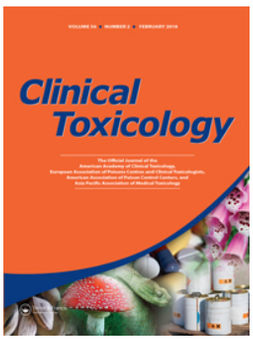

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CLINICAL RESEARCH

Epidemiology and clinical outcomes of snakebite in the elderly: a ToxIC database study*

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ABSTRACT

Introduction: Epidemiologic studies of snakebites in the United States report typical victims to be young men. Little is known regarding other demographics including children and the elderly. The objective of this study was to describe the epidemiology and clinical manifestations of snake bite in elderly patients reported to the ToxIC (Toxicology Investigators Consortium) North American Snakebite Registry (NASBR)

Methods: This was a multicenter analysis of a prospectively collected cohort of patients with snakebite reported to the ToxIC NASBR between 1 January 2013 and 31 December 2015. Inclusion criterion was age >65. Variables collected included patient demographics, medical comorbidities, medications, date the case was reported to the registry, location of exposure, bite location, snake species, clinical manifestations, outcomes, and management.

Results: Of the 450 cases reported, 30 (6.7%) occurred in elderly patients, with an average age of 74 years. Rattlesnake envenomations were common (93.3%). The majority of patients were men (66.7%) and reported at least one medical comorbidity (83.3%). Most patients were on cardiac medications (60%) and use of antiplatelet or anticoagulant medications was common (33%). Hemotoxicity occurred in 30% of patients on initial presentation and 11.5% of patients on initial follow-up. No clinically significant early or late bleeding was observed.

Conclusions: Elderly patients with North American snake envenomation are likely to have co-morbidities and to take medications that may increase their risk for hemotoxicity, however risk of bleeding or other complications was not increased in this group.

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Introduction

Approximately 10,000 snake bites are treated in US Emergency Departments (EDs) each year resulting in significant morbidity and rare mortality [1]. Although epidemiologic studies have shown typical snake bite victims to be young men [1–3], little is known regarding outcomes of demographic groups at potential higher risk, such as the elderly or pediatric populations.

Most snakebites in the US are due to native snakes, predominantly the crotalids of the *Viperidae* family (rattlesnakes, cottonmouth, and copperheads). Coral snakes of the *Elapidae* family are responsible for a much smaller subset of native envenomations in the United States. The rare elapid envenomation classically results in neurologic toxicity. Crotalid envenomations, conversely, are characterized by hematologic toxicity including thrombocytopenia and hypofibrinogenemia, as well as direct tissue toxicity. Anaphylaxis and shock can also occur.

The number and severity of medical comorbidities, as well as use of prescription medications is higher in the elderly population compared to that of a younger cohort. Specifically, the elderly commonly suffer from cardiovascular disease and are frequently prescribed antiplatelet or anticoagulant medications [4]. As such, this population may be at increased risk of cardiovascular or hematologic complications after a crotalid envenomation. To date, there is no literature focusing on the geriatric population after snake envenomation. This study aims to describe the epidemiology, clinical manifestations, and complications of US snake bites in the elderly using data reported to the Toxicology Investigators Consortium (ToxIC) North American Snakebite Registry (NASBR).

Methods

This was a multicenter cohort study of prospectively collected data from the ToxIC NASBR. Data reported to the ToxIC NASBR between 1 January 2013 and 31 December 2015 were reviewed.

The ToxIC Registry was established in 2010 by the American College of Medical Toxicology (ACMT) as a novel,

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prospective toxico-surveillance and research tool. It records all cases cared for at the bedside by medical toxicologists at each of more than 50 sites across the United States that actively contribute cases to the registry. The Registry allows for pooling of detailed, de-identified clinical information from across all Registry centers.

The Registry is Health Insurance Portability and Accountability Act (HIPAA) compliant and no patient identifiers are available on the database. Participation in the Registry is done in accordance with local institutional and Western Internal Review Board (IRB) policies and procedures.

ACMT's ToxIC NASBR Sub-Registry is a database that gathers de-identified, detailed, prospective information regarding snake bite, clinical manifestations of envenomation, and response to treatment for patients who receive bedside care from medical toxicologists across the United States. Criteria of age was a mandatory field in the Registry database. The Sub-Registry was established in 2013.

Inclusion criterion was age >65 years. Data collected included patient demographics, medical comorbidities, medications, date the case was reported to the registry, location of exposure, bite location, snake species, clinical manifestations, outcomes, and management. Method of identification of snake was not specified. Hemotoxicity was defined as thrombocytopenia (platelet (PLT) <120 K/mm^3) or coagulopathy (fibrinogen (Fib) <170 mg/dL). Severe hemotoxicity was defined as severe thrombocytopenia (PLT <50 K/mm^3) or severe coagulopathy (Fib <80 mg/dL). Prothrombin time (PT) was analyzed separately to avoid confounding with use of anticoagulant medications. Data for late bleeding events (defined as bleeding after the initial hospitalization) were obtained from direct patient contact or telephone interview. Descriptive statistics were used.

Results

Cases

Between 1 January 2013 and 31 December 2015, 450 cases were reported to the NASBR registry. Ten states and 14 sites were represented. Thirty cases (6.7%) were in patients over age 65. All elderly cases occurred in six states, representing eight individual sites. Similar to the larger registry, the majority of elderly cases occurred in Arizona (see Table 1). Elderly envenomations were evenly distributed over the study period with 11 envenomations in 2013, 9 in 2014, and 10 in 2015. The greatest number of cases (66.7%) were reported between May and September.

Table 1. Elderly and total snake bites by state.

US state	Total cases	Elderly cases (% total)
Arizona	163	20 (12)
Texas	158	2 (1)
California	33	4 (12)
North Carolina	30	0
Missouri	27	0
Colorado	14	2 (14)
New Mexico	7	0
Utah	14	1 (7)
Pennsylvania	2	1 (50)

Types of snakes

There were 28 native rattlesnake snake bites reported and two envenomations in which the type of snake was not reported. Rattlesnakes were not consistently identified by species. Two Western Diamondbacks, one Timber, one Southern Pacific, one Great Basin, and one Arizona Black rattlesnake were reported, the remainder were not identified. There were no non-native envenomations. One envenomation occurred after exposure to a captive rattlesnake.

Demographics and medical history

Twenty patients (66.7%) were men and 10 (33.3%) were women. The median age was 73 years (IQR: 70–78). One (3.3%) patient was over age 89. One occupational bite occurred in a venomous animal educator. Acute alcohol intoxication was reported in two cases. The majority of patients were on cardiac medications. Use of antiplatelet or anticoagulant medications was common (33.3%), with eight (26.7%) reporting antiplatelet and two (6.7%) reporting anticoagulant medication use. See Table 2 for prescription medication details.

Medical comorbidities were present in 25 (83.3%) cases. Eighteen (60%) had two or more conditions, nine (30%) had three or more conditions, and six (20%) had four or more conditions. Cardiovascular comorbidities, defined as hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, valvular disease, and history of CABG, were present in 21 patients (70%). The most common comorbidity was hypertension (60%), followed by hyperlipidemia (27%), coronary artery disease (17%), cancer (17%), atrial fibrillation (13%), and benign prostatic hypertrophy (10%) (see Table 3).

Envenomation details

Seventeen (56.7%) upper extremity envenomations occurred, and the finger was the single most common site of envenomation. Thirteen (43.3%) lower extremity envenomations occurred (see Figure 1). Six (20%) bites were "illegitimate bites", or subsequent to intentional interactions, all of which were to the upper extremities in men. Eleven (36.7%) of the "legitimate bites", subsequent to unintentional interactions with the snake, were to the upper extremity (see Figure 2).

Outcomes and management

Field therapy was performed in five (16.7%) cases. In three cases, a tourniquet or make-shift tourniquet was applied.

Table 2. Patient characteristics.

Demographic	Cases (% total elderly)
Age >65	30 (100)
Age 66–79	23 (77)
Age 80–89	6 (20)
Age >89	1 (3)
Men	20 (67)
Medical comorbidities	25 (83)
Cardiac medication	18 (60)
Diabetic medication	2 (7)
Antiplatelet/anticoagulant medication	10 (33)

Table 3. Medical comorbidities in snake bites in the elderly.

Medical condition	Cases (% total)
Hypertension	18 (60)
Hyperlipidemia	8 (27)
Coronary artery disease	5 (17)
Cancer	5 (17)
Atrial fibrillation	4 (13)
BPH	3 (10)
Hypothyroid	2 (7)
Gout	2 (7)
CABG	2 (7)
GERD	2 (7)
Peripheral neuropathy	1 (3)
Diabetes	2 (7)
CVA	1 (3)
Valvular disease	1 (3)
Arthritis	1 (3)
OSA	1 (3)
Alzheimers	1 (3)
Herpes	1 (3)
Fibromyalgia	1 (3)
Depression	1 (3)

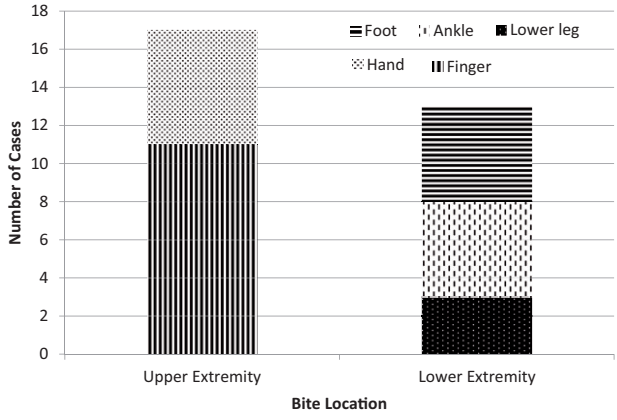

Figure 1. Anatomic location of snake bites in the elderly.

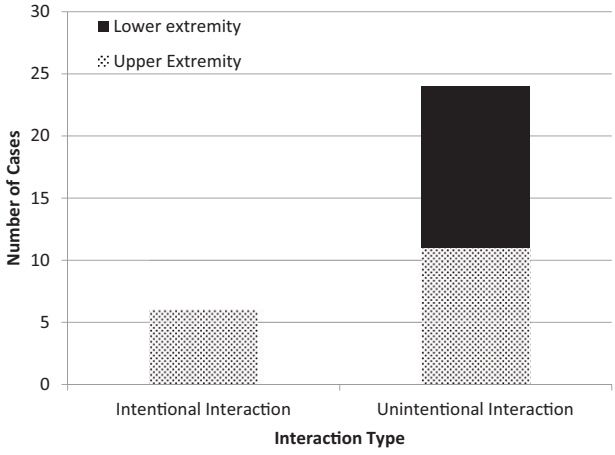

Figure 2. Patterns of intentional and unintentional snake bites in the elderly.

In one case a bandage was used. Ice was applied in one case. Time to healthcare was under 3 h in all cases except one (average 1.3 h, range 15 min to 5 h).

Antivenom (Crofab™, BTG International, West Conshohocken, PA) was administered in all 30 (100%) cases. A median of 10 vials (IQR: 8–14) was given per case. Upper extremity envenomations received a median 8.5 vials (IQR: 7.5–13), and lower extremity envenomations received a median 10.5 vials (IQR: 8.5–14). Median time to antivenom administration after snake bite was 2.5 h (IQR: 1.5–3.75, range: 30 min to 20 h). Five (16.7%) cases received first antivenom 5 or more hours after envenomation, with one case each at 8, 15, and 20 h. Twenty-six (86.7%) patients were admitted to an Intensive Care Unit. Hospital length of stay was less than 24 h in six (20%) patients, between 25 and 48 h in 16 (53%) patients, between 49 and 72 h in six (20%), greater than 73 h in one (3.3%), and not reported for one patient. Clinical manifestations of envenomation are described in Table 4.

Table 4. Incidence of clinical manifestations in snake bites in the elderly.

Clinical effect	Cases (% total)
Swelling	30 (100)
Ecchymosis	18 (60)
Erythema	14 (47)
Emesis	2 (7)
Neurotoxicity	3 (10)
Hypotension	4 (13)
Minor bleeding	2 (7)
Necrosis	0
Angioedema	1 (3)
Syncope	1 (3)

Table 5. Median laboratory results in snake bites in the elderly.

Hematologic parameter	Median (IQR)
Platelet nadir (K/mm^3)	177 (145.5–217) $n = 30$
Fibrinogen nadir (mg/dL)	264.5 (192–313.8)[a] $n = 28$
Prothrombin time peak (s)	14.1 (13.4–15.7)[b] $n = 29$

[a]For fibrinogen <30 or <60, values of 30 and 60, respectively, were used to calculate the median.
[b]For prothrombin time >120, a value of 120 was used to calculate the median.

Hemotoxicity occurred in nine (30%) individual patients during the initial presentation, with four cases of isolated thrombocytopenia (PLT <120 K/mm^3), three cases of isolated hypofibrinoginemia (Fib <170 mg/dL) and two cases of multicomponent hematologic toxicity. Total incidence of thrombocytopenia was six (20%) cases, and incidence of hypofibrinoginemia was five (16.7%) cases. Severe hemotoxicity occurred in six (20%) cases during the initial presentation. Two cases of isolated severe thrombocytopenia (PLT <50 K/mm^3), two cases of isolated severe coagulopathy (Fib <80 mg/dL), and two cases of combined severe hemotoxicity were reported. An additional six cases of coagulopathy defined as isolated PT >15 s were identified, raising the total incidence of hemotoxicity, inclusive of prolonged PT, to 15 (50%). The two patients on anticoagulants at baseline were included in the six cases of isolated prolonged PT. Initial PT for those two patients was 12.4 and 15.3 s, peaks were 15.3 and 19.7 s, respectively. Median laboratory results are described in Table 5.

Vasopressors were administered for hypotension in one (3.3%) case. Two (6.7%) patients received prophylactic antibiotics. No blood products were given. There were no cases of wound debridements or fasciotomies. The only procedure performed was an echocardiogram for evaluation of new onset atrial fibrillation. Adverse reactions to antivenom were reported in two (6.7%) cases, including one case of

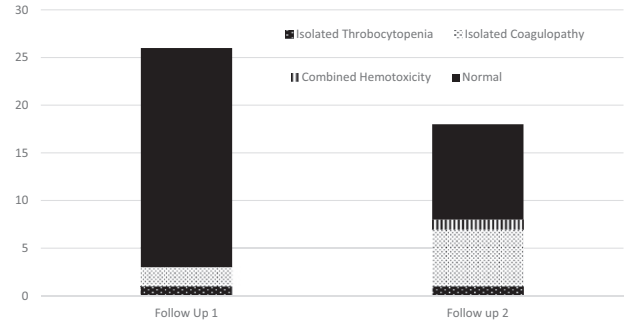

Figure 3. Late hemotoxicity after snake bite in the elderly.

bronchospasm and one case of perioral numbness. Steroid and antihistamine medications, respectively, were used to treat the adverse reactions.

After discharge, a first set of follow-up laboratory values was obtained in 26 (86.7%) cases, and in three of these (11.5%) cases, late hemotoxicity occurred (two isolated coagulopathy, one isolated thrombocytopenia). A second set of follow-up laboratory values was obtained in 18 (60%) cases, with eight (44.4%) cases of late hemotoxicity (six isolated coagulopathy, one isolated thrombocytopenia, one combined) in that group. On second follow-up, five (27.8%) cases of new late hemotoxicity (i.e., not present on initial follow-up), were identified. In total, eight unique cases of late hemotoxicity were identified in follow-up (see Figure 3). Of note, in three follow-up cases, severely elevated PT (PT >90) was accepted as defining coagulopathy because fibrinogen levels were not available.

One (3.3%) patient was readmitted and retreated on two separate occasions, once for late coagulopathy seven days post-bite, and once for late thrombocytopenia 15 days post-bite. This patient was a 68-year-old man with a lower extremity bite. Antivenom was administered 4 h after the envenomation. On initial presentation, severe coagulopathy and thrombocytopenia were present. He was on cardiac but no antiplatelet or anticoagulant medications. Follow-up labs in this patient were initially normal 5 days post-bite.

One (3.3%) case of minor late bleeding, in the form of persistent oozing after cat scratch, occurred. No cases of serum sickness were reported.

Discussion

In this elderly cohort, medical co-morbidities and use of antiplatelet, anticoagulant, and cardiac medications were common. The prevalence of medical comorbidities and concomitant medication use has not been previously reported in large cohorts of North American snakebite patients. This paper represents the first description of such factors and of the clinical course of rattlesnake envenomation in this elderly demographic group.

Most notably, early hemotoxicity was present in 30% of cases in this elderly cohort, with 20% thrombocytopenia and 16.7% hypofibrinogenemia. Compared to the entire NASBR population described during the same time period, hemotoxicity, defined by the same parameters as this study, occurred at a higher rate in this elderly population. In the larger NASBR cohort, initial thrombocytopenia was present in 10.6% and hypofibrinoginemia in 11.8% of cases, although total incidence of hemotoxicity was not reported [5]. Whether this increased prevalence of hemotoxicity in the elderly is related to age, medical comorbidities, medications, or another unidentified factor is not clear. Importantly, the NASBR registry includes various snake species, such as copperheads and cottonmouths, which traditionally manifest less severe hematologic toxicity. This elderly population was comprised of 93% rattlesnake envenomations. It is possible that this alone may have skewed the data towards more severe hematologic toxicity. Additionally, two other studies from Arizona involving rattlesnake bites found higher rates of initial hemotoxicity [6,7].

Despite the high rate of laboratory-identified hemotoxicity, there were no clinically significant cases of bleeding in this group. This result differs somewhat from a previous study by Levine et al. that found the incidence of early bleeding to be increased in patients taking anticoagulant and antiplatelet medications (9.7%) compared to those not taking such drugs (1.4%) [8]. Consistent with previous studies [9] and Levine's, however, overall incidence of early bleeding was low.

Given the high rate of anticipated anticoagulant medication use, PT was not used as a marker for coagulopathy in this study. The addition of prolonged PT to the definition of hemotoxicity raises the incidence to 50%, which is consistent with a previous study of rattlesnake envenomations in Arizona [6]. Only two patients in the current study of an exclusively elderly cohort reported use of anticoagulants, making confounding of this result from anticoagulant medications alone less likely.

At least one set of follow-up labs was obtained in most cases and late hemotoxicity in that group was 11.5%. One patient (3.3%) had hemotoxicity requiring retreatment with antivenom. Interestingly, the patient that required retreatment had normal labs at follow-up 5 days after envenomation. Guidelines typically recommend two sets of follow-up labs, the last of which is to occur 5–7 days post envenomation. In this patient, recurrent, clinically significant hemotoxicity would have been missed had no further labs been obtained beyond the 5-day mark. Furthermore, in this study, new hemotoxicity was identified on second follow-up in 27.8% of those tested. This finding highlights the importance of multiple sets of follow-up labs in patients with rattlesnake envenomations, and raises questions as to whether 5 days as a last point of contact is sufficient.

There were no significant late bleeding complications in this study despite a third of patients reporting use of anticoagulant or antiplatelet medications. This is reassuring, considering the increased risk of late bleeding associated with use of these medications reported in the study by Levine et al. [8]. However, this finding is consistent with other studies which have found late bleeding to be uncommon following rattlesnake envenomation [10].

There were no reports of tissue necrosis in this series. Although tissue necrosis is a well-recognized complication of rattlesnake envenomation, risk factors for its occurrence are not well described. In contrast to this study, a study out of Arizona found the incidence of tissue necrosis in upper

extremity rattlesnake envenomation to be 40% [11]. No association between necrosis and medical comorbidities or medications was found, however age was not specifically examined. This discrepancy in necrosis is notable, as the elderly would intuitively be expected to be at a higher risk for all complications of envenomations. Although small numbers in both studies limit the generalizability of these results, potential protective factors in the elderly population are intriguing.

Antivenom was administered in all cases, compared to 85% in the entire NASBR cohort [5]. Again, the larger cohort did include a significant number of copperhead envenomations, which may account for lower severity, including lower incidence of hemotoxicity and lower rates of treatment. When treatment was given, however the total vials of antivenom administered was similar to that of the larger group [5].

Length of stay in this elderly population may be longer than the larger group. In the entire NASBR population, 78% had a length of stay under 48 h [5], but only 53% of the elderly population had a length of stay within this timeframe. This increase in hospital stay occurred despite similar numbers of vials of antivenom and in the absence of bleeding complications. Further examination of such data may be useful in identifying the medical necessity, or lack thereof, of such prolonged hospital stays and serve as a target for reduction in hospital costs.

Limitations

This review of data reported to the NASBR Sub-Registry presents limitations inherent to voluntary reporting of data to a registry. Although the NASBR undergoes quality assurance review to identify and correct errors or omissions in data entry, it is possible that all errors were not identified. Notable limitations to this data include the small total numbers, a predominance of cases occurring in one state (Arizona), and the predominance of rattlesnake envenomations. These results may not be generalizable to envenomations occurring in other parts of the United States and to non-rattlesnake Crotalid envenomations. Additionally, follow-up may have been performed by non-NASBR participants and thus not included in this study.

Conclusions

Elderly patients with North American snake envenomation are likely to have co-morbidities and take medications that may increase their risk for hemotoxicity, however risk of bleeding or other complications was not increased in this group. In this cohort, complications were minimal and only one patient (3.3%) had late hemotoxicity requiring retreatment with antivenom.

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Disclosure statment

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