

Adverse Events in the Efficacy of Crotalidae Polyvalent Immune Fab Antivenom vs Placebo in Recovery from Copperhead Snakebite Trial

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Objective: To compare the incidence of hypersensitivity reactions following copperhead envenomation treated with Fab antivenom (FabAV) or placebo.

Methods: Patients with copperhead snakebites received treatment and follow-up in a prospective, randomized, double-blind, placebo-controlled trial of FabAV or placebo. The treatment allocation ratio was 2:1 (FabAV: placebo). All of the included patients received at least one dose of study treatment. We reviewed all treatment-emergent adverse events (AEs) using a previously published scale to classify likely hypersensitivity reactions as mild, moderate, or severe.

Results: We enrolled 74 patients at 13 sites. Forty-five patients received FabAV, and 29 patients received placebo. Five FabAV patients and 4 placebo patients had moderate envenomations; the rest were mild. Twenty-five FabAV patients and 8 placebo patients had at least 1 AE. Mild skin reactions occurred in 11 (24%) FabAV patients (pruritis, urticaria, rash, ecchymosis, erythema) and 1 (3%) placebo patient (pruritis). Moderate gastrointestinal AEs occurred in 7 (16%) FabAV patients (nausea, vomiting, constipation, diarrhea, oral paresthesia) and in 2 (7%) placebo patients (nausea). Respiratory AEs occurred in 3 (7%) FabAV patients (dyspnea, pulmonary embolism, nasal congestion, sneezing) and no placebo patients. Hypotension occurred in 1 patient in each group.

Conclusions: In a randomized controlled trial of FabAV for copperhead bites, the incidence of hypersensitivity reactions was low. Most reactions were mild skin reactions.

Key Words: *Agkistrodon contortrix*, antivenom, copperhead, hypersensitivity, snakebite

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Crotalidae polyvalent immune Fab (ovine) antivenom (FabAV) is the third most frequently used toxicant-specific antidote in the United States after naloxone and acetylcysteine.¹ In 2015, the American Association of Poison Control Centers' National Poison Data System recorded 6315 total snakebites, with known or suspected crotaline bites accounting for nearly 60% of cases.¹

Key Points

- Treatment-emergent adverse events were more common among patients receiving Fab antivenom (FabAV) when compared with placebo patients.
- Skin reactions (eg, itching, pruritis, rash, hives) were approximately three times more frequent among patients receiving FabAV. All of the reactions were mild, and none led to withdrawal from the study.
- Gastrointestinal reactions (eg, nausea, vomiting) were approximately twice as common among patients receiving FabAV. All of the reactions were mild, and none led to withdrawal from the study.
- Patient follow-up to a minimum of 28 days found no cases of delayed hypersensitivity (serum sickness).

Copperhead snakes accounted for nearly half of these, with the remainder being rattlesnakes, cottonmouths, and unknown crotaline snakes (based upon information from poison center callers, including healthcare providers or members of the lay public). Although crotaline envenomation causes significant morbidity, only 53% of the crotaline bite patients received FabAV.¹⁻⁵

Risk of adverse reactions to antivenom remains a concern for many clinicians and limits the use of this antidote.^{6,7} A 2012 systematic review and meta-analysis of studies involving patients treated with FabAV estimated the incidence of immediate hypersensitivity reactions or serum sickness as 8% and 13%, respectively⁸; however, limitations of the individual studies created uncertainty in the precision and generalizability of these point estimates. These authors conservatively attributed all of the effects to antivenom. None of the 11 studies in this meta-analysis included a placebo group; therefore, the authors were unable to distinguish venom reactions from antivenom reactions. Consequently, the true proportion of reactions attributable to antivenom remains unknown. In addition, seven studies were retrospective cohort studies,⁹⁻¹⁵ only one of which had trained and blinded data abstractors. Not following this accepted standard for retrospective studies creates the risk of bias in their results.^{16,17} Patients with rattlesnake envenomation predominated in these studies, whereas copperhead snakes cause approximately half of US envenomations.^{1,18} To the extent that adverse events (AEs) to venom, antivenom dose, and venom-antivenom complexes may affect the perceived incidence of AEs, these studies may not be representative of US snake envenomation patients overall. The true incidence of antivenom-induced hypersensitivity reactions remains elusive.

Our study objective was to determine the incidence of hypersensitivity reactions and other AEs in FabAV-treated crotaline envenomation compared with a placebo-treated population.

Methods

Study Design

We report the secondary safety analysis of AEs recorded in a multicenter, double-blind, randomized, placebo-controlled trial comparing FabAV with placebo in the treatment of copperhead (*Agkistrodon contortrix*) envenomation.¹⁹ The trial included prospective surveillance of predefined AEs recorded by investigators blinded to treatment allocation, which allowed comparison of the incidence of hypersensitivity reactions attributable to FabAV versus placebo in envenomated patients.

The Western Institutional Review Board and/or the institutional review board at each study site approved the study. An independent data monitoring committee oversaw study conduct, with onsite monitoring performed by the sponsor's clinical research associates. All of the participants gave written, informed consent, and the study was registered on clinicaltrials.gov under NCT01864200.

Patients

We screened consecutive patients with copperhead snakebites from August 2013 through November 2015 at 18 emergency departments in the southeastern United States. Inclusion criteria included mild or moderate verified copperhead envenomation to a single extremity distal to the knee or elbow, age 12 years and older, and enrollment within 24 hours of the bite. For this study, we defined "mild" envenomation as pain and swelling crossing zero or one major joint (ankle, knee, wrist, or elbow) from the bite location. We defined "moderate" envenomation as pain and swelling crossing two major joints at presentation. We defined "severe" envenomation as pain and swelling crossing three major joints, compartment syndrome, systemic symptoms (nausea, dyspnea, or systolic blood pressure <90 mm Hg), laboratory evidence of coagulopathy (international normalized ratio >2, platelet count <50,000 cells per microliter, or fibrinogen <50 mg/dL), or active bleeding distant from the bite. Exclusion criteria included pregnancy, multiple bitten extremities, and predefined severe envenomation.¹⁹

Intervention

Enrolled patients underwent randomization in a 2:1 ratio to receive either FabAV or placebo. Patients and treating physicians remained blinded to the treatment allocation. Patients received a loading dose of 6 vials of the study drug in 250 mL of normal saline (or 250 mL of normal saline as placebo) for approximately 1 hour. At the discretion of the treating physician, a patient could receive a second loading dose if the patient did not experience initial control of symptoms. We defined control of symptoms as cessation of progression of pain and swelling associated with the bite. We withdrew patients who did not achieve initial symptom control after two loading doses from the primary study to receive open-label antivenom at the discretion of the treating physician. Maintenance doses after establishing initial control were 2 vials of study drug (FabAV or placebo according to treatment assignment) every 6 hours for 18 hours (total of 3 maintenance doses).

Outcomes Collection and Definitions

All of the patients had at least 24 hours of observation with follow-up at hospital discharge. Scheduled in-person follow-up visits with blinded study personnel occurred at 3, 7, 14, 21, and 28 days after envenomation and additional telephone study follow-up on days 10, 17, and 24. Follow-up continued beyond 28 days in patients who had not yet fully recovered from their envenomations. Structured AE collection occurred at each visit from the time of first investigational product infusion through completion of all of the follow-up assessments using definitions determined a priori. We characterized each AE using the Medical Dictionary for Regulatory Activities taxonomy (version 16.1).²⁰ An AE was any untoward medical occurrence that developed after the patient received study medication, regardless of the degree of likelihood of a causal relation with the study medication, in accordance with the Code of Federal Regulations

Table. Treatment-emergent adverse events in patients receiving Fab antivenom or placebo

	Fab AV (n = 45)	Placebo (n = 29)	Overall (n = 74)	P
No. subjects with ≥ 1 TEAE (%)	25 (56)	8 (28)	33 (45)	0.0303
No. deaths (%)	0	0	0	
No. subjects with ≥ 1 serious TEAE (%)	1 (2)	1 (3)	2 (3)	>0.9999
No. subjects with ≥ 1 severe TEAE (%)	3 (7)	0	3 (4)	0.2753
No. subjects with ≥ 1 TEAE related to study treatment (%)	16 (36)	3 (10)	19 (26)	0.0274
No. subjects with ≥ 1 TEAE leading to withdrawal from study treatment (%)	3 (7)	2 (7)	5 (7)	>0.9999

Boldface type indicates statistical significance. FabAV, Fab antivenom; TEAE, treatment-emergent adverse event.

21 CFR Section 321.32(a).²¹ Study investigators blinded to the treatment allocation contemporaneously classified the degree of causal relation between symptoms and study treatment as “related,” “probable,” “possible,” “unlikely,” and “unrelated.”

Statistical Analysis

For this safety analysis, we included all of the patients who received at least one loading dose of study treatment. We report baseline characteristics for all of the patients treated. Frequencies and proportions describe categorical data with 95% confidence intervals. We used the Fisher exact test for comparisons of event frequencies. We classified AEs with onset < 7 days from enrollment as “acute” and AEs with onset at ≥ 7 days from enrollment as “late.” In addition, we performed a post hoc analysis of hypersensitivity reaction AEs using a previously published scale to classify likely reactions as “mild” (skin and subcutaneous tissues only), “moderate” (respiratory, cardiovascular, or gastrointestinal), or “severe” (hypoxia, hypotension, or neurological compromise).²² We excluded reactions assessed as “unlikely” or “unrelated” by investigators. The antivenom literature has used this approach to assess possible hypersensitivity reactions.²³

Results

Seventy-four patients (39 men, 35 women) at 13 sites received at least 1 dose of the study drug, including 45 patients (23 men, 22 women) treated with FabAV and 29 patients (16 men, 13 women) treated with placebo. The enrollment severity of envenomation was moderate (defined by the study as swelling across 2 major joints) in 5 of 45 FabAV patients and 4 of 29 placebo patients; the remaining patients had mild envenomations (defined as swelling across 0 or 1 major joint).

A total of 25 of 45 (56%) FabAV patients and 8 of 29 (28%) placebo patients reported at least 1 AE (Table). Of these, only 16 (36%) FabAV patients and 3 (10%) placebo patients had an AE judged to be related to study treatment. Three FabAV patients and two placebo patients had at least one AE leading to withdrawal from the study ($P > 0.99$).

Skin and subcutaneous tissue AEs occurred in 11 of 45 (24%) FabAV patients. These included pruritus in 6, urticaria in 5, and rash in 4 patients. None of these were “severe.” One of 29 (3%)

placebo patients reported “mild” pruritis. Nonhypersensitivity AEs were cellulitis (2), herpes zoster, and ecchymosis. Based on the Brown hypersensitivity criteria and our blinded causality assessment, 11 FabAV patients and 1 placebo patient had skin and soft tissue manifestations that were consistent with hypersensitivity and related to the study medication ($P = 0.19$).

Diphenhydramine was the most commonly used medication for possible dermatological symptoms (19 of 45 FabAV patients, 4 of 29 placebo patients). Investigators classified the reason as prophylaxis or unrelated to study treatment in 12 of 23 patients receiving diphenhydramine. Two FabAV patients received intravenous methylprednisolone in addition to diphenhydramine for itching; one of these patients also received ranitidine for itching. No other patients received corticosteroids or selective histamine-2 receptor antagonists.

Gastrointestinal AEs occurred in 7 of 45 (16%) FabAV patients. AEs causally related to study treatment included nausea in 4 patients and vomiting in 2. All of the patients rated these as “mild” in severity. Of 29 (7%) placebo patients, 2 had a gastrointestinal AE (nausea rated as “mild” in both). Additional AEs were constipation (2), diarrhea (2), herpes zoster, and ecchymosis.

Ondansetron was the most commonly used medication for possible gastrointestinal symptoms (12 of 45 FabAV patients, 10 of 29 placebo patients). Investigators classified the reason as prophylaxis or unrelated to study treatment in 19 of 22 patients receiving ondansetron. One FabAV patient received famotidine in addition to ondansetron for nausea.

Three of 45 (7%) FabAV patients reported respiratory AEs, including pulmonary embolism (with dyspnea), nasal congestion, and sneezing. Site investigators assessed all of these as unlikely or unrelated to study treatment. No patient who received placebo had a respiratory AE. Cardiovascular AEs included hypotension in one patient in each group. Both patients received intravenous normal saline, and neither required vasopressors. The actual blood pressures were unavailable in summary safety data for the study. Neurological AEs were paresthesia/hypoesthesia (4), headache (6), dizziness, and insomnia.

Only four patients (2 FabAV, 2 placebo) had AEs newly recorded at or after 7 days postenvenomation. One FabAV patient had cellulitis diagnosed 8 days after envenomation and received trimethoprim-sulfamethoxazole for 1 week. One FabAV patient

reported sneezing and nasal congestion for 9 days; this patient had chronically been taking loratadine before and during the study. One placebo patient reported itching at day 25 after taking diphenhydramine from days 2 through 21. One placebo patient had a fall resulting in a rib fracture 56 days after envenomation. None of these patients had symptoms such as fever, chills, or myalgias to suggest delayed hypersensitivity or serum sickness.

AEs other than potential hypersensitivity reactions included hypoglycemia, hypophosphatemia, arthropod bite/sting (2), cellulitis (2), herpes zoster, ecchymosis, pulmonary embolism, insomnia, vaginal bleeding, sneezing, nasal congestion, renal pain, paresthesia/hypoesthesia (4), headache (6), dizziness, extremity pain, peripheral edema, noncardiac chest pain, blurred vision, and anemia.

Discussion

Patients treated with FabAV had a higher rate of AEs, although the majority of AEs in both groups were mild and did not compel withdrawal from the study. More than 25% of the placebo patients experienced at least one AE. The majority of AEs in each group appear not to represent hypersensitivity reactions.

The portion of AEs differs from the estimates by Schaeffer et al.⁸ This likely results from the prospective surveillance for a variety of AEs in this study compared with the retrospective nature of most of the studies included in the meta-analysis.

The scale proposed by Brown rates the degree of anaphylaxis, but it may be an imperfect tool to classify AEs.²² For example, nasal congestion and sneezing are respiratory symptoms included in Brown's "moderate hypersensitivity" category, although the two patients with these symptoms rated them as "mild."

Isbister et al used the same hypersensitivity scale to assess antivenom-treated patients in the Australian Snakebite Project.²³ As with the present study, they retrospectively analyzed prospectively collected data and found similar rates but higher severity of hypersensitivity reactions. Key differences include the nature of the seven Australian antivenoms (all derived from equine serum), variety of snakes, absence of blinding of patients or investigators, and absence of a placebo control or placebo group.

Two single-patient, multicenter case series of repetitive use of FabAV suggest that FabAV is not sensitizing. Wilson in 2002 and Lavonas et al in 2013 described the same patient who had received a total of 153 vials of FabAV among 19 different occasions in 17 years in New Mexico and Colorado.^{24,25} Although he had "mild" urticaria and angioedema on the first occurrence, he had no AEs on the subsequent 18 visits, even without antihistamine or corticosteroid pretreatment on a majority of those visits. Abdelmalek et al described a similar patient with multiple emergency department visits in Missouri and Kansas.²⁶ He received 42 vials of FabAV across 5 occasions without AE.

A retrospective series by Gale et al found no adverse reactions among 44 patients receiving FabAV after copperhead snakebites.²⁷ Similarly, Kleinschmidt and colleagues reviewed AEs among 368 patients who received FabAV reported in the American College of Medical Toxicology North American Snakebite Registry and reported hypersensitivity reactions in

only 2.4% of patients receiving FabAV.²⁸ Our data, however, are most consistent with those of Bush et al, who undertook a prospective randomized controlled trial of F(ab')₂AV versus FabAV for North American Crotalinae envenomations.²⁹ Itching/pruritis (generally mild) was the most frequent AE in all three treatment groups. Prospective randomized controlled trials have systematic surveillance for AEs and typically record more AEs than do retrospective studies.

Conclusions

In a randomized, double-blind, placebo-controlled trial of FabAV for copperhead bites, AEs related to study treatment were more common with FabAV than with placebo. The majority of reactions were mild skin reactions. The incidence of moderate or severe hypersensitivity reactions was low.

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