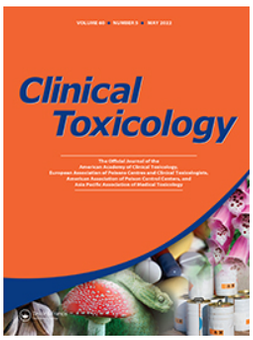

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Late hemotoxicity following North American rattlesnake envenomation treated with crotalidae immune F(ab')$_2$ (equine) antivenom and crotalidae immune polyvalent Fab (ovine) antivenom reported to the North American Snakebite Sub-registry

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CLINICAL RESEARCH

Late hemotoxicity following North American rattlesnake envenomation treated with crotalidae immune F(ab')$_2$ (equine) antivenom and crotalidae immune polyvalent Fab (ovine) antivenom reported to the North American Snakebite Sub-registry

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ABSTRACT

Introduction: Late hemotoxicity is common following rattlesnake envenomation treated with crotalidae immune polyvalent Fab (ovine) (FabAV). Initial clinical trials showed crotalidae immune F(ab')2 (equine) (Fab2AV) to be superior to FabAV in preventing late hemotoxicity, but this effect has not been demonstrated in broader populations. This study investigated late hemotoxicity in patients receiving Fab2AV or FabAV after rattlesnake envenomation.

Methods: This is a retrospective analysis of prospectively collected data from patients with snakebite reported to the ToxIC North American Snakebite Registry (NASBR) between January 1, 2019, and December 31, 2020. Inclusion criteria were rattlesnake envenomation and administration of antivenom. Patients were excluded if they received more than one type of antivenom. The primary outcome was occurrence of late hemotoxicity (platelets $\leq$120 k/mm^3 or fibrinogen $\leq$170 mg/dL) in patients receiving Fab2AV and FabAV. Data collected included demographics, envenomation characteristics, laboratory values, and treatment administered. Statistics including *t*-test and Fisher's exact test were used.

Results: A total of 201 rattlesnake envenomated patients receiving antivenom were reported to the NASBR in the study period; 144 were included. 49 received Fab2AV alone, 45 received FabAV alone and 50 received both antivenoms. Baseline patient and envenomation characteristics were similar between the groups. Late hemotoxicity occurred in 2/49 patients in the Fab2AV group (4% (95% CI 0.7–12.6)) and in 19/45 patients in the FabAV group (42% (95% CI 28.4–59.0); absolute risk reduction 39.1% (95% CI 21.2–46.2) ($p = 0.001$). On follow up, 0 patients (0%) receiving Fab2AV were retreated with antivenom; 4 patients (9%) receiving FabAV were retreated ($p = 0.049$).

Conclusions: In the North American Snakebite Registry, late hemotoxicity was less common in rattlesnake envenomated patients treated with Fab2AV compared to FabAV.

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Rattlesnake; envenomation; antivenom; hemotoxicity

Introduction

Of the 5,000 venomous snake bites reported annually to United States (US) poison centers, rattlesnake envenomations are associated with the most significant morbidity [1]. Local tissue swelling and hemotoxicity, in the form of thrombocytopenia and coagulopathy, characterize the envenomation syndrome typically seen after rattlesnake bites. First-line treatment for rattlesnake envenomations is antivenom [2]. From 2000–2018, the only commercially available antivenom in use was Crotalidae Immune Polyvalent Fab antivenom (ovine) (FabAV). Though safe and very effective against initial hemotoxicity, the imbalance of FabAV's short half-life compared to the longer half-life of rattlesnake venom components allows for new occurrence or reemergence of hemotoxicity (late hemotoxicity) after the patient is discharged from the hospital [2]. These properties of FabAV prompted recommendations for maintenance dosing of antivenom at the time of initial treatment, and multiple follow up visits after discharge to assess for late hemotoxicity [3]. Late hemotoxicity can require readmission to the hospital and retreatment with antivenom. Late bleeding events can also occur [2]. This clinical challenge lead to investigations into a new antivenom, Crotalidae Immune F(ab')$_2$ (Equine) Antivenom (Fab2AV).

In 2015, a phase-3 randomized clinical trial found (Fab2AV) to be as effective against initial hemotoxicity as FabAV, but with fewer cases of late hemotoxicity [4]. Fab2AV did not become available for clinical use until 2018 and data on occurrence of late hemotoxicity in broader and larger populations are thus far very limited [5,6]. How these initial data translate into real world management of rattlesnake envenomation is not yet clear. Could follow-up visits to

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assess for late hemotoxicity be reduced or eliminated? Does the reduction in occurrence of late hemotoxicity translate into fewer late bleeding events? More information is needed.

This study aims to compare occurrence of late hemotoxicity after administration of Fab2AV verses FabAV in rattlesnake envenomated patients reported to the North American Snakebite Registry (NASBR), a Sub-Registry of the Toxicology Investigators Consortium (ToxIC), over a two-year period.

Methods

This is a retrospective analysis of prospectively collected data from patients with snakebite reported to the ToxIC NASBR Registry between January 1, 2019 and December 31, 2020.

The ToxIC Registry was established in 2010 by the American College of Medical Toxicology (ACMT) as a novel prospective multicenter toxico-surveillance and research tool. It records consecutive patients cared for at the bedside or *via* telemedicine by medical toxicologists at each of more than fifty sites across the US that actively contribute patients to the Registry. The methods and scope of the ToxIC Registry has been previously reported [7].

ACMT's ToxIC NASBR Sub-Registry gathers detailed prospective information regarding snake bite, clinical effects of envenomation, and response to treatment for patients who receive bedside or telemedicine care from medical toxicologists across the United States. General best practice guidelines exist; however, follow-up visits after rattlesnake envenomation are not standardized for the Sub-Registry. Variation between individual sites for follow-up visit number and timing exist. The Sub-Registry was established in 2013.

Patients with rattlesnake envenomation who received antivenom (Fab2AV or FabAV) were included. Patients were excluded if less than one set of follow-up laboratory values was obtained. Patients were also excluded from primary analysis if more than one type of antivenom was given to a single patient. Data collected included demographics, envenomation characteristics, laboratory values, bleeding complications, and treatment administered. Statistics including *t*-test, Mann–Whitney U-test and Fisher's exact test were used. Patients receiving both types of antivenom were examined separately using descriptive statistics for comparison purposes.

Hemotoxicity was defined as the presence of either thrombocytopenia (platelets $\leq$ 120 k/mm^3) or coagulopathy (fibrinogen $\leq$ 170 mg/dL), consistent with previous publications [6]. Late hemotoxicity was defined as inclusive of both delayed and recurrent hemotoxicity. Delayed hemotoxicity described thrombocytopenia or coagulopathy detected on follow-up but not present on initial hospitalization. Recurrent hemotoxicity described thrombocytopenia or coagulopathy that was present on initial hospitalization, improved with treatment, and then was detected again on follow up labs.

Bleeding events were defined by the Registry as nuisance (gingival, epistaxis, oozing from puncture site, or other) or major (gastrointestinal, intracranial, retroperitoneal, or other).

Protein content for antivenom was calculated based on values of 120 mg/vial for Fab2AV and 1000 mg/vial for FabAV.

ToxIC has been reviewed by the Western Institutional Review Board (IRB) and operates in pursuant to the approval of the participating site IRBs. All data collected by ToxIC are deidentified and is compliant with the Health Insurance Portability and Accountability Act.

Results

Two hundred and one patients with rattlesnake envenomation receiving antivenom were reported to the NASBR between January 1, 2019, and December 31, 2020. After exclusion due to lack of at least one follow-up laboratory value documented, 144 patients were included. Of those included, 94 received only one type of antivenom and were included in final analysis; 49 received only Fab2AV and 45 received only FabAV. (Figure 1). Fifty patients received both Fab2AV and FabAV and were examined separately. Baseline patient characteristics were similar including age, gender, and use of home antiplatelet or anticoagulant medications.

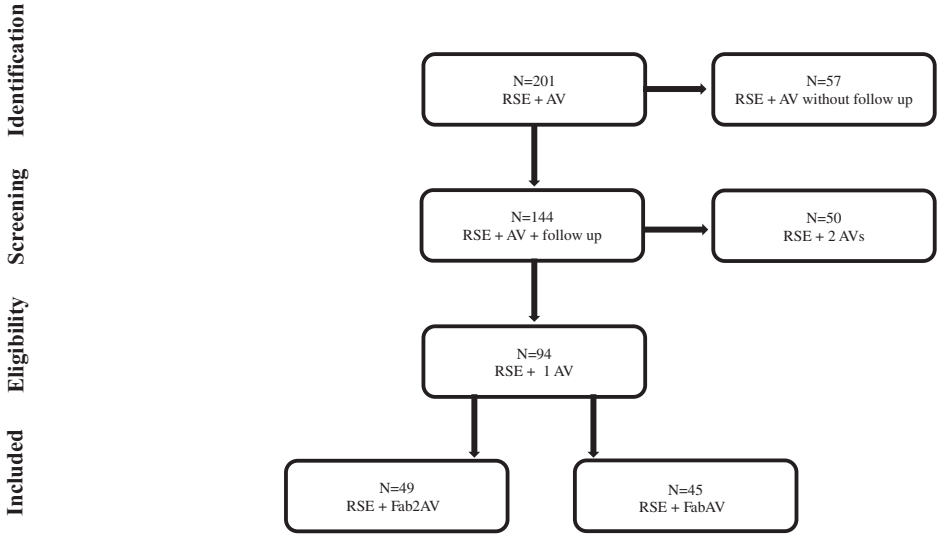

Figure 1. Patient Identification and Inclusion. RSE: rattlesnake envenomation. AV: antivenom

Most patients treated with Fab2AV were located in Arizona ($N = 42$, 86%) or New Mexico ($N = 5$, 10%) compared to 40% ($N = 18$) in Arizona and 22% in California ($N = 10$) for those treated with FabAV ($p < 0.001$). Other envenomation characteristics were similar including bite location, presence of hemotoxicity, swelling or systemic toxicity during the initial hospitalization. Systemic toxicity was defined as presence of hypotension, diarrhea, or emesis (Table 1).

For patients receiving a single type of antivenom, Fab2AV patients received more vials compared to FabAV patients (18 vs. 12 $p < 0.001$). Antivenom protein content in grams administered was lower in the Fab2AV group 2.4 (1.2–3.1) vs 13.6 (8.0–17.5); $p < 0.001$. Time to antivenom administration was similar between the two groups (Table 2).

Late hemotoxicity occurred in only two (4%) patients receiving Fab2AV compared to 19 (42%) receiving FabAV (absolute risk reduction 39.1% (95% CI: 21.2–46.2) $p < 0.001$) (Table 3). Five (11%) patients in the FabAV group were readmitted due to late hemotoxicity. Four (9%) FabAV patients were retreated with antivenom; no patients (0%) in the Fab2AV group were retreated on follow up ($p = 0.049$). One patient receiving Fab2AV alone was readmitted for non-hematologic concerns including wound debridement and incision and drainage for wound infection, ultimately requiring skin graft. There was no difference in late bleeding events between those treated with Fab2AV ($N = 4$; 33%) vs FabAV ($N = 2$; 22%) ($p = 0.618$). The four late bleeding events in Fab2AV patients were all described as nuisance bleeding. This included oozing from blebs in the patient readmitted for a wound infection, epistaxis in two patients, and oozing from puncture site in one patient. None required treatment. The two bleeding events in FabAV patients were nuisance bleeding events. One was bleeding from an unroofed bleb requiring bandage placement and one was epistaxis. No blood products were administered to any patient receiving Fab2AV compared to one patient (2.2%) in the FabAV group ($p = 0.479$). Hospital length of stay did not differ between the two groups; most patients' hospital length of stay was $\leq$48 h (Fab2AV 67% vs FabAV 76%; $p = 0.672$).

Fifty patients received both Fab2AV and FabAV. Six (12%) of these patients developed late hemotoxicity; five of which were recurrent hemotoxicity (83%). All were given FabAV as the initial antivenom treatment, followed by Fab2AV. In this group, the average total Fab2AV dose was 25 vials (range 12–38 vials), and average total FabAV dose was eight vials (range 6–15 vials). All late hemotoxicity was thrombocytopenia. None of these patients were readmitted or retreated with antivenom.

Discussion

This NASBR ToxIC Registry study found a very low occurrence of late hemotoxicity in patients receiving exclusively Fab2AV, consistent with the phase-3 trial [4] and with early clinical data from regional centers in Arizona and New Mexico [5,6]. Importantly, this study was representative of a large national registry and was not limited to a single geographic location or medical center. Outside of clinical trials, this is the largest comparison study of Fab2AV and FabAV to date. This study thus broadens the generalizability and confirms previous observations that late hemotoxicity occurs less commonly in patients treated with Fab2AV than in those receiving FabAV alone. Both Fab2AV patients with late hemotoxicity reported in this study were previously identified in the publication from Arizona [6], a contributing site to NASBR. No new occurrence of late hemotoxicity associated with Fab2AV were discovered in this study.

In both Fab2AV patients with late hemotoxicity, it was characterized as isolated thrombocytopenia, compared to a more mixed picture of late thrombocytopenia (58%) and coagulopathy (32%) or both (11%) in the FabAV group on

Table 1. Baseline demographic and envenomation characteristics of patients receiving Fab2AV vs FabAV.

	Fab2AV (%)	FabAV (%)	*p* value
Number of cases	49	45	—
Age (yrs) [median (IQR)]	38 (22–58)	45 (20.5–62.5)	0.319
Gender			
Male	34 (69)	31 (69)	0.958
Home medications			
Antiplatelet medications	1 (2)	5 (11)	0.101
Anticoagulant medications	2 (4)	3 (7)	0.668
Top Participating Sites			
Arizona	42 (86)	18 (40)	<0.001
California	1 (2)	10 (22)	
Colorado	1 (2)	9 (20)	
New Mexico	5 (10)	5 (11)	
Other	0 (0)	3	
Bite location			0.835
Lower extremity bite	29 (59)	25 (56)	
Upper extremity bite	20 (41)	20 (44)	
Trunk or face bite	0 (0)	0 (0)	
Initial clinical presentation			
Swelling	49 (100)	43 (96)	0.224
Hemotoxicity	17 (35)	14 (31)	0.827
Systemic toxicity	4 (8)	8 (18)	0.167

Table 3. Late hemotoxicity for patients receiving Fab2AV vs FabAV.

	Fab2AV (%)[a]	FabAV (%)[a]	*p* value
Late hemotoxicity	2 (4)	19 (42)	<0.001
Thrombocytopenia	2 (100)	11 (58)	
Coagulopathy	0 (0)	6 (32)	
Combined	0 (0)	2 (11)	
Delayed hemotoxicity	1 (2)	14 (31)	<0.001
Thrombocytopenia	1 (100)	10 (71)	
Coagulopathy	0 (0)	4 (29)	
Combined	0 (0)	0 (0)	
Recurrent hemotoxicity	1 (2)	6 (13)	0.050
Thrombocytopenia	1 (100)	2 (33)	
Coagulopathy	0 (0)	3 (50)	
Combined	0 (0)	1 (17)	

a: Percentages for thrombocytopenia, coagulopathy, and combined hemotoxicity are expressed as percent of the total late, delayed, and recurrent hemotoxicity subgroups.

Table 2. Characteristics of Antivenom Administration for Patients Receiving Fab2AV vs FabAV.

	Fab2AV	FabAV	*p* value
Mean time to antivenom (hours)	7.4	5.8	0.290
Median (IQR) vials AV	18 (10–26)	12 (8–20)	<0.001
Median (IQR) protein content AV (grams)	2.4 (1.2–3.1)	13.6 (8.0–17.5)	<0.001

follow-up. Small numbers prevent any conclusions from this discrepancy and the clinical implications are not clear. Notably, however, fewer ($N = 0$, 0%) patients receiving Fab2AV were retreated for hematologic parameters compared to the group treated with FabAV ($N = 4$, 9%) ($p = 0.049$), highlighting the minor clinical significance of late hemotoxicity the patients treated with Fab2AV.

Late hemotoxicity in patients treated with FabAV, can not only require readmission retreatment with antivenom but can be severe and life threatening. Retreatment with FabAV, unfortunately does not always resolve late hemotoxicity [2,8]. Associated serious bleeding events and deaths have been reported [9,10]. This risk led experts to recommend a mandatory follow up period for rattlesnake envenomated patients treated with FabAV [3]. Included in this follow-up period are restrictions on physical activity, holding of antiplatelet and anticoagulant medications, and repeat laboratory testing twice in the week following hospital discharge. Initial data and personal experience have led some sites to reconsider the follow-up period in patients treated with Fab2AV. A single follow-up visit to assess for late hemotoxicity after Fab2AV treatment is currently common practice in certain locations. The low rate of late hemotoxicity, and the absence of clinically significant late hemotoxicity in this study serves as one piece of evidence to support reevaluation of the follow up policy in patients receiving only Fab2AV in the proper clinical setting. Larger numbers may be needed for more universal policy changes. Late bleeding events after rattlesnake envenomation are uncommon, but can be severe, and additional studies are needed to better evaluate occurrence of late bleeding events in patients treated with Fab2AV. Notably, in this study, there was no difference in late bleeding events in patients treated with Fab2AV or FabAV, and all were classified as nuisance bleeding.

Interestingly, in patients receiving both Fab2AV and FabAV, late hemotoxicity appeared to be less common than that in patients treated with FabAV alone (12% vs 42%). Late hemotoxicity was also characterized as isolated thrombocytopenia, similar to the Fab2AV only group. These patients on average received higher relative doses of Fab2AV compared to FabAV and all were given FabAV as their first antivenom. The importance of such factors in possible protection against late hemotoxicity, including order of administration of different antivenoms and relative doses, remains to be seen. This study was not designed to compare patients receiving both types of antivenom to Fab2AV or FabAV alone and further studies are needed.

This study found a significant difference in number of vials of antivenom administered between the two antivenom groups. Given the initial dose of Fab2AV is higher than that of FabAV (10 vials compared to 6 vials), this finding is not surprising or necessarily of clinical significance. Additionally, the protein content of Fab2AV (120 mg/vial) is lower than that of FabAV (1000 mg/vial), and though the Fab2AV group received more vials of antivenom, the protein content (i.e. effective drug) received was lower. Other studies investigating the difference in *doses*, not vials, of Fab2AV and FabAV are ongoing and may have more significant implications regarding cost and hospital length of stay.

Morbidity after rattlesnake envenomation is not limited to hemotoxicity. This study did not assess all potentially serious outcomes after rattlesnake envenomation such as tissue toxicity, neurotoxicity, and hypersensitivity reactions.

Limitations in this study include those inherent in voluntary reporting to a registry database. The NASBR undergoes rigorous quality assurance processes to both identify and correct errors or omissions in data entry, however it is possible that all errors were not identified. Although these data are representative of a large national registry inclusive of patients from multiple states, the majority of patients receiving Fab2AV occurred in Arizona. Species specific differences in venom or regional differences in treatment practices could have influenced the outcome. This study only included patients envenomated by North American rattlesnakes and results cannot be extrapolated to non-native species or similar species outside of the United States.

Conclusion

In patients envenomated by rattlesnakes reported to the NASBR ToxIC Sub-Registry, late hemotoxicity in patients treated with Fab2AV was less common than in those treated with FabAV. Additional studies are needed to evaluate late hemotoxicity in patients treated with multiple antivenoms.

Previous presentations

This work was previously presented as an abstract platform presentation at ACMT's Annual Scientific Meeting 2021 virtually.

Disclosure statement

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