

TITLE PAGE

I. Title of project:

**RATTLESNAKE ENVENOMATIONS IN CHILDREN: ARE THEY MORE SEVERE THAN
ENVENOMATIONS IN ADULTS?**

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ABSTRACT

Specific Aims: The aim of this study is to compare characteristics, clinical treatments, severity, and outcomes in pediatric rattlesnake envenomation cases as compared to adults to better understand the current differences in envenomation management between the two populations.

Methods: This is a retrospective descriptive study utilizing the electronic medical records (EMR) from the Arizona Poison and Drug Information Center (APDIC). Rattlesnake bites requiring care at a healthcare facility and followed to the outcome by the APDIC between January 1, 2017 and September 30, 2020 were included. Dry bites, cases transferred to another poison center, cases where the patient left against medical advice, or otherwise unable to be followed to the outcome were excluded. Information obtained for analysis include patient demographics, location of bite on body, time of bite, whether the patient received anti-venom, if the patient experienced coagulopathy and other symptoms.

Main Results There was no significant difference in the amount of antivenom vials used between the adult and pediatric groups ($\chi^2(1) = 8.520$, $p = 0.503$, with a mean rank score of 229.25 for adults and 240.62 for pediatrics). Also, there was no significant difference between the mean Abbreviated Snakebite Severity Score between both the adult and pediatric groups (mean; 3.1, 3.4, respectively, $p = 0.373$). Other symptoms that were evaluated showed no significant differences in coagulopathy, late coagulopathy, peak edema, and hematologic toxicities.

Conclusions The comparison of characteristics, clinical treatments, severity, and outcomes in pediatric to adult rattlesnake envenomations, showed no significant differences in envenomation management between the two populations.

RATTLESNAKE ENVENOMATIONS IN CHILDREN: ARE THEY MORE SEVERE THAN ENVENOMATIONS IN ADULTS?

INTRODUCTION

Pediatric and adult rattlesnake envenomations are considered a life-threatening medical emergency and account for the highest incidence of mortality and morbidity in the United States (US) over any other native venomous snake species. Rattlesnake envenomations are acute conditions with varying clinical presentations and outcomes based on severity, location of the inflicted bite, and laboratory findings. Currently there is limited data comparing rattlesnake envenomations in the pediatric population, which is defined as those who are under the age of 18 years, with the adult population. Thus, there is a need to compare available data in both populations, to better understand how to properly manage envenomations regardless of patient age.

In the Arizona Poison and Drug Information Center (APDIC) 2019 Annual Report, rattlesnake bites accounted for 179 of bite/sting cases, a reported 15% increase since 2018. It was also reported that those aged 0-18 years accounted for 15.2% of rattlesnake bites in 2019.¹ Correspondingly, pediatric snakebite envenomations are an important public health concern and it is imperative that healthcare providers are informed on the management of the envenomed pediatric patient. Therefore, the purpose of this study is to compare rattlesnake envenomation characteristics in the pediatric population with the adult population.

Design: This is a retrospective descriptive study comparing rattlesnake envenomation characteristics in the pediatric population with the adult population.

Subjects: Inclusion criteria were as follows: age 0 to 89 with a rattlesnake bite requiring treatment at a healthcare facility and followed to the outcome by the Arizona Poison and Drug Information Center (APDIC) occurring between January 1, 2017 and September 30, 2020. Snake bites that did not require antivenom, dry bites (where the snake did not release venom), animal envenomation cases, cases that were not treated at a healthcare facility, cases

transferred to another poison center, cases where the patient left against medical advice, or otherwise unable to be followed to the outcome were excluded. This study was approved by the University of Arizona Human Subjects Protection Program.

Measures: The ToxSentry Web Query builder was used to identify cases, demographic information (gender and age), time and date of snake bite exposures. The ToxSentry database was used after cases were identified, to obtain specific clinical information such as: fang-to-vial time, bite location, coagulopathy on presentation, and swelling (edema) on presentation. The primary outcome measured was the total number of antivenom vials administered to the patient.

Secondary outcomes measured were whether more than one loading dose of antivenom was required, level of inpatient coagulopathy, presence of systemic symptoms, level of peak edema, presence of blebs or bullae, the Abbreviated Snakebite Severity Score (ASSS), presence of late coagulopathy, and adverse reactions to venom. Coagulopathy was defined as fibrinogen and/or platelets with values less than $150 \times 10^9/L$, coagulopathy that occurred while being treated in a healthcare facility was defined as initial; late coagulopathy was defined as occurrence after healthcare facility care discharge. The ASSS was used to assess envenomation severity by total score in the following categories: Neurologic-Systemic effects, local effects, hematologic effects, and the presence of bleb/bullae. Neurologic-Systemic effects were defined as dizziness, chills, paresthesia, fasciculations, lethargy, or altered mental status.

Data Collection: Data was collected using the Arizona Poison and Drug Information Center, ToxSentry Web Query Builder, ToxSentry Database, and exported to Microsoft Excel 2018. Additionally, specific clinical information was collected manually from the ToxSentry Database and entered into a data collection form (**Appendix A**).

Data analysis: There were a total of 704 snake-bite cases reported, after exclusions 461 cases were included for analysis. Cases were separated into pediatrics (<18 years of age) and adults (18-89 years of age) groups. The pediatric group contained 71 cases and the adult group contained 390 cases. The data was stratified by anti-venom type and pediatric groups of

(0-6, 7-12, and 13-17 years of age). Continuous variables were analyzed by calculating summary means and standard deviations then using a Kruskal-Wallis Test or Mann-Whitney Test to see if there was a significant difference. Categorical variables were analyzed by calculating frequencies and percentages then tested either using a Fisher's Exact Test or Chi-square test for significance. The a priori alpha level was 0.05.

RESULTS

There were 704 unique snakebite cases identified, 243 cases were excluded based on exclusion criteria found on **Figure 1**. A total of 461 envenomation reported cases were analyzed, which included 71 pediatric and 390 adult cases. Overall, most patients were males in the pediatric and adult groups ($N=41$; 58%, $N=246$; 63% respectively). The location of the snakebite predominated in the lower extremities in both the pediatric ($N=48$; 68%) and adult ($N=204$; 52%) groups. The demographic and baseline characteristics of envenomation analyzed are represented in **Table 1**.

To compare treatment outcomes, a Mann-Whitney test was used; from this data there were no statistically significant differences in the total number of anti-venom vials received between the adult and pediatric groups ($p = 0.503$). There was also no statistically significant difference in the number of vials given when by antivenom brand, with a mean rank score of 222.59 for Anavip, 244.30 for Crofab, and 257.88 for a combination of both types of antivenom administered ($p=0.172$)(**Table 2**). Yet, when comparing if more than one loading dose of anti-venom was administered, there was a higher incidence amongst the pediatric group ($N=40$; 56%) as compared to the adult group ($N=183$; 47%) although this finding was not statistically significant ($p=0.517$)(**Table 3**).

In addition, the analyzed secondary clinical outcomes were found to have similar distribution between the pediatric and adult cases, in which initial coagulopathy did not occur ($N=37$; 52%, $N=214$ 55%, respectively). Another similarity was Neuro-Systemic involvement, 67

out of 71 (94%) of pediatric cases and 357 out of 390 (92%) adult cases reported no Neuro-Systemic involvement. The incidence of peak edema in the affected extremity was also found to be not statistically significant between the pediatric and adult groups ($p=0.678$). There was a similarity between the pediatric (39/71, 54.9%) and adult (209/390, 53.6%) cases where peak edema affected less than half of the bitten extremity (**Table 3**).

Characteristics of pediatric patients stratified by age are provided on **Table 4**. While there are no statistically significant differences between any of the clinical characteristics, notably the genders for the youngest age group (age 0-6) were equally distributed with 16 male and 16 female patients, whereas the older age groups are predominantly male (**Table 4**).

DISCUSSION

The treatment for rattlesnake bites, in pediatric and adult patients, involves the evaluation of the severity of physical and systemic symptoms such as: coagulopathy (initial and late), swelling (edema) of the affected extremities, dizziness, chills, paresthesia, fasciculations, lethargy, or altered mental status.² If these signs are present, the use of intravenous antivenom should be administered as soon as possible and within 6 hours of the snakebite.³ The amount of antivenom vials to be administered varies between brands of antivenom, CroFab initial dosing is 4 to 6 vials and Anavip initial dosing is 10 vials to gain control of the envenomation progression, regardless of patient age.^{3,4} The evaluation of achieving control is the halting of edema in the affected extremity, a positive trend in improvement of coagulopathy, and resolution of dizziness, chills, paresthesia, fasciculations, lethargy, and altered mental status.^{2,3,4} If no improvement is seen within one hour of administration of Crofab or Anavip, antivenom dosing recommendations are to repeat 4 to 6 vials of CroFab and 10 vials of Anavip.^{3,4} In this study, there were no significant differences in the outcome of the total number of antivenom vials administered between the adult and pediatric groups. Additionally, there was no difference in anaphylactoid,

anaphylaxis, serum sickness, or other adverse reactions to antivenom administration in both the pediatric and adult groups.

A similar study evaluating clinical and laboratory parameters, Levine *M et al*, also showed that there was no significant difference in the total of number vials. The administration of antivenom is not dependent on the size or age of the patient, it is determined by the clinical severity of the envenomation itself. Thus, since both this study and Levine *M et al* show that pediatric and adult populations experience similar envenomation characteristics; it is important that a healthcare team evaluates the severity of envenomation of the individual patient and treat accordingly based on patient presentation and not solely on age or body weight.⁵

The laboratory findings, this study concluded, showed that there was no significant difference in the rate of initial hematologic (coagulopathy) toxicities between the pediatric and adult groups. Also, there was no significant difference in the occurrence of late coagulopathy, late coagulopathy that did not occur, or recurrent late coagulopathies. In contrast, Levine *M et al* showed that the rate of early hematologic toxicity was lower in the adult population than in the pediatric population, but there was no significant difference in the rate of early bleeding, and early thrombocytopenia. Early hypofibrinogenemia and early prothrombin time prolongation were more common in pediatric patients than in adult patients.⁵

Additionally, Levine *et al*, demographic data results showed that adult males and pediatric boys were more likely to sustain snakebite injury and envenomation.⁵ The location of the inflicted snake bite also differed between sex and age, but there was a higher incidence of upper extremity involvement among the adult male population, whereas lower extremity involvement was predominant among pediatric boys.⁵ Comparably, in this study demographic data also resulted with a higher incidence of injury and envenomations between adult males and pediatric males. Moreover, bite location in this study showed higher incidence of lower extremity involvement in both the pediatric and adult populations with no statistically significant difference between the two groups.

Thus, comparing this study with the limited amount of current data available, further demonstrates that characteristics, clinical treatments, severity, and outcomes in the pediatric populations do not significantly differ to the data found in the adult population. Taking these results into consideration, antivenom treatment should be approached by the severity of the envenomation in both pediatric and adult populations; underdosing a pediatric patient has the greatest risk of mortality and morbidity.

One limitation of this study is that it relies on the information contained within electronic medical records and the presumed reliability that the information is accurate. Another limitation is that the data is limited to exposures that are reported to and tracked by the APDIC, the data does not account for rattlesnake bites on a national level, instead these cases are limited to those reported in Arizona alone. Lastly, this study does not evaluate the varying effects between the 17 different venomous rattlesnake species native to the state of Arizona.

CONCLUSIONS

The purpose of this study was to compare characteristics, clinical treatments, severity, and outcomes in pediatric rattlesnake envenomation cases as compared to adults to better understand the current differences in envenomation management between the two populations. The findings are consistent with other published literature that show that there are no significant differences between pediatric and adult patients, when it comes to rattlesnake envenomations, treatment should be based on clinical severity regardless of patient age.

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TABLES AND FIGURES

Figure 1. Group envenomations meeting inclusion criteria into pediatric or adult groups

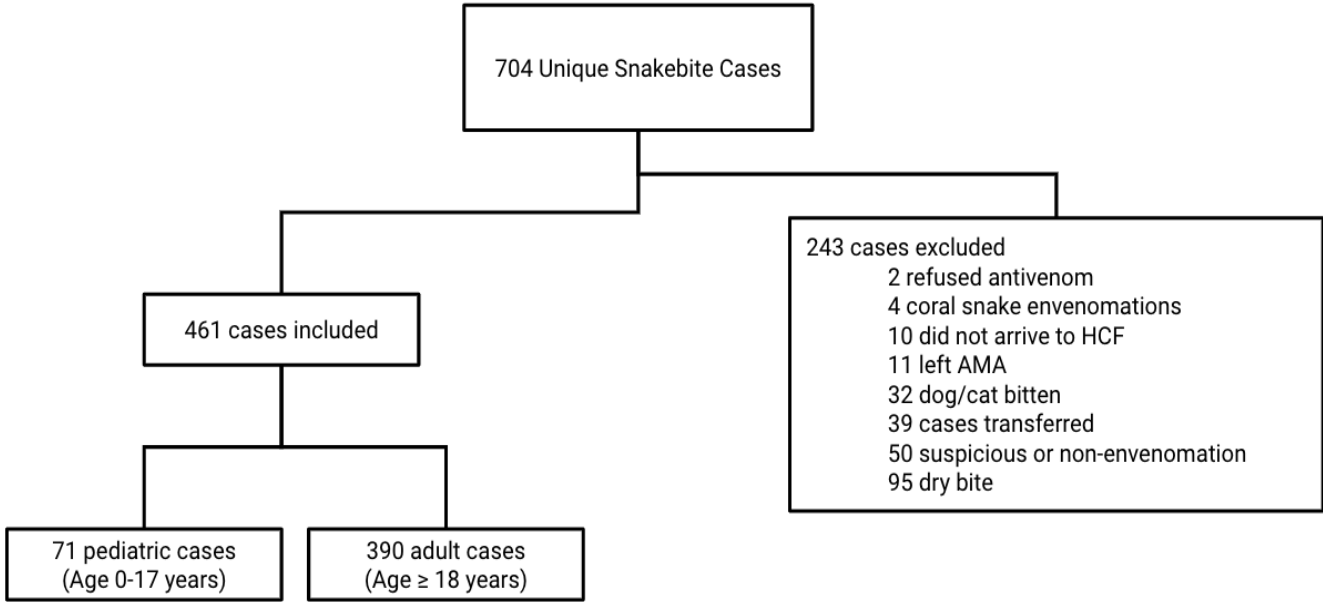


Table 1. Baseline Characteristics of Envenomation

Characteristics	Pediatrics	Adults	<i>p-value</i>
Number	71	390	
Gender (N; %)			
Male	41 (58%)	246 (63%)	0.426 ^a
Female	30 (42%)	144 (37%)	
Bite location (N; %)			
Dominant Hand	14 (20%)	122 (31%)	0.143 ^b
Non-dominant hand	9 (13%)	56 (14%)	
Other upper extremity	0 (0 %)	4 (1%)	
Lower extremity	48 (68%)	204 (52%)	
Face, neck, or other	0 (0%)	4 (1%)	
Fang-to-vial time in minutes (mean, SD)	157.3 (143.2)	187.2 (217.9)	0.631 ^a
Initial Coagulopathy (N; %)			
Present	34 (48%)	169 (43%)	0.517 ^b
Not Present	37 (52%)	221 (57%)	
Initial Level of Edema (N; %)			
None	2 (3%)	22 (6%)	0.398 ^b
5-7.5 cm	45 (63%)	257 (66%)	
< ½ of extremity	20 (28%)	101 (26%)	
> ½ of extremity	4 (6%)	10 (3%)	

^a*p-value is for a Fisher's Exact Test*

^b*p-value is for a Pearson Chi-Square Test*

Table 2. Antivenom Brands Administered

Brand	Pediatric	Adult	N
Anavip	51 (17%)	244 (83%)	295
Crofab	23 (16%)	123 (84%)	146
Combination of both Anavip and Crofab	3 (15%)	17 (85%)	20

Table 3. Primary and Secondary Outcomes

Outcome	Pediatrics	Adults	<i>p-value</i>
Primary Outcome			
Total number of anti-venom vials used (Mean, SD)	15.4 (57.5)	15.1 (5.87)	0.503 ^a
Secondary Outcomes			
More than 1 loading dose of antivenom needed (N;%)			
Yes	40 (56%)	183 (47%)	0.517 ^b
No	31 (44%)	207 (53%)	
Hematologic Platelets or Fibrinogen (N; %)			
>150	37 (52%)	214 (55%)	0.776 ^b
100-150	11 (16%)	72 (19%)	
50-100	8 (11%)	41 (10%)	
20-50	6 (8%)	31 (8%)	
Undetectable	9 (13%)	32 (8%)	
Neuro-Systemic Symptoms (N;%)			
Present	4 (6%)	33 (8%)	0.634 ^b
Not present	67 (94%)	357 (92%)	
Peak Edema (N; %)			
None	0 (0%)	1 (0.3%)	0.678 ^c
5 – 7cm	13 (18.2%)	92 (23.6%)	
< ½ of extremity	39 (54.9%)	209 (53.6%)	
> ½ of extremity	18 (25.4%)	77 (19%)	
Beyond extremity	1 (1.4%)	11 (3%)	
Blebs/Bullae (N; %)			
Present	18 (25%)	66 (17%)	0.096 ^b
Not present	53 (75%)	324 (83%)	
Abbreviated Snake Severity Score (Mean; SD)			
	3.4 (2.14)	3.1 (1.59)	0.373 ^a
Late Coagulopathy (N; %)			
None	45 (66%)	186 (60%)	0.513 ^c
Recurrent	15 (22%)	70 (23%)	
Delayed	8 (12%)	53 (17%)	
Adverse Reaction to Antivenom (N; %)			
None	69 (97.2%)	371 (95.1%)	0.417 ^c
Anaphylactoid	0 (0%)	7 (1.8%)	
Anaphylaxis	1 (1.4%)	1 (0.3%)	
Serum Sickness	1 (1.4%)	7 (1.8%)	
Other	0 (0%)	4 (1%)	

^a *p-value is for a Mann-Whitney Test*^b *p-value is for a Fisher's Exact Test*^c *p-value is for a Pearson Chi-Square Test*

Table 4. Characteristics of pediatric patients stratified by age

Characteristic	0-6 (n=32)	7-12 (n=18)	13-17(n=21)
More than 1 loading dose of antivenom needed (N;%)			
Yes	20 (62.5%)	10 (55.6%)	10 (47.6%)
No	12 (37.5%)	8 (44.4%)	11 (52.4%)
Initial Coagulopathy (N; %)			
Present	17 (53.1%)	8 (44.4%)	9 (42.9%)
Not Present	15 (46.9%)	10 (55.6%)	12 (57.1%)
Neuro-Systemic Symptoms (N;%)			
Present	2 (6.3%)	1 (5.6%)	67 (94.4%)
Not present	30 (93.8%)	17 (94.4%)	20 (95.2%)
Peak Edema (N; %)			
None	0 (0%)	0 (0%)	0 (0%)
5 – 7cm	4 (12.5%)	2 (11.1%)	7 (33.3%)
< ½ of extremity	15 (46.9%)	13 (72.2%)	11 (52.4%)
> ½ of extremity	12 (37.5%)	3 (16.7%)	3 (14.3%)
Beyond extremity	1 (3.1%)	0 (0.0%)	0 (0.0%)
Blebs/Bullae (N; %)			
Present	6 (18.8%)	4 (22.2%)	8 (38.1%)
Not present	26 (81.3%)	14 (77.8%)	13 (61.9%)
Late Coagulopathy (N; %)			
None	23 (71.9%)	11 (61.1%)	11 (61.1%)
Recurrent	6 (18.8%)	5 (27.8%)	4 (22.2%)
Delayed	3 (9.4%)	2 (11.1%)	3 (16.7%)
Adverse Reaction to Antivenom (N; %)			
None	31 (96.9%)	18 (100%)	20 (95.2%)
Anaphylactoid	0 (0%)	0 (0%)	0 (0%)
Anaphylaxis	0 (0%)	0 (0%)	1 (4.8%)
Serum Sickness	1 (3.1%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)

APPENDICES

Appendix A: Data Collection Form

*Assigned ID #	
Exclusions:	0=INCLUDE 1=Animal bitten 2=Suspicious or non-venom 3=Coral Snake 4=No arrival to HCF 5=Transferred case 6=Left AMA 7=dry bite 8 = patient age >89 years
Date (mm/yyyy):	
Time of bite (am/pm):	
Age (years):	
Sex:	Male=1 Female=2
Bite Location on body:	Dominant hand=1 Nondominant hand=2 Other upper extremity=3 Lower extremity=4 Face, neck, or other=5
Zip code of bite site or zip ^a HCF Presentation	
City	
County	
Presence of Edema	None=0 W/in 5-7.5cm=1 Under half extremity=2 Over half extremity=3 Beyond extremity=4

Fang marks	0=unclear 1=1 fang 2=2 fang 3=3 or more fang marks (bitten twice)
Anti-Venom Brand	None=0 Crofab=1 Anavip=2 Combo=3
Start Time 1st Vial	
Time from bite to 1st vial ^b AV (HH:MM)	
Time to bite (converted to minutes)	
More than one loading dose:	No=0 Yes=1
Total Vials received:	
Reaction to antivenom:	None=0 Anaphylactoid=1 Anaphylaxis=2 Serum sickness=3 Other=4
Initial Platelets	
Peak Platelets	
Trough Platelets	
Discharge Platelets	
Initial Fibrinogen	
Peak Fibrinogen	
Trough Fibrinogen	
Discharge Fibrinogen	
Initial Coagulopathy Present	0=no 1=yes

Hematologic Platelets or Fibrinogen	Above 150=0 150-100=1 100-50=2 20-50=3 Undetected=4
Systemic symptoms (excluding coagulopathy)	None=0 Nausea=1 Vomiting=2 Diarrhea=3 Hypotension=4 Cranial abnormalities=5 Other=6
Neuro-Systemic	No=0 Present=1 dizziness chills paresthesia fasciculations lethargy, AMS
Local Effects: Peak Edema	None=0 W/in 5-7.5cm=1 Under 1/2 extremity (7.5-50cm)=2 Over 1/2 extremity (50-100cm)=3 Beyond extremity (>100cm)=4
Bleb/Bullae	0=none 1=clear 2=blood
°ASSS (total N + L + H + B)	
Late Coagulopathy	0=none 1=recurrent 2=delayed 3=lost outpatient
Trough Platelets Outpatient	Does not include d/c values
Trough Fibrinogen Outpatient	Does not include d/c values

Additional labs required	No=0 Yes=1 N/A
Retreatment required	No=0 Yes=1 N/A

^aHCF = *Healthcare Facility*

^bAV = *Anti-Venom*

^cASSS= *Abbreviated Snakebite Severity Score*