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Predictors of FabAV use in copperhead envenomation

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ABSTRACT

Context: Crotaline snake envenomation is a serious medical condition affecting thousands of Americans each year. Variation in the treatment of Crotaline snakebites exists among physicians in the United States. Management of copperhead snakebites is controversial with some experts advocating minimal intervention, rarely necessitating antivenom use and, even more rarely, surgical intervention. This study assessed the use of Crotaline Polyvalent Immune Fab antivenom (Ovine) (FabAV) and explored factors influencing the decision to prescribe antivenom for copperhead envenomation in patients in Northeastern Oklahoma.

Methods: A retrospective cohort study examining electronic medical records of patients with copperhead snakebites from July 1, 2014 to August 31, 2019. Data collected included: patient demographics, transfer information, snake species, bite site, progression of local tissue effects, additional clinical and lab results, patient comorbidities, and treatment strategy. Associations between patient variables and treatment were evaluated using the chi-square test of independence, median test, and logistic regression analysis. Associations were statistically significant if $p < 0.05$.

Discussion: Of the 130 patients bitten by a copperhead, a majority (75%) received FabAV. Symptoms of copperhead envenomation were mostly limited to the progression of tissue damage. Predictors of treatment with FabAV included progression of venom effects across major joints, younger age, comorbidities, and upper extremity bites.

Conclusions: Patients who have multiple comorbidities, upper extremity bites and progression of venom effects across major joints are more likely to be treated with FabAV. The high usage of FabAV at the study site underscores the need for continued work to optimize the use of antivenom for copperhead envenomations.

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Introduction

The subfamily *Crotalinae* (pit viper) is within the family *Viperidae*, the largest family of venomous snakes in North America, and includes rattlesnakes, cottonmouths, and copperheads [1]. Crotaline envenomation is a serious medical condition that affects more than five-thousand Americans each year, 45–52% of which are by copperhead snakes (*Agkistrodon contortrix*) [2–4]. In the United States, snakebite incidence remains highest in the southern states, especially in Arkansas, Georgia, Louisiana, Mississippi, North Carolina, Oklahoma, and Texas [2,5]. Venomous snakebite treatment has evolved over the last century. Treatment advancements and the modern use of antivenom have decreased the death rate of crotaline envenomation by over 90% [6,7].

In October 2000, the FDA approved the use of ovine-derived Crotalidae polyvalent immune Fab anti-venom [8]. Initially, copperhead snakebites were excluded from FabAV clinical trials for several reasons including lack of copperhead bites at the study sites, FabAV cost, less severe or self-limited envenomation, along with concerns for drug toxicity [7,9–19]. FabAV's safety was later established in copperhead envenomation; however, its use is not entirely benign. Approximately 5% of patients experience an adverse event related to FabAV dosing including skin reaction (pruritic rash, urticaria, angioedema), gastrointestinal and respiratory symptoms, and/or hypotension [20–24]. Some randomized controlled trials of FabAV use in copperhead victims have shown benefit to its use, specifically lower pain scores, reduced limb disability and faster limb recovery with early administration [22,24–27]. These factors have led to conflicting practices regarding the administration of FabAV in copperhead envenomation [7,14,15,28]. The current unified treatment guideline for Crotaline envenomation in the United States attempts to reduce variation in care through evidence-informed guidelines but does not offer guidelines based specifically on identified snake species [29].

Treatment indications for FabAV administration in crotaline envenomation include progressive local tissue findings or systemic toxicity [29–31]. While snake genus alone should not be used to determine the likelihood of severe envenomation, the current treatment guidelines for the management

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of crotaline snake envenomation in the US may be too liberal for copperhead snakebites [7,13–15,18]. This study was an exploratory analysis of factors influencing the decision to prescribe antivenom for copperhead envenomations.

Materials and methods

The Institutional Research Ethics Board of Saint Francis Health System (Tulsa, Oklahoma) reviewed and approved this study along with a waiver of consent. In this retrospective cohort study of electronic medical records (EMR), we collected data from patients diagnosed with venomous snakebites from July 1, 2014 to August 31, 2019 *via* the methodology described below.

Sample selection

For the first round of data extraction, we defined a venomous snakebite as any hospital encounter assigned with one or more of the International Classification of Disease, Ninth & Tenth (ICD-9/ICD-10) diagnosis codes in Table 1. We used a combination of ICD-9 and ICD-10 diagnosis codes due to a mandated nationwide use of ICD-10 for all inpatient medical coding after October 1, 2015. An initial list of patients diagnosed with one or more of these ICD codes during the study period was requested from Medical Informatics. We further reviewed the EMR for each patient on the list to confirm they met the required inclusion criteria. We cross-referenced pharmacy distribution reports of FabAV administration during the study time period to determine if any patients were missed during the initial data pull. Based on our review, the second round of data was extracted with an expanded ICD-10 list (Table 1). We excluded encounters if: (1) the case was self-identified by the patient as a bite from a non-copperhead or unknown snake species, (2) the patient was observed (no FabAV treatment in-hospital) but received therapeutic or sub-therapeutic FabAV prior to arrival (due to a lack of clear information available to retrospective chart review including symptoms, comorbidity, laboratory values, and other findings that may have informed the decision to provide FabAV), or (3) the encounter was determined to be a duplicate or follow-up for a prior snakebite. We included patients in the observation/control group if they did not receive FabAV either prior to arrival (PTA) or in-hospital. We defined a therapeutic treatment as receiving at least four vials of FabAV. These definitions approximate manufacturer recommendations which are to provide a minimum of four vials within six hours of envenomation [8,10,29,32,33].

Snake identification

Identification of snake species relied upon patient or bystander reports. There was no consistency among encounters in describing the method of identification – we, therefore, did not include snake identification in our retrospective analysis. Methods of identification included sharing photographs with providers, providing a sample snake cadaver, or providing a description of the snake.

Data extracted and coded

Variables we collected from the EMR are listed in Table 1. We used pharmacy distribution reports of FabAV administration to determine the number of vials administered. Using the data collected, we gave progressive local tissue effects a threshold of crossing a major joint (wrist, elbow, shoulder, ankle, or knee) and quantified 0 = none, 1 = one, 2 = two, 3 = three corresponding to the number of joints crossed [29]. We measured systemic signs attributable to snake envenomation by vital signs (blood pressure, heart rate and pulse oximetry) and systemic symptoms on initial presentation. We considered a patient to have cardiovascular symptoms if on initial presentation there was evidence of hemodynamic compromise indicated by: systolic blood pressure (SBP) $<$ 90 mmHg; diastolic blood pressure (DBP) $<$ 50 mmHg; and/or heart rate (HR) $>$ 130 bpm [10,15]. We designated other systemic manifestations of envenomation by which the organ system was affected (Table 1) [15]. We defined hemotoxicity attributable to snake envenomation in binary fashion as any deviation in serum laboratory values including PT/INR $>$ 1.5, aPTT $>$ 40 s, platelet count $<$150,000/mm^3, and/or fibrinogen level $<$ 200 mg/dL [14,15]. Additionally, we categorized patient comorbidity by organ system including cardiovascular, hematology/oncology, psychiatric/abuse, pulmonary, and others (Table 1). Disease processes in the "Other" category included renal, gastrointestinal, neurologic, endocrine, and prior snake envenomation [34].

Statistical analysis

After calculating descriptive statistics for study variables, we evaluated associations between patient variables and hospital FabAV treatment (yes/no) using the chi-square test of independence, Fisher exact probability test, median test, and logistic regression analysis in SPSS (Version 27). For all statistical tests, the significance level was $p < 0.05$.

Results

Among the 130 patients bitten by a copperhead, 58% were male, 82% were white, and 95% were non-Hispanic. The average age was 31.8 ± 21.6 years, ranging from one to 81 years. Of these patients, 30% had psychiatric/abuse and 27% had cardiovascular comorbidities. The majority of patients ($n = 76$, 59%) were transferred to St. Francis Hospital from an outlying healthcare facility.

FabAV treatment

The majority of patients received therapeutic doses of FabAV ($n = 98$, 75%, Table 2). For these 98 patients, the median vial number was 10 (IQR: 6–14 vials), ranging from four to 24 vials. Of these patients, nine received therapeutic doses of FabAV PTA with a median dose of 4 vials (IQR: 4–7 vials), ranging from four to 18 vials (Table 2). Five patients also received FabAV PTA, but doses were subtherapeutic, with a median dose of two vials (ranging from one to three vials).

Table 1. Data was collected from the EMR and pharmacy reports.

Variable	Description
ICD-9/10 Code Data Pull 1	Primary diagnosis Snake envenomation 989.5, E905.0/T63.001A Venomous snakebite 989.5, E905.0/T63.004A Rattlesnake bite 989.5, E905.0/T63.011A Rattlesnake bite initial encounter 989.5, E980.9/T63.014A
ICD-10 Code Data Pull 2	T63.[002]A–[003]A, 012–013, 061–064, 091–094, 121–124, 191–194
Date/Time of Admission	
Date/Time of Discharge	
Transfer information	Transferred from another healthcare facility
Age	Years
Gender	
Race	
Ethnicity	
Insurance type	
Snake identification	Copperhead
Bite site	
Progression of local tissue effects	
Initial vital signs	Pulse, blood pressure and oxygen saturation
Laboratory studies	Platelets, INR, PTT, Fibrinogen, CK, D-dimer
Systemic symptoms	Cardiopulmonary Gastrointestinal Musculoskeletal Neurological
Comorbidities	Cardiovascular Hematology/Oncology Other Psychiatric/Abuse Pulmonary
Provider treatment	Observation Antivenom administration or discontinuation
FabAV *vial*s administered	Number of *vial*s administered to a patient prior to arrival and post-admission

Table 2. No. Patients by FabAV treatment category.

Category	No. Patients
Excluded	
PTA FabAV (none In-hospital)	8
Sub-therapeutic PTA FabAV (none In-hospital)	1
Treatment with Anavip	1
Control	
Observation (no FabAV)	32
Treatment	
In-hospital FabAV (none PTA)	84
In-hospital FabAV & PTA	9
In-hospital FabAV & Sub-therapeutic PTA	5
Total (Control + Treatment)	130

Table 3. Association of parameters with observation or FabAV treatment for 130 patients hospitalized for copperhead snake bite.

Variables	Observation ($n = 32$) [*n* (%)]	FabAV ($n = 98$) [*n* (%)]	χ^2 (*df*)
Sex			
Male	16 (21.3)	59 (78.7)	
Female	16 (29.1)	39 (70.9)	1.03 (1)
Race			
Non-white	8 (34.8)	15 (65.2)	
White	24 (22.4)	83 (77.6)	1.56 (1)
Ethnicity			
Non-Hispanic	30 (24.2)	94 (75.8)	
Hispanic	2 (33.3)	4 (66.7)	0.61[1]
Transfer			
No	19 (35.2)	35 (64.8)	
Yes	13 (17.1)	63 (82.9)	5.56 (1)*
Envenomation site			
Toe/Foot/Ankle	27 (31.0)	60 (69.0)	
Finger/Hand	2 (5.6)	34 (94.4)	9.17 (1)**
Progression			
No	18 (56.3)	14 (43.8)	
Yes	14 (14.3)	84 (85.7)	22.89 (1)***
Systemic symptoms			
No	25 (27.5)	66 (72.5)	
Yes	7 (17.9)	32 (82.1)	1.33 (1)
Hemotoxicity			
No	29 (25.0)	87 (75.0)	
Yes	3 (21.4)	11 (78.6)	0.09 (1)
Comorbidities			
No	17 (29.3)	41 (70.7)	
Yes	15 (20.8)	57 (79.2)	1.24 (1)

Bivariate analysis of variables associated with FabAV treatment

Transferring into the hospital from an outlying facility was associated with an increased likelihood of FabAV treatment (Table 3). Eighty-three percent of patients who transferred in received FabAV while 65% of patients who presented directly received FabAV, $\chi^2(1)=5.56$, $p = 0.018$ (Table 3). Other variables associated with the increased likelihood of FabAV treatment were envenomation site in the finger/hand and progression of venom effects across major joints. Regarding the former, the most common sites of envenomation included the toe, ankle, and foot ($n = 87$, 67%) or finger and hand ($n = 36$, 28%, Tables 3,4). Patients with upper extremity bites were more likely to receive in-house FabAV (94%) compared to patients with lower extremity bites (69%), $\chi^2(1)=9.17$, $p = 0.002$. Progression of venom effects ranged from none ($n = 32$, 25%), to passing one ($n = 81$, 62%), two ($n = 14$, 11%), or three ($n = 3$, 2%) major joints (Table 4). Additionally, progression across major joints was associated with FabAV treatment with 84 patients with progression (86%) compared to 14 patients (44%) without progression receiving FabAV, $\chi^2(1)=22.89$, $p < 0.001$ (Figure 1, Table 3).

Multivariate analysis with binary logistic regression

In a multivariate model of FabAV treatment (yes/no), upper extremity envenomation site and increased progression of venom effects remained significantly associated with FabAV treatment, while transfer status did not. Holding all other variables constant, finger/hand envenomation (aOR = 10.19, 95% CI 1.75–59.41) progression of venom effects (aOR = 9.87, 95% CI 3.12–31.17), and increased comorbidities (aOR = 2.69, 95% CI 1.32–5.47) were all predictive of FabAV treatment (Tables 5 and 6). However, increased age was associated with a higher likelihood of observation (no FabAV), (95% CI 0.92–0.99).

Altogether 14 patients (11%) had hemotoxicity (Table 7). For patients 65 years and older ($n = 11$), two had hemotoxicity. Of 54 patients (aged 0 to 18 years), six (11%) developed hemotoxicity. Six of 65 patients aged 19–64 years had hemotoxicity.

Discussion

According to the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) from 1989 to 2019, copperheads were responsible for 45–52% of bites annually [3,4]. The North American Snakebite Registry (NASBR), a multi-center database of detailed, prospectively collected information regarding snake envenomation in the United States, does not include Oklahoma, despite ranking the second most prevalent state for venomous snakebites in childhood as reported by US Poison Control Centers [32,35,36]. We were unable to locate prior studies detailing information regarding copperhead snake envenomation and treatment in Oklahoma.

Using AAPCC data, Seifert et al. reported that 26% of copperhead envenomation were treated with antivenom from 2001 to 2005 [17]. In our study, the percentage of patients receiving FabAV was 75%, which is close to three times that found by Seifert et al. While our study found significantly higher usage of FabAV for copperhead envenomations, it is also important to note that the study from Seifert et al. took place during the early years of FabAV use [15]. During this time FabAV was mainly used for rattlesnake

Table 4. Bite site of patients presenting for copperhead envenomation.

Site	No. Patients	Observation	FabAV
Toe	19	3	16
Heel	2	1	1
Ankle	21	9	12
Foot	47	15	32
Lower leg	3	1	2
Finger	27	1	26
Hand	9	1	8
Wrist	1	0	1
Upper arm	1	1	0
Total	130	32	98

Table 5. Binary logistic regression predicting the likelihood of FabAV treatment.

Variable	Unstandardized Coefficient	Adjusted Odds ratio	95% Confidence Interval
Sex			
Male	0.33 (0.57)	1.39	0.46, 4.23
Race			
White	1.14 (0.73)	3.11	0.75, 12.98
Transfer Status			
Outlying Facility	0.75 (0.57)	2.11	0.69, 6.46
Age	−0.05 (0.02)	0.96	0.92, 0.99
Progression	2.29 (0.59)	9.87	3.12, 31.17
Hemotoxicity			
Yes (hemotoxic)	0.61 (0.88)	1.84	0.33, 10.28
Systemic symptoms	0.61 (0.54)	1.83	0.63, 5.29
Comorbidities	0.99 (0.36)	2.69	1.32, 5.47
Site			
Finger/Hand	2.32 (0.90)	10.19	1.75, 59.41
Constant	−2.04 (0.97)	0.13	

Notes: $n = 130$. Pseudo $R^2 = 0.49$. Numbers in parentheses are standard errors. Independent variables sex, race, transfer status, hemotoxicity, and site were binary coded.

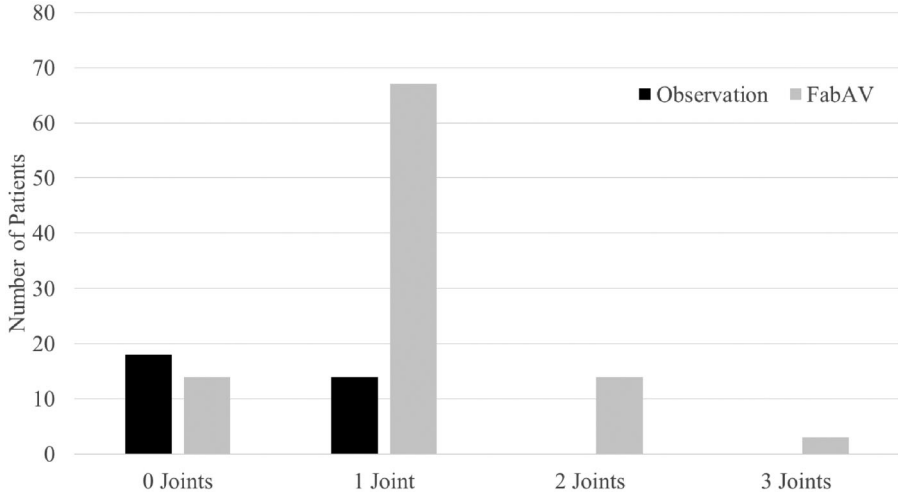

Figure 1. The number of patients without and with the progression of venom effects across major joints according to treatment (observation and FabAV administration).

Table 6. Comorbidities by organ system.

Comorbidities	No. Patients	Observation	FabAV
Cardiovascular	35	9	26
Hematology/Oncology	10	1	9
Psychiatric/Abuse	40	8	32
Pulmonary	17	2	15
Other	23	3	20

Table 7. Laboratory profile of patients with hemotoxicity.

Category	No. Patients	Values	Normal values	Units
Low platelet count	4	7	>150	k/cubic cm
		53		
		136		
		146		
Decreased fibrinogen	7*	181	>200	mg/dL
		184		
		189		
		189		
		190		
		193		
		195		
INR	1	1.55	<1.5	–
PTT	3*	40.5	<40	Seconds
		44.4		
		47.4		

*One patient has both elevated PTT and decreased fibrinogen.

envenomation. We believe these differences likely highlight both the variability of treatment strategies among experts as well as the steady expansion of treatment to include copperhead envenomations, although further research is needed to confirm this. Our results also suggest the potential treatment of patients who might not meet specific treatment criteria. Further research is needed to compare hospital systems across different geographic areas to determine if and why rates of treatment may differ with national averages.

More than half of our patients were transferred from an outlying healthcare facility likely reflecting limited FabAV availability from transferring facilities or lack of familiarity with current clinical guidelines. Five patients received sub-therapeutic FabAV prior to arrival to the hospital including one patient who received one vial. Given these findings, we believe that facilities with adequate FabAV supply and expertise on venomous snakebite management should publicize themselves as snakebite treatment centers to the public and EMS to expedite the delivery of quality, evidence-based care [37]. Beyond this, educational outreach and partnerships between rural hospitals and hospitals in which FabAV is more commonly used and available could help with consistent and appropriate treatment for patients that are eventually transferred from outlying facilities. Future research should further explore the link between transfer status and FabAV use to determine why this relationship exists as well as how stronger working collaborations between hospitals might impact the outcomes of patients with copperhead envenomations.

Copperhead bites were more common in the lower extremities within our study population. The public should be educated and encouraged to wear protective footwear in regions where venomous snakes are endemic. Upper extremity bites were, however, more likely to be treated with FabAV compared to lower extremity bites. This finding is not particularly surprising given previous literature regarding upper extremity bites [30,38,39]. Edema, pain and swelling in the upper extremity can be perceived as more severe, thus more likely to be treated aggressively, compared to a lower extremity bite. Upper extremity bites are more likely to be due to an intentional interaction with a snake rather than an accidental encounter [30,31,34,40].

Since prevention of snakebites should be the first line of defense, we recommend expanded public health education regarding common places, and activities that might increase the risk of individuals encountering copperheads and other crotaline snakes. This could include joint public health campaigns between agencies such as health departments, wildlife conservation departments, and/or the National Park Service during seasons in which snakes are most active. Since younger age was also a predictor of FabAV use, educational initiatives should also take place in primary care clinics. These initiatives could include providing additional informational materials and guidance to parents regarding the dangers of copperhead envenomations, how to reduce potential encounters, and what to do if a child is believed to have been bitten by a copperhead.

Limitations

Due to the study's retrospective nature, we had limited control over population sampling and quality of data collected from the EMR. We were unable to determine the exact time of the bite and we were unable to identify the rationale for subtherapeutic FabAV. Additionally, we analyzed data from a single institution thus findings may not be generalizable to other parts of the country. Given the absence of a standardized method to identify snakes, there is a possibility that patients reported incorrect species at the time of presentation. Misidentification could result in the inclusion of patients bitten by a non-venomous species or a rattlesnake resulting in either a lower severity of the injury or a more severe injury warranting FabAV. It is also likely that referral bias played a role in the use of FabAV since more severe cases of envenomation were likely transferred to our facility. Finally, we did not have information on clinical outcomes including active bleeding, petechiae, bruising, etc.

Conclusions

FabAV treatment was more likely among patients who were younger, had progression of envenomation across major joints, had multiple comorbidities, or had upper extremity bites. Given the lack of expert consensus on the use of FabAV for copperhead envenomations, we believe stronger collaboration between rural hospitals and larger centers with expertise treating envenomations would likely improve treatment inconsistencies for individuals that are ultimately transferred. We also believe our first and best line of defense against copperhead envenomations is prevention in the form of multi-layered, multidisciplinary public health educational outreach.

Disclosure statement

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