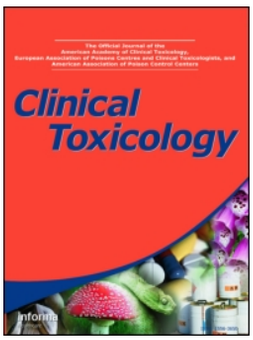

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: http://www.tandfonline.com/loi/ictx20

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To cite this article: Victoria E. Anderson, Charles J. Gerardo, Malin Rapp-Olsson, Sean P. Bush, Michael E. Mullins, Spencer Greene, Eric A. Toschlog, Eugenia Quackenbush, S. Rutherfoord Rose, Richard B. Schwartz, Nathan P. Charlton, Brandon Lewis, Kurt C. Kleinschmidt, Kapil Sharma & Eric J. Lavonas (2018): Early administration of Fab antivenom resulted in faster limb recovery in copperhead snake envenomation patients, Clinical Toxicology, DOI: 10.1080/15563650.2018.1491982

To link to this article: https://doi.org/10.1080/15563650.2018.1491982

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2018.1491982

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CLINICAL RESEARCH

Early administration of Fab antivenom resulted in faster limb recovery in copperhead snake envenomation patients

Victoria E. Anderson[a], Charles J. Gerardo[b], Malin Rapp-Olsson[a], Sean P. Bush[c], Michael E. Mullins[d], Spencer Greene[e], Eric A. Toschlog[f], Eugenia Quackenbush[g], S. Rutherfoord Rose[h], Richard B. Schwartz[i], Nathan P. Charlton[j], Brandon Lewis[k], Kurt C. Kleinschmidt[l], Kapil Sharma[l] and Eric J. Lavonas[m]

[a]Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, CO, USA; [b]Division of Emergency Medicine, Duke University School of Medicine, Durham, NC, USA; [c]Department of Emergency Medicine, Brody School of Medicine, Greenville, NC, USA; [d]Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO, USA; [e]Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, USA; [f]Department of Surgery, Brody School of Medicine, Greenville, NC, USA; [g]Department of Emergency Medicine, University of North Carolina, Chapel Hill, NC, USA; [h]Department of Emergency Medicine, Virginia Commonwealth University, Richmond, VA, USA; [i]Department of Emergency Medicine and Hospital Services, Medical College of Georgia, Augusta, GA, USA; [j]Department of Emergency Medicine, University of Virginia, Charlottesville, VA, USA; [k]Texas A&M Health Science Center, College Station, TX, USA; [l]Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; [m]Department of Emergency Medicine and Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, CO, USA

ABSTRACT

Background: No previous research has studied whether early snake antivenom administration leads to better clinical outcomes than late antivenom administration in North American pit viper envenomation.

Methods: A secondary analysis of data from a clinical trial of Fab antivenom (FabAV) versus placebo for copperhead snake envenomation was conducted. Patients treated before the median time to FabAV administration were classified as receiving early treatment and those treated after the median time were defined as the late treatment group. A Cox proportional hazards model was used to compare time to full recovery on the Patient-Specific Functional Scale (PSFS) instrument between groups. Secondary analyses compared estimated mean PSFS scores using a generalized linear model and the estimated proportion of patients with full recovery at each time point using logistic regression. To evaluate for confounding, the main analysis was repeated using data from placebo-treated subjects.

Results: Forty-five subjects were treated with FabAV at a median of 5.47 h after envenomation. Patients in the early treatment group had a significantly shorter time to full recovery than those treated late (median time: 17 versus 28 days, $p = .025$). Model-estimated PSFS scores were numerically higher at each time point in the early group. No difference was found between patients treated early versus late with placebo.

Conclusions: In this secondary analysis of trial data, recovery of limb function was faster when Fab antivenom was administered soon after envenomation, as opposed to late administration.

ARTICLE HISTORY
Received 11 March 2018
Revised 12 June 2018
Accepted 13 June 2018

KEYWORDS
Agkistrodon; snake bites; recovery of function; antivenins

Introduction

Antivenom has been used to treat snake envenomation in the United States since the 1960s [1]. The effectiveness of antivenom therapy to reduce or eliminate the acute effects of snake venom, such as tissue inflammation and necrosis, hypotension, defibrinogenation, thrombocytopenia, and neurotoxicity has long been established [2–7]. More recently, a placebo-controlled clinical trial demonstrated that antivenom administration improves recovery from venom-induced limb injury in copperhead snake (*Agkistrodon contortrix*) envenomation 14 days after envenomation [8].

Although standard treatment recommendations call for administration of antivenom as soon as possible after envenomation, the question of whether early antivenom administration is more effective than late administration has not previously been studied. This question is important because some authors, citing cost and/or risk of hypersensitivity reactions, recommend a "wait and see" approach with close observation for progression of the envenomation syndrome in clinically stable patients who have mild or moderate acute venom effects [9–13].

The only antivenom currently approved by the US Food and Drug Administration (FDA) and marketed for the

CONTACT Victoria Anderson victoria.anderson@rmpdc.org Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, CO, USA

Supplemental data for this article can be accessed here.

A subset of these data was presented as a platform at the 2017 Annual Meeting of the North American Congress of Clinical Toxicology, Vancouver, British Columbia, on October 13, 2017. The abstract publication was: Anderson VE, Rapp-Olsson M, King T, Gerardo CJ, Lavonas EJ. Early FabAV treatment improves time to full limb function recovery in patients with copperhead envenomation. *Clin Toxicol* 2017; 55(7):692.

treatment of envenomation by crotaline snakes (rattlesnakes, cottonmouth/water moccasins, and copperhead snakes) is a Fab antivenom (FabAV) produced in sheep (Crotalidae polyvalent immune Fab (ovine origin), CroFab®, BTG International, West Conshohocken, PA; hereafter, FabAV). We conducted a multi-center, randomized, placebo-controlled clinical trial of FabAV to determine whether administration of FabAV leads to improved recovery from venom-induced limb injury, compared with placebo [8]. Patients were eligible if they enrolled within 24 h of envenomation by a copperhead snake. The time the snakebite occurred and the time the first dose of study drug (FabAV or placebo) were recorded in all cases. The trial protocol included assessments of limb function until full recovery or 28 days, whichever was longer. The purpose of this study is to determine whether patients who received FabAV prior to the median time to treatment resulted in shortened recovery compared to later FabAV administration in this trial.

Methods

Study design

A secondary analysis of the multi-center, Phase IV, randomized, double blind, placebo controlled trial of FabAV in copperhead envenomation was performed (NCT01864200). The methods of this trial, including participant selection, randomization, treatment, and the full study protocol, have been previously published [8]. Briefly, patients aged 12 years or older with copperhead envenomation to the forearm, hand, lower leg, or foot were randomized to receive FabAV or saline placebo. Clinical severity was assessed and recorded at the time of randomization. Mild envenomation was defined as swelling crossing zero to one major joint (wrist, elbow, ankle, or knee) and moderate envenomation as swelling crossing two major joints. Progression of venom effects was not required for study eligibility. Patients with severe envenomation, envenomations proximal to the elbow or knee or on more than one extremity, and those presenting more than 24 h post-envenomation were excluded. The trial was approved by the Western Institutional Review Board and the institutional review board at each study site. All participants provided informed consent. The trial and this secondary analysis was funded by BTG International.

Study protocol

Patients received six vials of FabAV (or placebo) in 250 mL of normal saline solution as initial treatment. Patients failing to achieve initial control after the initial dose were given a repeat dose of six vials. All patients were then treated with two vials of FabAV or placebo at 6, 12, and 18 h after initial control in accordance with the current FDA approved dosing instructions. Open-label rescue therapy was permitted if the patient progressed to severe envenomation or at the discretion of the treating physician.

Measures

The primary outcome measure for the trial and this secondary analysis was the Patient Specific Functional Scale (PSFS), a widely utilized patient-oriented outcome assessment instrument [14–16]. The reliability and overall validity of this instrument are well-established and our group has validated its use in the setting of snake envenomation [17]. This tool first asks patients to identify three important activities that they are unable to do or are having difficulty doing as a result of their snakebite. At each post-envenomation time point, patients rate their ability to perform each activity 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 score from all three activities is calculated, with larger values indicating more complete recovery of limb function and a mean score of 10 indicating full recovery. The PSFS was administered 3, 7, 10, 14, 17, 21, 24, and 28 days post-envenomation. The PSFS could not be administered on Day 0 post-envenomation as the patients were receiving care for acute envenomation and were unable to assess their ability to perform the chosen activities. Patients who had not achieved full recovery by Day 28 were followed monthly for up to 4 months total.

Data analysis

All statistical tests were applied to the FabAV arm of the modified intent-to-treat population. Time to treatment was defined as the time from envenomation to the time of first FabAV dose. In all statistical models, the time to treatment was considered a categorical variable with two levels differentiated at the median time to treatment. The cutoff for the early and late treatment categories was chosen *a priori* to be the median time to treatment in the FabAV group in order to maximize the statistical power of our existing data.

A Cox proportional hazards model was used to assess the difference in time to full recovery by time to treatment group. Time to full recovery was defined as the time from first treatment to the first day the patient achieved a mean PSFS of 10. Differences between time to treatment groups were summarized using Kaplan Meier curves.

Mean estimated PSFS scores were analyzed over time using a repeated measures generalized linear model (GLM) with robust standard error estimates. The model included fixed effects for sex, repeat initial FabAV dosing, time to treatment category, visit day, and the interaction between time to treatment category and visit day. A random subject effect was included to account for within-subject correlation. Severity of envenomation at the time of randomization, anatomic location of envenomation (upper versus lower extremity), age (adult versus adolescent), and repeat initial FabAV dosing were found to be non-significant and were removed from the model and the model was refit. Results are presented as least squares means with 95% confidence intervals.

The difference in full recovery between time to treatment groups was analyzed over time using a repeated measures logistic regression model with fixed effects for time to

treatment group, visit day, and a random subject effect. Results are presented as least squares means representing the probability of recovery at each time point.

Sensitivity analyses

Because our study had an imbalance in the number of patients with moderate severity envenomation at time of enrollment between time to treatment groups, the regression analyses were repeated with the moderate severity subjects excluded.

Analysis of patients randomized to receive placebo

It is possible that the early and late treatment groups differed systematically in ways other than effect of treatment. In order to look for this type of confounding, we repeated the Cox proportional hazards model using data from subjects randomized to receive placebo in the clinical trial.

Results

Demographics and baseline characteristics

Forty-five patients were treated with FabAV in the clinical trial. The median time to treatment was 5.47 h (range 3.08, 25.88). Twenty-two patients (49%) who were treated less than 5.47 h post-envenomation were defined as receiving early treatment and the late treatment group comprised 23 patients who were treated 5.47 or more hours post-envenomation (Figure 1). The baseline and clinical characteristics were well balanced between groups with the exception of the five patients with moderate envenomation at the time of enrollment, all of whom were treated late (Table 1).

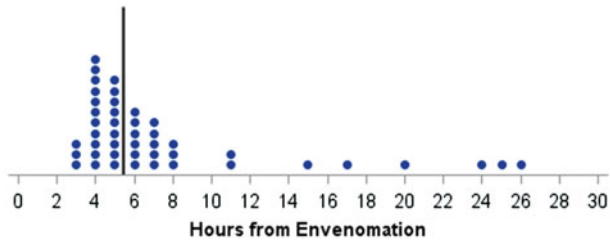

Figure 1. Distribution of Times to Treatment. Vertical line indicates median time to treatment of 5.47 h. Data to the left of the line represent the early time to treatment group ($N = 22$) and data to the right represent the late treatment group ($N = 23$).

Table 1. Subject demographics and baseline clinical characteristics.

Demographics	Early ($N = 22$)	Late ($N = 23$)
Age, years		
Mean (SD)	41.2 (15.73)	46.5 (19.84)
Range	12–69	14–86
Sex, No. (%)		
Male	12 (54.5)	11 (47.8)
Race, No. (%)		
White	19 (86.4)	21 (91.3)
Black	1 (4.5)	1 (4.3)
Asian	1 (4.5)	0 (0)
Other	1 (4.5)	1 (4.3)
Ethnicity, No. (%)		
Hispanic or Latino	2 (9.1)	1 (4.3)
Not Hispanic or Latino	20 (90.9)	22 (95.7)
Envenomation location, No. (%)		
Upper extremity	7 (31.8)	9 (39.1)
Lower extremity	15 (68.2)	14 (60.9)
Pretreatment Envenomation Severity, No. (%)		
Mild	22 (100)	18 (78.3)
Moderate	0 (0)	5 (21.7)
Baseline Pain Score		
Mean (SD)	5.5 (3.16)	5.6 (2.89)
Range	1–10	0–10

Primary outcome

Patients in the early treatment group had a significantly shorter time to full recovery than those treated late (median time: 17 versus 28 days, $p = .025$; Figure 2). A greater proportion of subjects treated early had recovered at each time point compared with those treated late (Table 2). All subjects in both groups recovered by the end of the 4-month trial with the exception of one subject who was lost to follow-up.

Secondary outcomes

Using a repeated measures GLM, the model estimated least squares mean PSFS scores were numerically higher in the early treatment group at all time points compared to the late treatment group (Table 3). These differences were statistically significant at 21, 24, and 28 days post-envenomation (Table 3).

The model estimated probability of achieving full recovery by time to treatment group at each time point was compared using repeated measures logistic regression (Table 4). Those in the early treatment group had a greater probability of being fully recovered at each time point, with statistically greater probabilities of reaching full recovery noted at 10 and 17 days.

Sensitivity analyses

Repeating the analysis of PSFS scores over time to include only the 40 patients with mild envenomation did not change the pattern of results. The model estimated PSFS scores over time in the early time to treatment group remained higher than those in the late treatment group at each day post-envenomation, and the estimated probability of recovery at each time point when excluding patients with moderate envenomation continued to consistently favor the early time to treatment group (Supplementary Tables S1 and S2).

Additionally, results of unadjusted analyses were not different.

Results from placebo subjects

No significant difference in time to recovery was found between subjects who received placebo early (5.47 h or less) or late in the clinical trial ($p = 0.45$; Supplementary Figure 1).

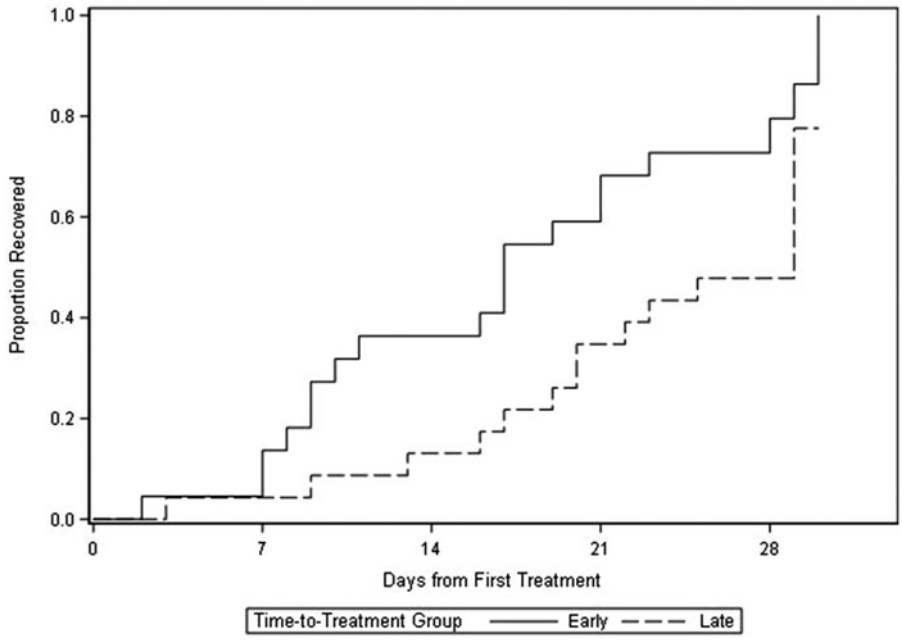

Figure 2. Proportion of patients with mild or moderate copperhead envenomation fully recovered at each assessment. Overall *p*-value for difference, $p = .025$.

Table 2. Proportion of patients with mild or moderate copperhead envenomation fully recovered at each assessment.

Day post-envenomation	Early antivenom treatment (%)	Late antivenom treatment (%)	Odds ratio (95% CI)
3	4.5	4.3	1.05 (0.06, 18.03)
7	22.7	8.7	3.09 (0.53, 18.06)
10	36.4	8.7	6.00 (1.10, 32.73)
14	40.9	17.4	3.29 (0.83, 13.04)
17	54.5	21.7	4.32 (1.17, 15.90)
21	68.2	34.8	4.02 (1.16, 13.97)
24	72.7	43.5	3.47 (0.99, 12.14)
28	86.4	65.2	3.38 (0.76, 15.06)

Table 3. Mean score on the patient-specific functional scale, patients with mild or moderate copperhead envenomation; repeated measures generalized linear model estimates.

Days post-envenomation	Early antivenom treatment	Late antivenom treatment	Odds ratio (95% CI)
3	3.56	2.75	1.45 (0.70, 3.01)
7	6.14	5.71	1.19 (0.56, 2.52)
10	7.55	6.84	1.42 (0.66, 3.04)
14	8.78	8.01	1.76 (0.79, 3.91)
17	9.16	8.40	2.03 (0.84, 4.91)
21	9.76	8.84	4.58 (1.62, 12.92)
24	9.79	9.20	3.44 (1.25, 9.46)
28	9.93	9.46	5.26 (1.35, 20.48)

The range of possible scores on the PSFS is (0, 10), with 10 indicating full recovery [14,15]. $N = 45$.

Table 4. Probability that a patient with mild or moderate copperhead envenomation will reach full recovery on specific dates after envenomation, repeated measures logistic regression model estimates.

Days post-envenomation	Early antivenom treatment	Late antivenom treatment	Odds ratio (95% CI)
3	0.05	0.04	1.10 (0.07, 18.31)
7	0.23	0.09	3.19 (0.54, 18.72)
10	0.37	0.07	7.51 (1.34, 42.19)
14	0.42	0.16	3.67 (0.90, 14.89)
17	0.54	0.20	4.83 (1.19, 19.72)
21	0.62	0.33	3.36 (0.97, 11.59)
24	0.67	0.44	2.48 (0.74, 8.36)
28	0.81	0.66	2.17 (0.55, 8.61)

Discussion

The results of this study may have important implications in the management of crotaline snake envenomation that is not life-threatening. While no reasonable practitioner would withhold antivenom from a patient experiencing life-threatening venom effects, the question of whether one can reasonably adopt a "wait and see" approach to the management of mild to moderate severity crotaline snake envenomation is longstanding. In an effort to avoid antivenom use, current recommendations suggest watching for progression [10]. It is unclear if this recommendation and potential delay in treatment results in any harm. Although the clinical trial on which this study was based was not designed to study early versus late administration of FabAV, the dataset is well-suited to this purpose. The results of this study suggest that early treatment leads to better clinical outcomes within the first 28 days after envenomation, but all patients eventually recovered at 4 months.

These findings are concordant with existing data from envenomations by other pit viper species outside of the US [18–25]. Prior studies showed a consistent association between time to treatment and severity of outcome. However, these studies primarily evaluated systemic symptoms in South American pit viper species, which tend to have more severe envenomation syndromes. In milder envenomation syndromes, such as those typical of copperhead snakes, the value of early administration of FabAV on limb recovery had not been evaluated. This analysis provides additional evidence that early administration of antivenom may provide clinical benefit in patients with mild envenomation.

Although our study had an imbalance in the number of patients with moderate envenomation between time to treatment groups, sensitivity analyses that included only patients with mild envenomation showed a similar time to treatment effect as the full analyses. These data further support the main study results that the effect driving recovery in this population is time to treatment. In a prior study of copperhead envenomation, most patients who presented with mild envenomation progressed to moderate severity [12]. Therefore, it is likely that treatment delay led to both the worsened initial severity in some subjects and to delay in full recovery overall. The dataset in this study is insufficient to test this hypothesis, which, if true, only supports the conclusion that early FabAV therapy leads to improved outcomes.

Based on these data, practitioners should offer FabAV to symptomatic copperhead envenomated patients who present within the first 24 h, including those with and without signs of progressing tissue injury. As all patients eventually recovered, a patient-centered discussion of benefits, risks, costs, and alternative therapies is appropriate.

Limitations

This is a secondary analysis of prospectively collected data. Although we were careful to design and execute our statistical analyses only once and performed sensitivity analyses to test critical statistical assumptions, the usual limitations of secondary analyses apply. Additionally, our study population consisted of patients with copperhead envenomation only who presented for treatment within 24 h of envenomation. We do not know if there is a similar time to treatment effect in patients with other North American pit viper envenomation or in patients presenting greater than 24 h post-envenomation. However, it is reasonable to assume that early treatment is even more important in more severe pit viper envenomation syndromes. To our knowledge, no study has assigned an economic value to earlier recovery, making a pharmacoeconomic analysis impossible. Finally, our study involved a small sample size of only 45 patients who received FabAV.

Conclusions

In this secondary analysis of a clinical trial of mild and moderate copperhead envenomation, recovery of limb function as measured with the PSFS was faster when FabAV was administered less than 5.5 h post-envenomation, as opposed to greater than 5.5 h post-envenomation.

Disclosure statement

SG and SRR have received funding personally from BTG International Inc. for consulting. All authors report grant money to their respective institutions to conduct research conceived and sponsored by BTG International Inc. VEA, MRO, and EJL's institution, Denver Health, has received grant funding from BTG International Inc. for industry-initiated research, investigator-initiated research, as well as consulting fees and for writing part of this manuscript. BTG International, Inc. did not contribute to the design or execution of this analysis.

Funding

BTG International Inc. funded this work.

ORCID

Michael E. Mullins http://orcid.org/0000-0001-8605-0217

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