The Efficacy of Crotalidae Polyvalent Immune Fab (Ovine) Antivenom Versus Placebo Plus Optional Rescue Therapy on Recovery From Copperhead Snake Envenomation: A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial

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Study objective: Copperhead snake (*Agkistrodon contortrix*) envenomation causes limb injury resulting in pain and disability. It is not known whether antivenom administration improves limb function. We determine whether administration of antivenom improves recovery from limb injury in patients envenomated by copperhead snakes.

Methods: From August 2013 through November 2015, we performed a multicenter, randomized, double-blind, placebo-controlled, clinical trial to evaluate the effect of ovine Crotalidae polyvalent immune Fab (ovine) (CroFab; FabAV) antivenom therapy on recovery of limb function in patients with copperhead snake envenomation at 14 days postenvenomation. The study setting was 18 emergency departments in regions of the United States where copperhead snakes are endemic. Consecutive patients aged 12 years or older with mild- to moderate-severity envenomation received either FabAV or placebo. The primary outcome was limb function 14 days after envenomation, measured by the Patient-Specific Functional Scale. Additional outcomes included the Patient-Specific Functional Scale at other points; the Disorders of the Arm, Shoulder, and Hand, Lower Extremity Functional Scale, and Patient's Global Impression of Change instruments; grip strength; walking speed; quality of life (Patient-Reported Outcomes Measurement Information System Physical Fucntion-10); pain; and analgesic use.

Results: Seventy-four patients received study drug (45 FabAV, 29 placebo). Mean age was 43 years (range 12 to 86 years). Fifty-three percent were men, 62% had lower extremity envenomation, and 88% had mild initial severity. The primary outcome, the least square mean Patient-Specific Functional Scale score at 14 days postenvenomation, was 8.6 for FabAV-treated subjects and 7.4 for placebo recipients (difference 1.2; 95% confidence interval 0.1 to 2.3; P=.04). Additional outcome assessments generally favored FabAV. More FabAV-treated subjects experienced treatment-emergent adverse events (56% versus 28%), but few were serious (1 in each group).

Conclusion: Treatment with FabAV reduces limb disability measured by the Patient-Specific Functional Scale 14 days after copperhead envenomation. [Ann Emerg Med. 2017;70:233-244.]

Please see page 234 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Approximately 5,000 to 9,000 people seek emergency care in the United States for crotaline snakebites annually, including rattlesnake, cottonmouth, and copperhead envenomation.[1] The copperhead (*Agkistrodon contortrix*) is responsible for nearly half of reported bites.[2] Copperhead envenomation is generally less severe than rattlesnake envenomation.[3-5] More than 95% of copperhead victims develop significant pain and swelling of the envenomated limb, but systemic venom effects are uncommon and death is rare.[6-9] Current data support only a crude understanding of the time course of recovery from limb injury with or without antivenom therapy. Although most patients

Editor's Capsule Summary

What is already known on this topic

Copperhead envenomation is rarely life threatening but may cause prolonged limb injury.

What question this study addressed

This multicenter randomized controlled trial evaluated the effect of antivenom administration on limb function in a cohort of patients with predominantly mild copperhead envenomations.

What this study adds to our knowledge

Seventy-four patients were enrolled in the study, of whom 45 were randomized to antivenom administration. Antivenom improved Patient-Specific Functional Scale score at day 14 (8.6 versus 7.4; Δ=1.2; 95% confidence interval 0.1 to 2.3). All patients recovered by 4 months regardless of intervention. Opioid use was lower in the antivenom group.

How this is relevant to clinical practice

Outcomes in mild to moderate copperhead envenomation are generally good. Antivenom may improve limb function early in the course and minimize the need for prolonged opioid analgesia. Given associated costs, an individualized risk-benefit discussion should occur.

recover enough to return to work within 2 to 4 weeks, residual symptoms can last a year or more.[6,10]

Importance

Crotalidae polyvalent immune Fab (ovine) (CroFab; FabAV) (BTG International Inc, West Conshohocken, PA) is the only antivenom currently Food and Drug Administration approved and marketed for the treatment of crotaline snake envenomation. Although FabAV is approved for the treatment of envenomation by all North American crotaline species, copperhead-envenomated patients were excluded from the registry trials because it was considered unethical to expose these patients to then-experimental antivenom (personal communication, R. C. Dart, Rocky Mountain Poison and Drug Center, 2012).[11,12] The safety of FabAV was subsequently established, and observational studies demonstrated that FabAV administration is associated with cessation of progression of tissue injury in copperhead victims.[8,13,14] Whether this leads to improved recovery of limb function is unstudied, and the role of FabAV in the management of patients with nonlife-threatening envenomation is controversial. Although many experts recommend treating all crotaline envenomation patients according to clinical presentation, irrespective of species, others recommend withholding FabAV from copperhead victims.[4,5,9,15-18] These conflicting recommendations have resulted in wide practice variation, with 0% to 90% of patients at individual hospitals receiving antivenom.[5,6,10,19-21] In 3 recent prospective studies, the proportion of copperhead patients receiving FabAV ranged from 14% to 75%, and in the largest study there was poor correlation between snakebite severity score and the decision to use antivenom (r^2=0.06).[4,22,23] A 2004 editorial called for a clinical trial to study the efficacy of FabAV therapy for copperhead snake envenomation, but no such research has been performed.[24]

Goals of This Investigation

The purpose of this study is to determine whether administration of antivenom improves recovery from limb injury in patients envenomated by copperhead snakes.

MATERIALS AND METHODS

Study Design

We performed a multicenter, randomized, double-blind, placebo controlled, clinical trial to evaluate the effect of FabAV administration on limb recovery. The study was approved by the Western Institutional Review Board and the institutional review board at each study site. In addition to on-site monitoring by the sponsor's clinical research associates, study conduct was overseen by an independent data monitoring committee. Informed consent was obtained from all participants.

Selection of Participants

We enrolled consecutive patients from August 2013 through November 2015 at 18 emergency departments (EDs) in regions of the United States where copperhead snakes are endemic. Patients were nonpregnant adults ($\geq$18 years) or adolescents (12 to 17 years) presenting with mild- to moderate-severity envenomation by a copperhead snake on only one extremity (distal to the elbow or knee) that occurred within 24 hours of enrollment. Mild envenomation was defined by swelling crossing 0 to 1 major joints (wrist, elbow, ankle, or knee), and moderate envenomation by swelling crossing 2 major joints. Copperhead species was confirmed by examination of the snake or photograph of the snake brought to the ED, patient identification of a copperhead from an array of snake photographs, envenomation in an area where only

copperheads are endemic, or envenomation by a captive copperhead snake.

Patients with severe venom effect at presentation (defined as swelling to an entire extremity [crossing the hip or shoulder joint], coagulopathy of possible medical importance [International Normalized Ratio >2.0, fibrinogen level <50 mg/dL, or platelet count <50,000 cells/μL], hypotension, compartment syndrome, or more than minimal bleeding) were excluded. The full protocol is provided in Appendix E1, available online at http://www.annemergmed.com.

Subjects were assigned in a 2:1 ratio to receive FabAV or placebo, using centralized computer randomization, stratified by envenomation site (upper versus lower extremity), severity (mild versus moderate), and age (adolescent versus adult). All study personnel (except the unblinded study pharmacist) and patients were unaware of treatment assignments.

Interventions

Subjects in the FabAV group received 6 vials of FabAV in 250 mL normal saline solution as initial treatment, repeated once if needed to halt progression of venom effects. They then received 2 vials of FabAV 6, 12, and 18 hours later, in accordance with current Food and Drug Administration–approved dosing instructions. Placebo subjects received visually identical normal saline solution. Subjects were monitored for progression to severe venom effect and for adverse events during and after completion of treatment.

Patients who developed severe venom effect at any time moved into standard-of-care rescue treatment, which could include open-label FabAV at the discretion of the treating physician. Patients or physicians could also request withdrawal from the protocol treatment at any time. Subjects were evaluated according to the original treatment group assignment, with blinding maintained unless required for patient safety.

Data Collection and Processing

Study personnel collected data about the signs and symptoms of the envenomation and treatment delivered during the initial hospitalization. Protocol-specified in-person study assessments were performed at hospital discharge and on days 3, 7, 14, 21, and 28 after envenomation, with procedures for telephone follow-up in case of missed study visits. Subjects also completed follow-up assessments by telephone on days 10, 17, and 24. Patients who had not reached full recovery on the primary study outcome by the 28-day visit completed monthly telephone assessments until full recovery or 4 months, whichever occurred first.

Outcome Measures

The primary outcome, chosen a priori, was the Patient-Specific Functional Scale score at envenomation plus 14 days.[25] The scale is a patient-oriented outcome that has been extensively validated in numerous musculoskeletal disorders, including copperhead snake envenomation.[22-35] Patients were asked to choose 3 activities they were unable to do or were having difficulty with because of their snake envenomation, and at each assessment reported their ability to perform these tasks on a scale of 0 ("unable to perform activity") to 10 ("able to perform activity at the same level as before injury or problem"). The mean of these 3 values is the Patient-Specific Functional Scale score, with a score of 10 indicating full recovery. The Patient-Specific Functional Scale has excellent interrater reliability and test-retest validity.[27,30,34] It assesses both upper or lower extremity conditions, thereby decreasing the sample size required to evaluate copperhead envenomation. The scale is closely correlated with limb-specific tools such as the Disorders of the Arm, Shoulder, and Hand, and the Lower Extremity Functional Scale instruments, but is more efficient to administer.[22,26-29]

All additional study outcomes were chosen a priori and serve to further inform the results of the primary outcome; they were not intended as hypothesis testing. Additional outcomes were comparisons of the Patient-Specific Functional Scale at other points, time to full functional status recovery as measured by the Patient-Specific Functional Scale, scores on the Disorders of the Arm, Shoulder, and Hand and Lower Extremity Functional Scale instruments (administered to subjects with upper and lower extremity envenomation, respectively), physical function-related quality of life measured by the Patient-Reported Outcomes Measurement Information System Physical Fucntion-10 (PROMIS PF-10),[36] numeric pain rating scale,[37] opioid analgesic use, and the Patient's Global Impression of Change–1 instrument.[38] For upper extremity envenomation subjects, grip strength was measured with a Jamar hand dynamometer (Lafayette Instruments, Lafayette, IN)[39]; lower extremity subjects completed a 7.62-m walking speed test.[40] The proportion of patients moved to rescue therapy was also a tertiary outcome. All outcome instruments are included in the protocol in Appendix E1, available online at http://www.annemergmed.com.

Structured adverse event collection occurred from the first investigational product infusion through completion of all follow-up assessments. Blinded site investigators characterized each event as serious or nonserious, using standard criteria, and determined whether the adverse event was related to study drug administration.[41] Each adverse event was characterized with Medical Dictionary for Regulatory Activities taxonomy (version 16.1).[42]

Primary Data Analysis

All statistical tests were determined a priori and applied to the modified intent-to-treat population, composed of all patients who received at least one dose of study medication. The primary efficacy endpoint was analyzed by ANOVA. Least squared mean Patient-Specific Functional Scale score was calculated for each treatment group, using a linear mixed-effect model that included factors for the stratification variables: anatomic location of envenomation, severity of snakebite, and age. Treatment effect was computed as difference in mean Patient-Specific Functional Scale score at day 14. The last observation carried forward method was used to impute data for missing assessments. A supportive analysis assessed the difference in least squared mean Patient-Specific Functional Scale scores between treatments, using a repeated-measures ANOVA. The full statistical analysis plan is provided in Appendix E1, available online at http://www.annemergmed.com.

Time to full recovery on the Patient-Specific Functional Scale was analyzed with a Cox proportional hazards model, including stratification variables as above. Other efficacy endpoints were analyzed with ANOVA to compare the least squared mean of the other outcome assessments between the treatment groups at each measured point. The

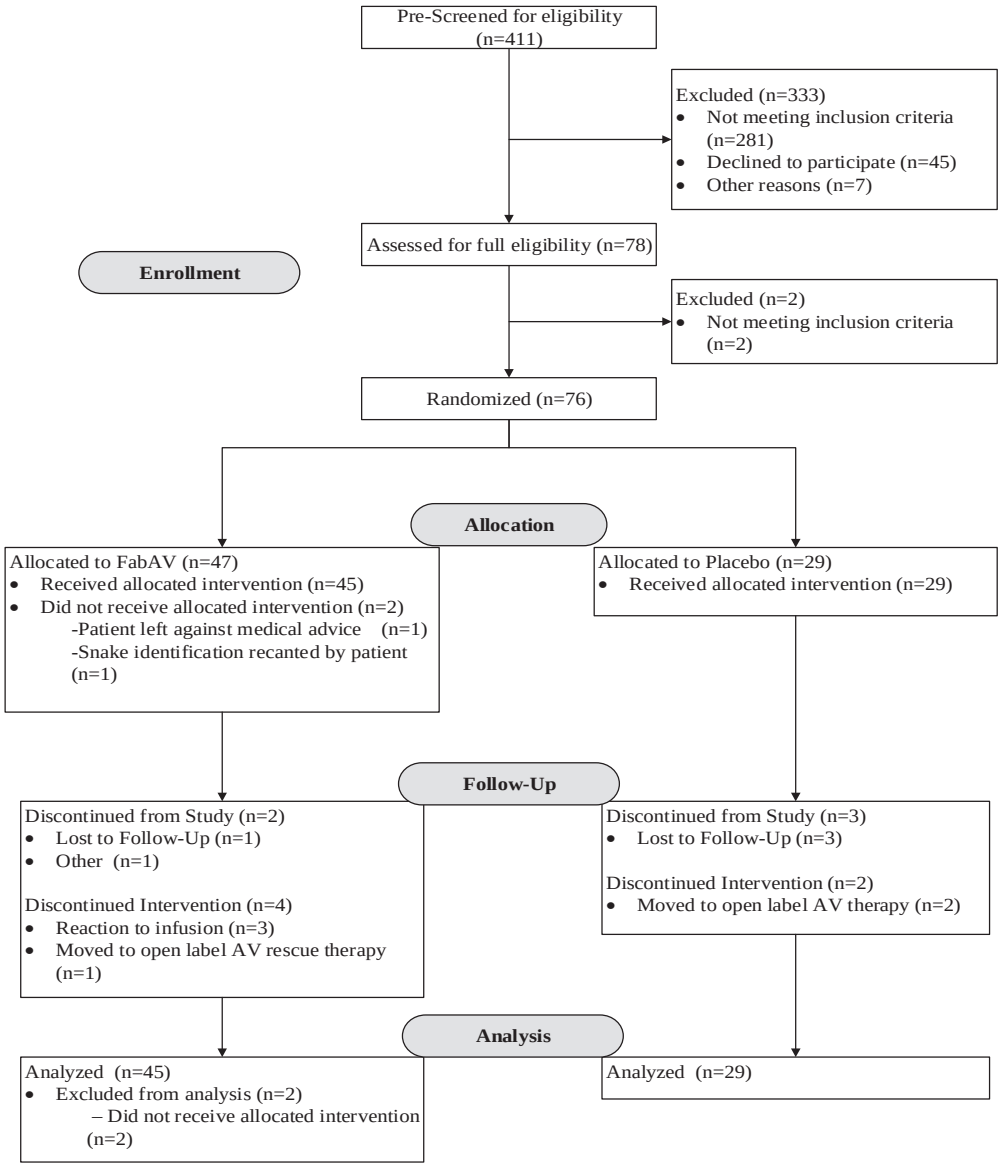

Figure 1. Patient flow. The unblinded investigational pharmacist at the investigative site accessed the Interactive Response Technology system to receive the treatment arm assignment for the subject. Only the unblinded pharmacy personnel had access to the treatment assignment to facilitate preparation of the study intervention. The subject, the investigator, and investigative site personnel remained blinded to the treatment assignment.

only departure from the statistical plan was that the original plan called for comparing analgesic use as any/none, but later it became clear that current opioid use was more clinically relevant. Thus, the opioid/no-opioid comparison is post hoc.

In accordance with a clinical difference of 1 SD in the prospective observational pilot data,[22] we calculated that a sample size of 182 evaluable subjects would produce 80% power to detect a statistically significant difference in the primary study outcome, with overall 2-sided α of 5.0% and one interim analysis. The original study plan was to enroll these patients during 2 complete snakebite seasons and perform an interim analysis after the first season. However, after the first full season it became clear that we would not reach target enrollment and the decision not to perform an interim analysis was made and communicated to all study sites. This decision was made in a blinded fashion before review or analysis of any data. According to pilot study data, the original sample size was understood to be underpowered for the additional outcome measures; therefore, they did not affect the interim analysis decision.

RESULTS

Characteristics of Study Subjects

Seventy-six patients were randomized and 74 received study drug (modified intent-to-treat population) (Figure 1). Two patients were randomized, but withdrew from the study before administration of the study drug. One patient requested withdrawal because of a family emergency and left the hospital against medical advice. The other patient was unable to identify the snake as a copperhead. Forty-five patients received FabAV and 29 received placebo. Sixty-nine subjects (93.2%) completed the study through final follow-up, with 2 withdrawals from the FabAV group and 3 from the placebo group. Baseline characteristics were well balanced between groups (Table).

Table. Patient demographic and baseline characteristics (modified intent-to-treat population).

Demographics	FabAV Treated Patients (N=45)	Placebo Treated Patients (N=29)	Total Treated Patients (N=74)
Age, y			
Mean (SD)	43.9 (17.9)	41.7 (17.2)	43.0 (17.6)
Range	12–86	13–69	12–86
Age strata, No. (%)			
Adult	42 (93.3)	24 (82.8)	66 (89.2)
Adolescent	3 (6.7)	5 (17.2)	8 (10.8)
Sex, No. (%)			
Male	23 (51.1)	16 (55.2)	39 (52.7)
Race, No. (%)			
White	40 (88.9)	25 (86.2)	65 (87.8)
Black	2 (4.4)	2 (6.9)	4 (5.4)
Asian	1 (2.2)	0	1 (1.4)
Other	2 (2.2)	2 (6.9)	4 (5.4)
Ethnicity, No. (%)			
Hispanic or Latino	3 (6.7)	4 (13.8)	7 (9.5)
Not Hispanic or Latino	42 (93.3)	25 (86.2)	67 (90.5)
Anatomic location, No. (%)			
Upper extremity	16 (35.6)	12 (41.4)	28 (37.8)
Lower extremity	29 (64.4)	17 (58.6)	46 (62.2)
Severity at enrollment, No. (%)			
Mild	40 (88.9)	25 (86.2)	65 (87.8)
Moderate	5 (11.1)	4 (13.8)	9 (12.2)
Study site, No. (%)			
Duke University, Durham, NC	16 (35.6)	12 (41.4)	28 (37.8)
University of North Carolina, Chapel Hill, NC	12 (26.7)	4 (13.8)	16 (21.6)
St. Joseph Regional Health Center, Bryan, TX	8 (17.8)	4 (13.8)	12 (16.2)
Virginia Commonwealth University Medical Center, Richmond, VA	2 (4.4)	2 (6.9)	4 (5.4)
Vidant Medical Center, Greenville, NC	2 (4.4)	1 (3.4)	3 (4.1)
Barnes-Jewish Hospital, St Louis, MO	2 (4.4)	1 (3.4)	3 (4.1)
Other sites	3 (6.7)	5 (17.3)	8 (10.8)
Method of snake species identification			
Snake or photograph brought to hospital	11 (23.4)	10 (47.6)	21 (27.6)
Patient or parent chose copperhead from photograph array	22 (46.8)	16 (55.2)	38 (50.0)
Envenomation occurred in an area endemic only to copperheads	14 (29.8)	3 (10.3)	17 (22.4)

Other sites enrolling subjects were Ben Taub General Hospital and Texas Children's Hospital, Houston, TX; Marshall Health Medical Center, Huntington, WV; University of Virginia Medical Center, Charlottesville, CA; and Augusta University Medical Center, Augusta, GA.

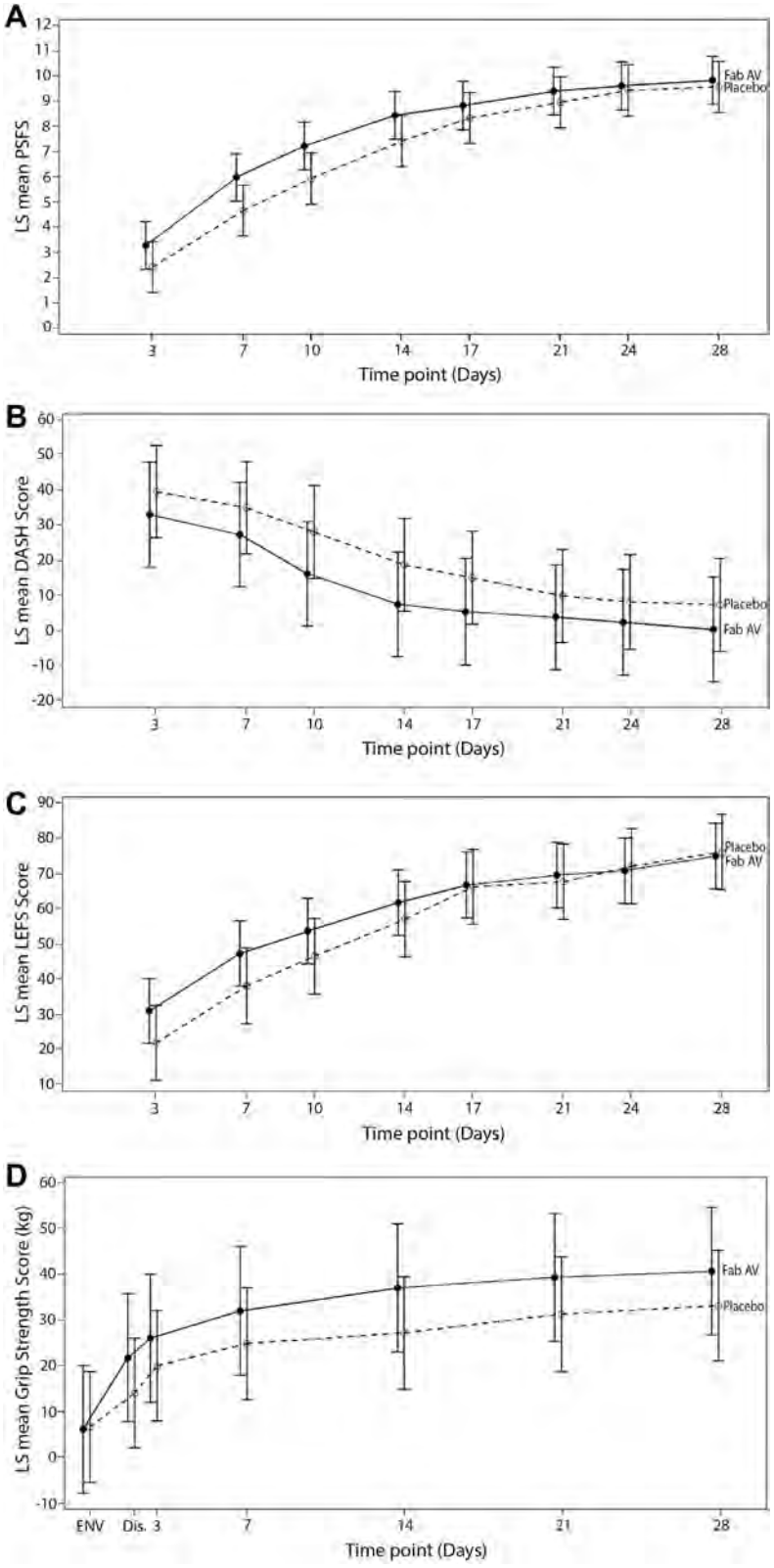

Figure 2. Supportive outcomes: recovery in copperhead envenomation patients treated initially with FabAV or placebo. *A*, PSFS scores. *B*, DASH scores. *C*, LEFS scores. *D*, Grip strength. *E*, NPRS scores. *F*, PROMIS PF-10 scores. *G*, Time to return to normal function in copperhead envenomation patients treated with FabAV or placebo. Error bars=95% confidence interval for each treatment group. The 95% confidence interval for the difference between treatment groups is analyzed with pooled standard error and is narrower. DASH: A lower score indicated better function; best possible score is 0. LEFS: A higher score indicated better

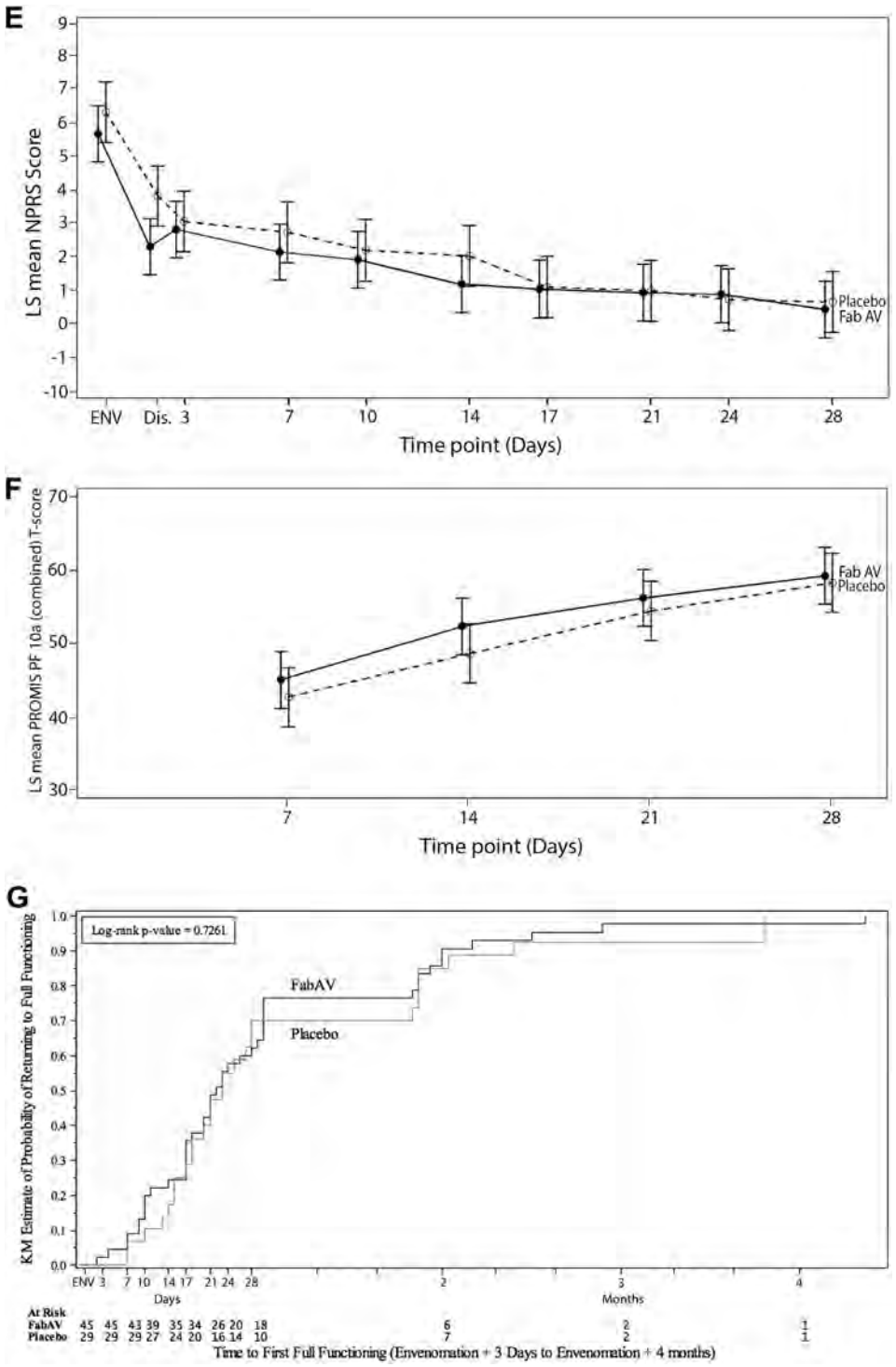

Figure 2. Continued.

function; best possible score is 80. Grip strength: A value of 0 kg was imputed for subjects unable to perform the test. NPRS: A lower score indicated less pain; range of possible scores is 0 to 10. PROMIS PF-10: A higher score indicated better quality of life; US population mean score is 50. Sample sizes: DASH (*B*) and grip strength (*D*): N=17 for the FabAV group and N=12 for placebo; LEFS (*C*): N=28 for the FabAV group and N=17 for placebo. All other assessments (*A*, *E* to *G*): N=45 for the FabAV group and N=29 for the placebo group. *PSFS*, Patient-Specific Functional Scale; *DASH*, Disorders of the Arm, Shoulder, and Hand; *LEFS*, Lower Extremity Functional Scale; *NPRS*, numeric pain rating scale.

The primary outcome, the least squared mean Patient-Specific Functional Scale score on day 14, was 8.6 for FabAV-treated subjects and 7.4 for placebo recipients (difference 1.2; 95% confidence interval 0.1 to 2.3; P=.04).

The point estimates for the additional outcomes routinely favored recovery in the FabAV group compared with placebo. The difference in the point estimates of the least squared mean Patient-Specific Functional Scale score favored FabAV at all other measured points. Patient-Specific Functional Scale total scores at each point are listed in Table E1, available online at http://www.annemergmed.com. Results from the limb-specific outcome measures; Disorders of the Arm, Shoulder, and Hand; Lower Extremity Functional Scale; and grip strength, pain assessments, and the global measure of recovery, PROMIS PF-10, in general favored the FabAV group as well (Figure 2*A* to *F*). No apparent difference was observed between treatments in time to full recovery (score of 10) on the Patient-Specific Functional Scale (Figure 2*G*) or walking speed. Opioid analgesic use was less in the FabAV-treated patients at all points (Figure 3). Two patients in each group moved to rescue treatment (Table E2, available online at http://www.annemergmed.com). No patients required emergency unblinding of study group assignment. All patients recovered by 4 months.

In the per-protocol population, the least squared mean Patient-Specific Functional Scale score on day 14 was 8.4 for FabAV-treated subjects and 7.1 for placebo recipients (difference 1.5; 95% confidence interval 0.4 to 2.7). No important differences were observed between the modified intent-to-treat and per-protocol analyses in supportive outcome analyses.

More patients had adverse events determined to be related to treatment per the blinded site investigator in the FabAV group (16/45; 36%) than did the placebo group (3/29; 10%). One patient in each group had a serious adverse event as determined by the blinded site investigator (Table E3, available online at http://www.annemergmed.com). The most common adverse events were headache, pruritus, nausea, dizziness, urticaria, and pyrexia. All adverse events are presented in Appendix E1, available online at http://www.annemergmed.com.

LIMITATIONS

This study had several limitations. It was designed and funded to enroll for 2 full snakebite seasons, and enrollment was concluded at this point without reaching the target sample size. Even at target enrollment, the study was known to be underpowered for its supportive analytic endpoints. The trial was not stopped early for benefit and consequently is not subject to the reported limitations of this approach.[43,44] However, the smaller-than-optimal sample size leads to imprecision in the estimate of treatment effect.

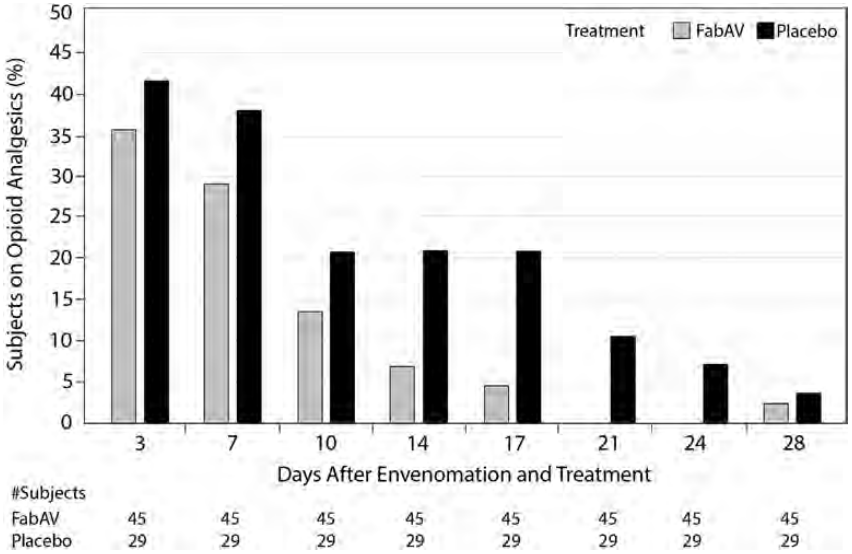

Figure 3. Opioid analgesic use in the previous 24 hours in copperhead envenomation patients treated initially with FabAV or placebo. Proportion of subjects who reported using an opioid analgesic (including tramadol) to treat snakebite-related pain in the 24 hours before each assessment. Sample size: FabAV, N=45; placebo, N=29.

The precise minimal clinically important difference in snakebite is unknown. For other disease states previously studied, the minimal clinically important difference is generally in the range of the average treatment effect observed in this trial.[27,33-35] However, it remains unknown how the difference varies by disease state, by upper versus lower extremity, or how it varies along the ordinal Patient-Specific Functional Scale. Additionally, the effect size found in this study may be artificially lower because of enrollment of a low-severity cohort. The majority (88%) of subjects in this study had minor-severity swelling at study entry. This is distinctly different from the subjects enrolled in the copperhead pilot study conducted by our group in many of the same study centers, 80% of whom had moderate envenomation.[22] We speculate this is because patients with minor envenomation are more willing to enroll in a placebo-controlled study than those with more severe disease. Acknowledging these limitations, we believe the benefit from FabAV administration observed in this study is likely clinically important to patients because the Patient-Specific Functional Scale reliably measures functional outcomes that the patient chooses and values.

Although this trial included 18 centers, most patients came from 3 sites in North Carolina and Texas. Because there is some geographic variation in within-species venom composition, the generalizability to all copperhead envenomation populations is questionable.[45] Thirteen centers from West Virginia to Texas contributed subjects, and exploratory analyses showed no apparent between-site differences. We believe the results are generalizable to copperhead victims as a whole, unless high-quality geographically specific data contradict our findings. A recent observational study in North Texas followed copperhead envenomation patients by telephone.[23] Although direct comparison is not possible, recovery appeared to be faster than in either the copperhead recovery pilot study or the present work.[21]

Children younger than 12 years, rattlesnake and water moccasin victims, and patients with severe envenomation were excluded from this study. There remains no direct evidence of the effect of FabAV on recovery of limb function in these populations. Because relatively few adolescent and elderly patients enrolled in this study, extrapolation from the overall results to these subgroups should be done with caution.

Finally, cost is an important consideration with modern antivenom use, and this study was not designed to support a pharmacoeconomic analysis. Currently, the cost to the hospital ranges from $2,000 to $2,900 per vial of FabAV. The charge to the payer is typically a multiple of this and includes the charge for care aside from the antivenom. The cost to the individual patient varies widely, depending on his or her insurance coverage. We suggest that the relationship between cost, potential harm, and potential benefits be discussed with patients during care.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial of adolescent and adult patients with mild- to moderate-severity copperhead snake envenomation, treatment with FabAV improved limb function recovery as measured by Patient-Specific Functional Scale score at envenomation plus 14 days. The greatest benefit of antivenom therapy was experienced from 1 to 2 weeks after treatment, and all patients experienced full recovery within 4 months. Robust additional assessments, determined a priori, supported the primary study outcome, and no new or major safety issues were identified compared with those discussed in the existing literature.[14,46]

Before the development of highly purified, ovine-derived FabAV, patients with nonlife-threatening copperhead envenomation were generally managed without antivenom because of the risks associated with equine antivenom therapy.[6] In addition to excluding copperhead patients, the registry trials leading to Food and Drug Administration approval of FabAV were comparatively small (42 total subjects) open-label studies designed to assess safety and short-term efficacy; limb recovery was not evaluated.[11,12]

Before the current study, to our knowledge the only investigations to prospectively assess limb recovery in crotaline snakebite were an open-label observational study[22] and a small clinical trial published only in abstract form.[47] In addition, 2 studies reported the time to return to full activities at work or school,[7,10] 1 study collected self-reported data about resolution of pain, swelling, and disability by telephone,[23] and 1 study reported limb outcomes in unstructured terms.[5] As expected from the heterogeneity of study design and outcomes assessed, estimates of duration of disability produced by these studies vary widely, and any important benefit from equine antivenom or FabAV was impossible to assess.

To our knowledge, this trial provides the only blinded prospective data on limb function recovery from crotaline snake envenomation and provides important data that can be used to inform risk-benefit discussions with patients about the effect of antivenom on their recovery from venom-induced limb injury. Although novel, these results are concordant with existing clinical trial evidence of FabAV efficacy in noncopperhead populations, using both short-term outcomes and venom effects aside from limb recovery.[11,12,48] The consistency of these findings and the

congruence of our additional outcome measures support the findings of our primary outcome.

Existing guidelines on the care and treatment of crotaline envenomation recommend treatment of mild envenomation if venom effects are progressing.[15,16] Progressive venom effects were not required for enrollment in this trial. Previous research has shown that this approach does not result in decreased antivenom administration.[19] Therefore, the strategy of delaying antivenom administration while watching for progression should be further evaluated.[17,19,48] This study also demonstrates that crude outcome measures, such as the need for surgical intervention, do not fully capture outcomes that are important to patients.[49]

In this study, patients treated with FabAV had lower pain scores and substantially less opioid use throughout recovery. Because prescribing opioid analgesia carries some risk of iatrogenic opioid abuse disorder and ED opioid prescriptions may contribute to the development of addiction, the role of FabAV in decreasing opioid requirements during recovery is intriguing.[50-54] Because these findings are exploratory, future research is necessary to determine the potential effect of FabAV treatment on long-term opioid use after envenomation.

In conclusion, administration of FabAV to patients with mild- and moderate-severity copperhead envenomation improves recovery of limb function at 14 days postenvenomation compared with placebo.

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Author contributions: CJG, KS, KK, SPB, SR, and EJL conceived the study and worked on the design. CJG, EQ, BL, SRR, SG, EAT, NPC, MEM, RS, DD, KS, and KK were principal investigators. CJG and EJL drafted the article. SR, VEA, and EJL provided biostatistical analysis and programming. MG provided study sponsor management and clinical supplies. All authors reviewed, commented on, and approved the final draft of the article. CJG takes responsibility for the paper as a whole.

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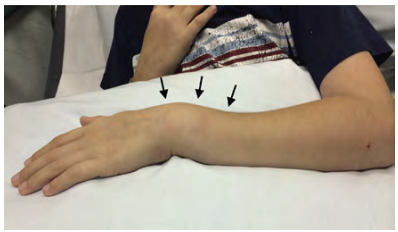

"Child With Dinner Fork Deformity" by Kardouni, February 2016, Volume 67, #2, pp. 165, 188.

Table E1. Patient-Specific Function Scale total score, at each point.

			PSFS Total Score*									
Subject ID†	Time from Env. to Treatment	Severity of Env.	Env. +3 Days	Env. +7 Days	Env. +10 Days	Env. +14 Days	Env. +17 Days	Env. +21 Days	Env. +24 Days	Env. +28 Days	Env. +2 Months	Env. +3 Months	Env. +4 Months
Treatment: FabAV													
001-002	6 h 48 min	Mild	4.33	8.33	8.67	10.00	10.00	10.00	10.00	10.00			
001-003	11 h 12 min	Mild	1.67	8.00	8.33	9.00	9.33	9.33	9.33	9.67	10.00		
001-004	24 h 36 min	Moderate	2.00	8.00	8.00	9.67	10.00	10.00	10.00	10.00			
001-005	7 h 53 min	Mild	2.00	6.67	4.00	7.00	8.67	8.67	10.00	10.00			
001-006	25 h 53 min	Moderate	0.67	3.67	3.67	3.67	3.00	3.67	6.67	8.00	10.00		
001-007	3 h 54 min	Mild	8.00	9.33	10.00	10.00	10.00	10.00	10.00	10.00			
001-009	4 h 4 min	Mild	1.33	2.00	6.00	5.67	7.33	7.67	8.33	9.00	10.00		
001-011	3 h 57 min	Mild	0.00	1.00	5.00	7.67	7.67	10.00	10.00	10.00			
002-001	5 h 20 min	Mild	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00			
002-002	5 h 35 min	Mild	4.33	5.33	8.00	9.33	9.33	10.00	10.00	10.00			
002-003	5 h 17 min	Mild	0.00	1.00	4.67	8.00	9.33	9.67	10.00	10.00			
002-005	5 h 26 min	Mild	4.67	6.00	5.33	6.33	8.00	9.00	8.67	10.00			
002-006	6 h 55 min	Mild	1.00	3.33	5.33	8.67	9.00	9.33	9.33	10.00			
002-007	6 h 6 min	Mild	5.33	8.33	9.33	9.33	9.33	9.33	9.33	10.00			
002-008	7 h 41 min	Mild	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00			
002-009	5 h 39 min	Mild	1.67	6.00	8.67	9.67	9.67	10.00	10.00	10.00			
002-012	20 h 22 min	Mild	4.00	5.00	5.33	5.33	8.00	8.00	9.33	9.33	10.00		
002-013	5 h 11 min	Mild	0.00	3.00	6.67	8.67	9.67	10.00	10.00	10.00			
002-014	4 h 35 min	Mild	3.00	6.33	6.00	6.67	7.33	9.67	9.67	9.67	10.00		
002-015	4 h 42 min	Mild	9.33	10.00	10.00	10.00	10.00	10.00	10.00	10.00			
003-001	3 h 34 min	Mild	0.67	2.33	10.00	10.00		10.00		10.00			
003-003	7 h 29 min	Mild	2.00	4.00	6.33	7.33	6.33	7.00	8.67	10.00			
003-007	8 h 26 min	Moderate	2.00	3.33	4.67	7.67	8.67	8.67	9.00	9.67	9.67	9.67	10.00
003-011	5 h 10 min	Mild	4.67	9.67	10.00	10.00	10.00	10.00	10.00	10.00			
003-013	4 h 16 min	Mild	1.67	4.00	7.00	9.00	10.00	10.00	10.00	10.00			
003-015	4 h 5 min	Mild	0.00	6.67	8.00	9.33	10.00	9.33	9.33	9.67	10.00		
003-016	7 h 5 min	Mild	5.00	6.00	8.33	8.33	8.33	9.00	9.33	10.00			
003-017	3 h 35 min	Mild	6.67	8.33	9.00	9.67	10.00	10.00	10.00	10.00			
003-018	3 h 34 min	Mild	2.00	3.00	4.67	8.67	8.33	9.67	9.67	10.00			
003-019	3 h 59 min	Mild	0.00	0.00	0.00	7.00		9.33	9.33	10.00			
003-021	5 h 38 min	Mild	0.33	1.67	2.67	5.67		9.33	8.67	9.00			
003-022	3 h 14 min	Mild	3.33	8.00	8.33	8.67	9.33	10.00	10.00	10.00			
003-024	3 h 52 min	Mild	9.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00			
003-027	6 h 17 min	Mild	0.00	2.33	6.33	7.33	8.33	9.00	10.00	10.00			
003-028	5 h 28 min	Mild	0.00	0.00	0.67	2.33	4.67	5.33	4.67	6.00	10.00		
003-029	4 h 4 min	Mild	0.33	4.00	4.00	5.33	6.00	9.00	9.33	9.33	10.00		
005-001	24 h 23 min	Moderate	0.00	4.67	9.33	10.00	10.00	10.00	10.00	10.00			
005-002	6 h 35 min	Mild	2.67	6.33	8.33	8.67	9.00	9.00	9.33	9.33	10.00		
006-001	3 h 26 min	Mild	2.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00			
006-002	3 h 5 min	Mild	7.33	10.00	10.00	10.00		10.00	10.00	10.00			
007-001	17 h 7 min	Mild	3.00	6.67	7.67	7.67	9.33	9.33		10.00			
007-004	15 h 20 min	Mild	2.33	5.67	8.33	9.00	9.67	10.00	10.00	10.00			
009-003	5 h 55 min	Moderate	2.33	6.67	4.33	7.33	4.33	7.33	7.67	6.00	9.00	10.00	
014-001	11 h 3 min	Mild	6.00	10.00		10.00							
014-002	5 h 20 min	Mild	5.33	9.00	9.00	10.00		10.00	10.00	10.00			

Table E1. Continued.

			PSFS Total Score*									
Subject ID†	**Time from Env. to Treatment**	**Severity of Env.**	**Env. +3 Days**	**Env. +7 Days**	**Env. +10 Days**	**Env. +14 Days**	**Env. +17 Days**	**Env. +21 Days**	**Env. +24 Days**	**Env. +28 Days**	**Env. +2 Months**	**Env. +3 Months**	**Env. +4 Months**
Treatment: Placebo													
001-001	6 h 25 min	Moderate	8.00	10.00	8.33	9.00	10.00	10.00		10.00			
001-008	11 h 44 min	Mild	6.33	8.67	8.33	8.33	9.00	9.33	10.00	10.00			
001-010	6 h 8 min	Mild	3.67	8.67	9.67	10.00	10.00	10.00	10.00	10.00			
001-012	16 h 40 min	Mild	0.00	9.33	9.67	9.67	10.00	10.00	10.00	10.00			
002-004	3 h 48 min	Mild	2.33	4.33	8.00	8.00	6.33	6.33	8.00	9.67			
002-010	6 h 18 min	Mild	0.00	0.00	3.00	3.00	4.00	8.33	9.33	9.67	10.00		
002-011	5 h 40 min	Mild	8.67	5.33	9.33	9.33	10.00	10.00	10.00	10.00			
002-016	3 h 49 min	Mild	1.33	7.00		10.00	10.00	10.00	10.00	10.00			
003-002	4 h 20 min	Mild	2.33	3.67	4.33	6.67	8.33	9.00	9.33	10.00			
003-005	4 h 13 min	Mild	0.00	0.00	2.67	4.67	6.00	7.00	7.67	9.00	10.00		
003-006	2 h 41 min	Mild	0.67	3.33	5.67	8.33	10.00	10.00	10.00	10.00			
003-008	3 h 36 min	Mild	1.00	2.00		2.00							
003-009	4 h 12 min	Mild	0.00	0.00	2.00	5.00	8.00	7.67	9.67	10.00			
003-012	3 h 22 min	Mild	3.67	10.00	10.00	10.00	10.00	10.00	10.00	10.00			
003-014	2 h 55 min	Mild	0.00	1.33	5.00	5.33	9.00	10.00	10.00	10.00			
003-020	6 h 46 min	Mild	0.00	3.00	5.67	8.33	9.00	9.33	9.33	9.67	10.00		
003-025	6 h 50 min	Mild	1.00	1.67	2.00	10.00	10.00	10.00	10.00	10.00			
003-026	4 h 21 min	Mild	0.00	0.00	0.00	1.00	4.00	4.33	5.33	6.00	10.00		
003-030	11 h 59 min	Mild	0.33	3.33	4.00	5.67	8.00	8.33	10.00	10.00			
005-003	6 h 21 min	Moderate	0.00	1.67	1.00	7.00	9.00	10.00	10.00	10.00			
007-002	19 h 2 min	Moderate	4.00	4.33	3.67	1.33	2.33	7.00	8.33	6.67	8.33	9.33	10.00
007-003	5 h 20 min	Mild	4.67	5.67	6.33	7.33	7.67	8.00	8.33	8.67	10.00		
008-001	5 h 45 min	Mild	0.00	1.00	5.67	9.67	10.00	10.00	10.00	10.00			
009-002	5 h 10 min	Mild	5.00	8.67	9.00	9.00	9.00	10.00	10.00	10.00			
020-001	3 h 40 min	Mild	3.33	10.00	10.00	10.00	10.00	10.00	10.00	10.00			
024-001	5 h 6 min	Mild	1.00	2.67	3.00	5.67	6.00	7.67	8.00	9.33	10.00		
024-002	3 h 17 min	Mild	4.00	5.67	9.67	10.00	10.00	10.00	10.00	10.00			
025-001	5 h 31 min	Mild	5.67	8.33	7.67	8.33	9.67	9.67	10.00	10.00			

mITT, Modified intention-to-treat population.

Time from env. to treatment=(date and time of first exposure to treatment–date and time of envenomation). PSFS total score=sum of activity scores divided by the number of activities reported. Each activity is rated on a scale of 0 to 10, where 0=unable to perform activity and 10=able to perform activity at the same level as before the injury or problem.

*A higher score indicates better recovery; best possible score is 10.

†The mITT population for the placebo group is composed of n=29 patients. However, one patient in the mITT patient population did not have any posttreatment observations and therefore does not appear in this table.

Table E2. Patients moved to open-label rescue therapy.

Age, Years/Sex	Treatment Group Assignment	Description
20/M	FabAV	Progressed to severe venom effect and moved to standard-of-care treatment per protocol. Received 6 vials of open-label FabAV, with good response.
20/F	FabAV	Developed recurrent local tissue venom effects after initial control. Received 2 vials of open-label FabAV at the discretion of the treating physician, with good response.
56/F	Placebo	Progressed to severe venom effect and moved to standard-of-care treatment per protocol. Received 4 vials of open-label FabAV with good response.
14/F	Placebo	Patient with a moderate envenomation and apparent good initial response to blinded study medication (placebo), but developed worsening local tissue venom effects (tenderness, ecchymosis, and edema) after the second maintenance dose of normal saline solution. She did not have coagulopathy, thrombocytopenia, hypotension, or other systemic venom effects. The investigator discontinued study medication and administered 6 vials of open-label FabAV as rescue therapy, with good response.

M, Male; *F*, female.

Table E3. Serious adverse events.

Age, Years/Sex	Treatment Group Assignment	Reason Event Was Serious	Description
71/M	FabAV	Life threatening	Patient with a mild envenomation developed a severe pulmonary embolism after receiving a full course of 18 vials of FabAV. The adverse event was considered not related to study treatment by the investigator because the patient was recovering from recent spinal surgery.
14/F	Placebo	Significant medical event, prolonged hospitalization	Patient with a moderate envenomation and apparent good initial response to blinded study medication (placebo), but developed worsening local tissue venom effects (tenderness, ecchymosis, and edema) after the second maintenance dose of normal saline solution. She did not have coagulopathy, thrombocytopenia, hypotension, or other systemic venom effects. The investigator discontinued study medication and administered 6 vials of open-label FabAV as rescue therapy, with good response.