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ABSTRACT

Introduction: The majority of venomous snake exposures in the United States are due to snakes from the subfamily *Crotalinae* (pit vipers). There are three types of US pit vipers: rattlesnakes (*Crotalus* and *Sisturus* spp.) copperheads (*Agkistrodon contortrix*), and cottonmouths (*Agkistrodon piscivorus*) also known as water moccasins. Cottonmouth bites are reported less frequently than other pit viper envenomations, and data on cottonmouth envenomation are limited. Our objective was to describe the epidemiology, clinical manifestations, and management of cottonmouth envenomations using prospective data reported to the Toxicology Investigators Consortium's (ToxIC) North American Snakebite Registry (NASBR)
Methods: Cottonmouth envenomation cases reported to NASBR for the period from January 1, 2013, through December 31, 2017 were reviewed. Variables collected included patient demographics, bite location, clinical manifestations, and management.
Results: Thirty-one cottonmouth envenomations were reported. Most bites occurred in children aged 7–12 (39%). Most bites involved the lower extremity (72%). Intentional interaction with the snake occurred in three cases (10%). Swelling was the most reported clinical effect and occurred in all patients. Gastrointestinal symptoms were reported in 19% of patients, and 19% developed coagulopathy. Antivenom treatment was used in 84% of patients. Nineteen patients (61%) required hospital stays of >24 hours.
Discussion: Our study represents the first systematic prospective data collection on cottonmouth bites. Our data demonstrate that cottonmouth envenomations cause primarily local effects and, occasionally, systemic toxicity. Our study also demonstrates that antivenom is often indicated for these envenomations per published guidelines and recommendations.
Conclusions: Cottonmouth envenomations are relatively infrequent. However, they can cause significant local and systemic toxicity. Most cottonmouth envenomations in this series were treated with antivenom and were hospitalized beyond 24 hours.

Introduction

There are an estimated 5,000–10,000 snake bites annually in the United States (US) [1–3]. Nearly 98% of envenomations are due to snakes from the subfamily *Crotalinae*, colloquially known as pit vipers. Coral snakes, from the family *Elapidae*, account for the remainder of envenomations from native snakes. There are three types of US pit vipers: rattlesnakes (*Crotalus* and *Sisturus* spp.), copperheads (*Agkistrodon contortrix*), and cottonmouths (*Agkistrodon piscivorus*) also known as water moccasins. Local tissue damage (e.g., swelling and ecchymoses) is present in nearly all pit viper envenomations [4]. Systemic toxicity, ranging from vomiting to shock, and hematologic toxicity are less common. Rattlesnake envenomations are associated with a higher incidence of hematologic toxicity and systemic effects than copperhead or cottonmouth envenomations [3].

Cottonmouth bites are reported much less frequently than other pit viper envenomations [1]. This may be due to their limited geographic distribution or misidentification as other species [5]. Cottonmouths are indigenous to Texas, Oklahoma, Louisiana, Arkansas, Mississippi, Alabama, Florida, Georgia, South Carolina, North Carolina, Kansas and some parts of Illinois, Tennessee, Kentucky, Indiana, Virginia, and Missouri [6]. Rattlesnakes and copperheads have a broader geographic distribution [7].

Given the relative infrequency of cottonmouth envenomations, data on their clinical presentations and treatment are much more limited than for rattlesnakes and copperheads. Previous reports have used retrospective Poison Center data to compare medical outcomes. However, because poison center data are limited and not collected in a systematic fashion, these studies cannot provide detailed characteristics

of *A. piscivorus* bites or their response to therapeutic interventions [7,8]. To our knowledge, no prospectively collected data concerning cottonmouth bites and envenomations have been published. Our objective was to describe the epidemiology, clinical manifestations, and management of cottonmouth envenomations using prospective data reported to the Toxicology Investigators Consortium's (ToxIC) North American Snakebite Registry (NASBR)

Methods

The NASBR was established in 2013 as a sub-registry of ToxIC [3]. The Toxicology Investigators Consortium is a voluntary, nationwide surveillance and research tool that prospectively records deidentified patient information from medical toxicologists providing bedside care for patients with envenomations or other poisonings [9,10]. To be part of the consortium, all medical toxicologists at participating institutions agree to enter data into the ToxIC Registry on all medical toxicology consultations performed. The term consultation is used in this report to describe any in-person encounter with a medical toxicologist in which a formal evaluation was conducted and placed in the medical record. Details on data collection within the ToxIC Consortium have been reported previously [10]. The NASBR represents a subset of ToxIC sites reporting more detailed data on snake envenomation across the United States. Prior to joining, prospective participants sign a memorandum of understanding in which they agreed to enter all their snakebite cases into the NASBR.

The NASBR, which gathers extremely detailed information, has previously been described [3]. Data collected in the NASBR include details on the snakebite encounter including snake genus and species, initial clinical presentation, diagnostic or laboratory tests, treatment, and any outpatient follow-up or re-admissions post-discharge. The NASBR undergoes centralized data quality oversight by American College of Medical Toxicology's (ACMT) research staff with review of all data entered with follow-up back to sites to resolve missing or incongruous data.

All ToxIC and NASBR data were collected and managed by ACMT using Research Electronic Data Capture (REDCap) tools hosted at the Vanderbilt University Medical Center, Institute for Clinical and Translational Research core [3,11]. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

The ToxIC Registry and the NASBR are compliant with the Health Insurance Portability and Accountability Act and do not collect any protected health information or otherwise identifying fields. Registry participation is pursuant to the participating institutions' Institutional Review Board approval and compliance with their policies and procedures. The Registry was also reviewed by the Western IRB and determined not to meet the threshold of human subject research under federal regulation 45 CFR 46 and associated guidance.

For this report, all cottonmouth (*Agkistrodon piscivorus*) envenomation cases reported to NASBR were identified for the period from January 1, 2013 through December 31, 2017. Snakes were entered as cottonmouths by the treating toxicologist; however, the exact method of identification was not recorded. Data reviewed for this study included bite location, patient age and demographics, local and systemic signs and symptoms, and details of antivenom use. Descriptive statistics were used to report results.

Results

There were 31 cottonmouth snakebites recorded in the registry from 2013 to 2017. These 31 snakebites represent 3.6% of the 870 snakebites in the NASBR. Patient demographics are shown in Table 1. All exposures occurred in Texas and involved wild, not captive, snakes. Most patients were male (68%) and were under 18 years old. Twelve of these (39%) occurred in children aged 7–12. Among all patients, only one patient reported alcohol use in the four hours preceding the bite. Most bites (72%) involved the lower extremity. Intentional interaction with the snake occurred in only three cases (10%), and all of these involved the upper extremity.

Local soft tissue effects were common (Table 2). Swelling was the most reported clinical effect and occurred in all patients. Most patients (81%) had swelling extending beyond at least one major joint. In 65% of patients, the swelling crossed one major joint, while more severe swelling extending beyond two major joints occurred in 16% of patients. Six patients (19%) had only localized swelling that did not cross a major joint. Other reported local effects were ecchymoses and erythema.

No patients developed cardiovascular effects such as hypotension or tachycardia following their snakebite. Gastrointestinal symptoms occurred in six patients (19%).

Table 1. Demographics of patients bitten by cottonmouth snakes in the NASBR[a].

Sex	
Males	21 (68%)
Females	10 (32%)
Age	
<24 months	2 (6%)
2–6 years	2 (6%)
7–12 years	12 (39%)
13–18 years	4 (13%)
19–65 years	11 (35%)
>65 years	0
Bite location	
finger	8 (26%)
hand	1 (3%)
toe	3 (10%)
foot	12 (39%)
ankle	4 (13%)
lower leg	3 (10%)
Circumstances of bite	
Intentional interaction	3 (10%)
Unintentional non-occupational interaction	26 (84%)
Unintentional occupational interaction	2 (6%)

[a]NASBR: North American Snakebite Registry

Table 2. Clinical features and treatments of cottonmouth snakebites reported to the NASBR.

		All patients	Age < 18	Age ≥ 18
Swelling		31 (100%)	19	12
	Localized swelling crossing no joint	6 (19%)	2	4
	Swelling crossing one major joint	20 (65%)	16	4
	Swelling crossing two major joints	5 (16%)	2	3
Ecchymosis		25 (81%)	17	8
Emesis		5 (16%)	4	1
Diarrhea		1 (3%)	1	0
Neurotoxicity	Extremity fasciculations	1 (3%)	0	1
Hematotoxicity				
	Thrombocytopenia	2 (6%)	1	1
	Hypofibrinogenemia	1 (3%)	1	0
	Coagulopathy	6 (19%)	6	0
Antivenom				
	Patients treated	26 (84%)	18	8
	Dose range	1–28 vials	4–28	1–18
Antibiotics				
	Prophylaxis	1 (3%)	0	1
	Empiric treatment of suspected infection	2 (6%)	1	1
Procedures				
	Fasciotomy	1 (3%)	0	1
	Debridement	0	0	0

The most common systemic symptom was emesis, which occurred in five patients. Four of these developed emesis before receiving treatment with opioids. Almost all patients that vomited were under 18 years old. The one adult patient who developed emesis was a 37-year-old male who also developed itching, rash, and wheeze and was presumed to have a hypersensitivity reaction to venom. His symptoms started within 10 minutes of the snake bite and prior to receiving antivenom. This patient was treated with subcutaneous epinephrine, antihistamines, and steroids. One patient developed diarrhea.

Hematologic abnormalities occurred in nine patients and consisted of thrombocytopenia (platelets <120 k/mm^3), in two patients (6%); hypofibrinogenemia (fibrinogen <170 mg/dL), in one patient (3%); and prolongation of prothrombin time (>15 seconds) in six patients (19%). Minimum platelet count recorded was 7 k/mm^3, and maximum prothrombin time recorded was 17.5 seconds. No patients had abnormalities in more than one hematologic parameter. None of these patients developed bleeding, and none were taking antiplatelet or anticoagulant medications. One patient developed nuisance bleeding, defined in the registry as epistaxis, gingival bleeding, or oozing from puncture sites; however, this patient did not have venom-induced thrombocytopenia or coagulopathy. Neurologic abnormalities occurred in one patient – a 24-year-old female with a history of two previous snake bites, who was bitten on the foot and developed fasciculations and paresthesias.

Antivenom treatment with Crotalidae Polyvalent Immune Fab (Fab AV; CroFab) was used in 26 patients (84%). A median of 10 vials was used per case (range 1–28). Median time to antivenom administration was 3.5 hours (range 1–29). Three patients received an initial bolus dose of antivenom (range 1–6) but were not treated with maintenance therapy. Frequency of antivenom use did not increase over the four-year study period. Three patients received empiric or prophylactic antibiotics, and one patient underwent fasciotomy for a bite involving the index finger with swelling beyond two major joints for suspected but unconfirmed compartment syndrome. Compartment pressures were not performed. Nineteen patients (61%) were hospitalized for >24 hours. All patients were discharged within 72 hours.

Follow-up attempts occurred in 10 patients. Follow-up times ranged between 3 and 17 days post-envenomation in nine of these patients and one at greater than one month. Six of these patients are documented as being lost to follow-up due to relocation, patient refusal, failed attempts at contact, and incarceration. Four patients (13%) had decreased mobility in the affected hand or digit at the time of final follow-up. Three of these patients were followed up 3 days after the envenomation and one at greater than one month.

Discussion

Our study represents the first systematic prospective data collection on cottonmouth bites. Literature on cottonmouth envenomation is limited. The few studies using poison center data lack details such as bite location, all clinical effects, and antivenom use [7,8].

Our data demonstrate that cottonmouth envenomations cause primarily local effects and, occasionally, systemic toxicity. A previous poison center study reported edema in 53% and ecchymoses in 15% of cottonmouth envenomations [7]. These were the most common local effects seen in our study, but we found that they occur more frequently, with swelling in 100% and ecchymoses in 81% of patients. Prothrombin time prolongation occurred in 19% of patients in our study, which is higher than reported in a previous study [7]. Prothrombin times were recorded in 29 patients. Hypofibrinogenemia occurred in 3% of patients and emesis in 16%. These effects have not been described in prior studies. However, in an earlier report describing all snakebites reported in the NASBR from 2013 to 2015, including a subset of this population of cottonmouth envennomations, the percentages of these findings were higher [3].

The number of cases in our study is small, which may be due to fewer human encounters with these snakes in an aquatic environment. It may reflect the more limited

distribution of cottonmouths compared to other pit vipers. It may also be due to the few registry sites that collected the data. The relatively few envenomations reported here and in previous literature may also suggest a reluctance of cottonmouths to bite [12,13].

Antivenom was used in 84% of patients in our study. This rate is higher than reported in a 2007 study using poison center data, where 30% of cottonmouth envenomations were treated with antivenom [7]. A possible explanation for this is that all entries into the NASBR are seen by a medical toxicologist, and the registry did not capture less severe envenomations managed without toxicology consultation. It may also reflect an overall increase in antivenom use, which has been previously described [14].

A consensus workgroup recommended that treatment with antivenom is indicated for patients with progressive local tissue effects, hematologic effects, or systemic signs attributable to venom [4]. Antivenom dosing is titrated to clinical response, consisting of arrest of the progression of local tissue effects, clearly improving trends in hematologic venom effects, and resolution of systemic venom effects. An initial dose of 4–6 vials of antivenom is recommended followed by maintenance therapy of two vials every 6 hours for three doses. Maintenance therapy may not be indicated in certain situations such as minor envenomations [4]. One patient in our study received one vial of antivenom at the initial facility prior to transport and evaluation by a toxicologist. This is not consistent with current dosing recommendations. This patient's symptoms consisted of localized swelling, ecchymoses at the bite site, and a hemorrhagic bleb. There were no systemic effects. Additional treatment with antivenom was recommended; however, the patient declined and left the hospital after a 5-hour period of observation.

Antibiotics were given in three cases, twice for suspected cellulitis and once for prophylaxis. However, it is important to note that venom-induced inflammation may mimic infection, though true bacterial cellulitis is uncommon in snakebite patients [15] and prophylactic treatment with antibiotics is not recommended [4].

One patient in our series underwent a fasciotomy for a suspected but unconfirmed compartment syndrome. Animal studies reflect that morbidity and mortality are increased following prophylactic fasciotomy when compared to antivenom [16,17]. In a review of 99 publications evaluating the efficacy of fasciotomy in animals and humans, the author could not identify any situation in which surgery was beneficial [18]. An expert panel consisting of trauma surgeons and medical toxicologists also concluded that prophylactic fasciotomy was not beneficial and was possibly harmful [19]. The same authors concluded that, even in the case of confirmed compartment syndrome, the initial treatment should be additional doses of antivenom, not fasciotomy. The rationale, supported by animal studies, is that elevated compartment pressure represents a severe envenomation but is not the cause of the morbidity. Rather, it is the venom causing the damage, and neutralizing the venom is the definitive treatment [20].

This study reflects that cottonmouth envenomations can cause significant local and systemic toxicity. It also demonstrates that antivenom is often indicated for these envenomations per published guidelines and recommendations [21]. Physicians may use this information to guide patient expectations and approach to management when presented with cottonmouth envenomations.

Limitations

There are several limitations with this study. Because participation in the registry is voluntary, data may be incomplete with some fields missing. However, the NASBR does have a quality assurance program to identify and obtain missing information. There are also relatively few cases included in this study. Cottonmouth envenomations are reported less commonly than bites from other *Crotalinae* species; this may be due to lower reporting to our registry or may suggest that cottonmouths are not as aggressive as classically considered [12,13]. Furthermore, species misidentification has been reported among healthcare providers, including physicians [5]. The method of species identification is not included in the registry, and there may be some variability as to the correct identification of *A.piscivorus*. It is possible that some of our cases were actually from other species. However, the registry does contain a category for unidentified pit vipers. Finally, all of the cases described in this series are from Texas. Cottonmouths have a broader distribution than Texas; there are two subspecies of cottonmouths distributed through the southeast, *A.conanti*, which is confined to Florida, and *A.piscivorus*. The clinical features of their bites may vary. Follow-up data and long-term outcomes are also limited, with only 10 patients available for telephone follow-up.

Conclusions

Cottonmouth envenomations are relatively infrequent. However, they can cause severe local and systemic toxicity. Most cottonmouth envenomations in our study were treated with antivenom and were hospitalized beyond 24 hours.

Acknowledgements

Disclosure statement

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