and copperhead bites have been safely treated with antivenin therapy [22]. The degree of envenomation is often subjective. The grading scale used in FabAV clinical trials to establish the need for initiation of antivenin therapy relies on local and systemic physical examination findings and laboratory analysis to determine the degree of envenomation. Bites are described as without envenomation or mild, moderate, or severe. Although some standardization is achieved, this scale is limited by its subjectivity. In order to better establish treatment protocols, prospective studies comparing FabAV use to supportive measures for treatment of mild rattlesnake envenomation, as well as non-rattlesnake envenomation, are necessary.

In this series, there was a statistically significant difference in the number of fasciotomies performed in the ACP group compared to the group receiving no antivenin; however, the patients in the no antivenin group may have had less severe envenomations. The majority of bites occur on the extremities, dysfunction of which is associated with significant morbidity. Bite location, especially of the hand and foot, should prompt a lower threshold to use antivenin because of the potential for significant morbidity. We do not recommend prophylactic fasciotomies, and none were performed in this series. The rates of fasciotomy were higher earlier in this series, particularly when ACP was the only antivenin available. It is not clear whether the decreased rate

is associated with a change in antivenin type or increasing surgeon comfort with the nature of these injuries.

In safety and efficacy trials of FabAV, patients with severe envenomation, bites greater than 6 hours after envenomation, bites from copperheads or cottonmouths, and patient less than 18 years of age were excluded. Thus the current manufacturer indication for FabAV antivenin treatment is a patient with minimal to moderate symptoms of crotalid envenomation treated within 6 hours of the bite. Our patient population included adults and children, copperhead and cottonmouth bites, severe envenomations, as well as patients receiving antivenin more than 6 hours after envenomation. Our study suggests that a significant proportion of antivenin is being used beyond the Food and Drug Administration-approved indication and beyond what has been studied in randomized controlled trials but that antivenin can be used safely in these cases. It is essential that these populations be studied in a prospective randomized fashion to determine if there is any true treatment benefit.

The limitations of this study include those found in any retrospective chart review. In particular, symptoms of crotalid envenomation may mimic allergic or anaphylactic reactions and this determination could not be made retrospectively. No standard grading scale was used for the assessment of envenomation, making it difficult to compare outcomes and antivenin use stratified by degree of envenomation. The length of stay data do suggest that bites are treated appropriately, as those who do not receive antivenin, presumably for mild envenomation, have shorter length of stay than those treated with antivenin. Another limitation of this study is that the species of snake was rarely independently identified and the victim's firsthand description identifying the snake was seldom documented.

Some authors have called for "rational" and "appropriate" use of antivenin and suggest that it should not be a routine adjunct in the management of crotalid envenomation [23–25]. Fatalities from rattlesnake bites are rare, estimated to be less than 20 per year in the United States, and copperhead and cottonmouth envenomations are universally survived. Thus, antivenin use as a life-saving treatment cannot be strongly argued. The utility in the use of antivenin must then be for reduction in morbidity. FabAV therapy has been shown to be efficacious in arresting the progression of tissue destruction and reversing coagulopathy in mild to moderate envenomation. Antivenin has also been demonstrated to lower compartment pressures in animal models and in 1 human case report. Thus, it can be concluded that in rattlesnake envenomations, and severe copperhead and cottonmouth envenomations, antivenin treatment likely does reduce the associated morbidity. Additionally, antivenin use likely increases patient comfort and reduces analgesic requirements by neutralizing tissue-destructive enzymes. Significant allergic reactions with ovine antivenin are extremely rare. It is thus the cost of antivenin that has become a greater consideration than the complications of therapy. It is difficult to determine the cost of snakebite management as antivenin has not been compared to placebo in clinical trials. While the absolute cost of antivenin is high, this may be less than the cost of management without antivenin. In cases of mild envenomation, which may be self-limited and resolve without antivenin therapy, the ben-

enefit of antivenin use is appropriately questioned. In cases of severe envenomation, there likely is benefit to antivenin therapy, especially in cases where compartment syndrome threatens a limb. These patients were unfortunately excluded from the original trials. Thus, it is our practice to treat all patients with moderate to severe envenomation with FabAV based on local and systemic signs regardless of snake species. Antivenin should not be withheld on the basis that non-rattlesnake envenomation is without sequelae. Treatment benefit has been observed with delayed administration of antivenin as well.

We conclude that crotalid FabAV has a significantly better safety profile compared to ACP, with only rare allergic reactions associated with FabAV, none in our series. There is an overwhelming lack of prospective data comparing treatments for snakebites. Long-term follow-up studies of snakebite victims are necessary to determine if antivenin use improves long-term limb function. While antivenin therapy is not usually a life-saving maneuver, its use may result in fewer fasciotomies, increased patient comfort, and improved long-term limb function.

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