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Research Article

Apparent Efficacy of Low-Dose Constant-Infusion Crotalidae Antivenom for Control of Defibrinogenation Recurrence Syndrome Following Envenomation by the Eastern Diamondback Rattlesnake (Crotalus adamanteus)

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Abstract

Background: Eastern Diamondback rattlesnake bites produce coagulopathy in the bite victims. The syndrome is treated with antivenom called Crotalidae Polyvalent Immune Fab. However following resolution of coagulopathy with the antidote, and sometimes days later, fibrinogen drops to very low levels. Rare bleeding may occur due to this recurrent defibrinogenation syndrome. No guidelines exist at this time of how these patients should be treated. However, many centers repeat the initial treatment protocol using another 6-18 vials of antidote acquiring significant treatment costs.

Methods: We analyzed all cases treated at the University of Florida between 2013 and 2014 for the rattlesnake bites. All cases were treated with Crotalidae Polyvalent Immune Fab as recommended per manufacturer recommendations upon initial presentation. However, upon the recurrence of defibrinogenation, we administered the antivenom 1 vial diluted in 250 ml of normal saline and administered by continuous IV infusion over 2 to 12 hours tapered over 2 to 3 days. The patients and their coagulation labs were monitored at least daily during the recurrence of the defibrinogenation.

Results: We identified 5 cases treated for Eastern Diamondback snake bites. All cases had recurrent defibrinogenation syndrome and treated as described above. All patients had normalization in their fibrinogen levels with the reinstitution of the antidote. Additionally, none of them had any further bleeding. No chills, fevers or cloudiness of solution reported during the continuous antidote administration.

Keywords: Crotalidae Polyvalent Fab, Eastern Diamondback snake, treatment, defibrinogenation

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Consent: We confirm that the patients have given the informed consents for the case reports to be published.

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Background

About 50 to 60 proteinaceous substances comprise North American pit vipers' venom, which evolved as ex vivo digestive aids. Each species' venom contains a protein pattern unique to that species yet some proteins are shared among many or most pit viper venoms.(1,2)

Some animals can develop immunity to these venoms by production of antibodies in the form of immunoglobulins. The immunoglobulins from these animals are harvested, purified, and manipulated into therapeutic antivenoms, which, when injected into humans, provide immunotherapy. The antivenom neutralizes most but not all of the offending proteins in the event of envenomation.

Sheep produce most of currently available antivenom by repeat inoculation of several species of snake venoms including the Eastern diamondback rattlesnake (Crotalus adamanteus), western diamondback rattlesnake (Crotalus atrox), Mojave rattlesnake (Crotalus scutulatus) and water moccasin (Agkistrodon piscivorus). After recovery of the immunoglobulins, the Fab fragments are modified from host IgG molecules by removal of the Fc component in order to minimize allergic reactions. This ovine antibody is called Crotalidae Polyvalent Immune Fab (ovine) (CroFab®) (Protherics, Nashville TN, USA) and hereafter referred to as FabAV in this report.

FabAV provides rescue from the majority of manifestations of envenomation syndrome elicited by bites of pit vipers native to the United States.

The primary venom protein responsible for the characteristic coagulation perturbations by Eastern diamondback rattlesnakeis crotalase, the thrombin-like enzyme having alpha-fibrinogenase activity which causes incomplete lysis of fibrinogen. (3) Fibrinogen is rapidly cleared from circulation upon envenomation, usually within 1-2 hours of envenomation. Additionally,even trivial envenomation (4)can result in extreme hypofibrinogenemia to the extent that more global coagulation tests, such as prothrombin time (PT) and partial thromboplastin time (PTT) are rendered "nonclottable" despite the lack of perturbations in the proteins of the clotting cascade with the exception of near total lack of fibrinogen, which is manifested by nonclottable PTs and PTTs when the fibrinogen level falls to less than approximately 50mg/dL. (3)Additionally,FabAV rapidly curtails crotalaseactivity as evidenced by reversal of this extreme hypofibrinogenemia and normalization of subsequent PTs and PTTs within hours of its administration.

Clinical investigation during the research and development phase of FabAV in premarketing studies discovered previously unappreciated recurrence syndromeusing a predetermined panel of laboratory studies.(5) "Recurrence syndrome" is understood to be a late manifestation or reappearance of any manifestation of envenomation. Recurrence as encountered clinically is primarily either extreme hypofibrinogenemia and/or thrombocytopenia occurring without evidence of any other recurrences of the envenomation syndrome, in that signs and symptoms such as pain, swelling, nausea, vomiting, hypotension, muscle fasciculation, and other symptoms are only rarely encountered following the administration of 6-18 vials of FabAV in the first 24-36 hours of treatment.(6)

In the defibrinogenation recurrence syndrome, fibrinogen levels may drop from approximately normal levels to levels <50mg/dL as frequently as in 50% of patients who had been effectively treated with FabAV. Usually this is discovered 48-72 hours after the last infusion of FabAV.(5,7) The PT and PTT typically appear prolonged, even "nonclottable," as a reflection of this very low fibrinogen level. Nearly all reports of this recurrence noticed the near total absence of return of any obvious or even subtle

hemorrhage which has caused considerable discussionregarding the importance or lack of importance of this "recurrence syndrome" as well as how to manage it. (6) Indeed, it has been stated there is no standard of care how to, or even if, any therapeutic actions need to be taken upon discovery of evidence of the defibrinogenationrecurrence syndrome. (8) On the other hand, Lavonis and colleagues (6) do report at least four cases in which hemorrhagic events occurred concurrently withthe reappearance of hypofibrinogenemia although causation cannot be directly incriminated. One case of fatal intracranial hemorrhage was reported from this institution. (9) It remains unsettled whether hypofibrinogenemic recurrence is strictly a laboratory phenomenon or a meaningful clinical occurrence.

This unexpected return of coagulopathy has caused many treaters, particularly those not experienced in this clinical situation, to assume that these findings represent a total collapse of control of the entire envenomation syndrome which results in their "starting over" with dosages and frequency of FabAV administration mirroring those used in their initial treatment. With further experience, as outlined in several of these papers,(5-9)it was soon realized that even administration of small amounts of FabAV would quickly reverse the hypofibrinogenemia but whether that correction translates into in decreased hemorrhage as well as improved morbidity and mortality is as yet unknown. (5,6,9)

In early 2013, we became aware of a report by Bush and colleagues (10) regarding their experience in treating five victims of hematologic recurrence syndrome (four with thrombocytopenia and one with hypofibrinogenemia) following initial control of the patient's acute envenomation syndrome using high-dose bolus administration in the usual fashion. They reported using a much lower dose to address this recurrence syndrome using a continuous (as opposed to bolus) infusion. This approach was rational because it allowed 1) titration of dose to match the observed effects; 2) allowing significantly fewertotal administered vials with subsequent decrease in antivenom exposure and well as savings in cost and arguably increased safety; and 3) this method directly addressed the putative pathophysiology supporting the concept of recurrence syndrome, namely that some 48-72 hours after the cessation of typicalinitial bolus treatment, small amounts of unbound venom are thought to percolate up from the wound and into the circulation at a time that there was no further circulating antivenom to neutralize these agents owing to the brief half-life of the FabAV. (5,11,12) This notion requires that the amount of venom is too small to cause return of other signs and symptoms of the envenomation syndrome, yet even tiny amounts of unbound crotalase can rapidly produce severe hypofibrinogenemia that is easily reversed by continuous infusion of small amounts ofFabAV.

Methods

After communicating with these clinicians, we wished to employ this approach with several of the more severe Eastern diamondback rattlesnake envenomations we encounter. We were aware of issues involving uncertainty of the sterility and stability of prepared FabAV solution but, having regularly and repeatedly witnessed reinstitution of massive doses of Fab using bolus administration by practitioners who thought this was a relapse of the entire envenomation syndrome, this new approach seemed to be more desirable. Here we report our experience in treating patients severely envenomated by Eastern diamondback rattlesnakes as well assubstantiatingthose observations of Bush and colleagues. (11)

We treated these five cases herein reported which represented the most severe envenomations by Eastern diamondback rattlesnakes in patients who were initially treated in (or soon transferred to) this institution over the warmer months of 2013 and 2014. This method has not been used by us in less

severely envenomated patients bitten by Eastern diamondback rattlesnakes or even contemplated being used for victimsenvenomated by pygmy rattlesnakes or water moccasins. Similarly, we did not preemptively use this method even in severe cases of envenomation prior to their development of recurrence syndrome with the possible exception of Cases 4 and 5, owing to our successes and experience gained by treating Cases 1-3. However, we did employ this continual infusion of decreasing doses of FabAV once the recurrence was identified by the return of severe hypofibrinogenemia. The FabAV was reconstituted with 250 ml of normal saline and administered by continuous infusion over 2 to 12 hour periods. In some instances, while dosage and frequency remained as ordered, pharmacy service insisted on a maximal 4-6 hr infusion time rather than a continual 12-24 hr infusion time.The doses were tapered over 2-3 day period. No solution cloudiness, fevers or chills were reported with longer infusions of the FabAV.

At all times we believed that our actions were based on our understanding of the syndrome, the apparent high degree of efficacy of low-dose continuous infusion of FabAV, and all were done in what we held to be in the patients' best interests. This case series was approved by University of Florida IRB. Patients were contacted by phone and agreed to our reporting their results. Upon subject consent, each chart was reviewed for clinical events, laboratory date and outcomes as approved by the IRB. A total of 6 patients were contacted and 5 consented to participate and are herein reported.

Results

Our results are presented in Table 1. Figure 1 is a graphic display of events of Case 3 which is representative of the key events of all five cases. The order in which these patients are reported in Table 1 represent our growing experience over 2013 and 2014 which allowed and justified our progressively briefer and lower doses of constant infusion FabAV. These successes resulted in our approach to Case 4 in which we anticipated recurrence and greatly curtailed it using this method, and to Case 5, in which recurrence was aborted quickly as it was anticipated to be evolving. Each of these two later cases received a total of only 6 vials over the last 3 days of treatment which in each case was on the first day of recurrence to receive 1 vial every 8 hours; on the second day, 1 vial every 12 hours; and on the third and last day, 1 vial over 24 hours, after which the fibrinogen level was followed for a day or so in order to warrant discharge.

All five patients were confirmed to have been envenomated by Eastern diamondback rattlesnakes. Note that four of these five patients were bitten in proximal large muscles which is an established risk factor for rapid, severe envenomation syndrome and initially all were treated with higher than usual doses of FabAV. Despite their blatant coagulopathy, hemorrhage to include several invasive procedures was minimal. The acute envenomation syndrome had been rapidlycontrolled in all five cases in the first 6-12 hours of care using typical bolus therapy. Our hematology service was not frequently consulted until the defibrinogenation recurrence syndrome became manifest and our hematologic experience was requested. None experienced significant hemorrhage. Additionally, we do not encounter durable or meaningful thrombocytopenia in Eastern diamondback rattlesnakes envenomation either initially or at recurrence, although the rattlesnake species encountered by patients reported Bush et al (10) in the Western US produce more thrombocytopenia yet less severe hypofibrinogenemia than we experience with bites from the Eastern diamondback rattlesnakes. (3,4)

Table 1 Case Summaries

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/Sex	70 M	20 M	12 M	19M	50M
Bite site	Calf	Ankle	Thigh	Thigh	Proximal arm
Bleeding	None	Minimal oozing at PICC line insertion site	Large thigh hematoma	Minimal oozing from bite site knife wound	Minimal oozing from cricothyroidotomy site
Initial studies					
PT, secs	19.2	>150	>50	34	>150
PTT, secs	30	>240	>240	49	>240
Fibrinogen level, mg/dL	<35	<35	<35	<35	<35
Platelet count, in 1000s	39	39	216	225	20
Initial treatment					
Total # vials	32	29	54	23	43
Over # days	3	3	8	2	6
Fibrinogen level, mg/dL at end of treatment	248	250	190	200	110
Interval till recurrence Days	3	2	2	+1Q12H x 2 with no recurrence	1
Fibrinogen level, mg/dL at recurrence	<35	<35	38	N/A	110
Recurrence treatment	20	8	6	N/A	6
Total # vials	5	3	3	N/A	3
Over # days	500	210	140	N/A	361
Fibrinogen level, mg/dL at termination					
Follow-up at 2-4 weeks	140	151	125	“Normal”	“Normal”
Fibrinogen levels, mg/dL	“Normal”	“Normal”	“Normal”	“Normal”	“Normal”
Platelets					

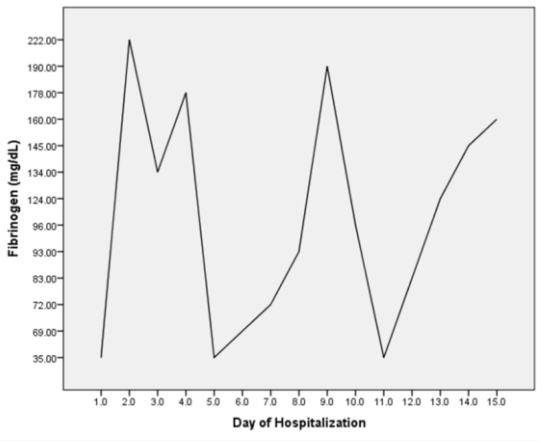

Figure 1 Typical improvement with early treatment followed by recurrent defibrogenation days later

Conclusion

These data are consistent with the hypothesis that hematologic recurrence syndrome seems easily controlled with low-dose constant infusion of FabAV over a 2-3 day period. Thus we agree with Bush and colleagues (10) that this is a feasible approach. Additionally, this approach seems to decrease total FabAV exposure. Obviously another interpretation of these data could be that all these patients were almost at a point in their hospitalizations that they were near spontaneous cure, even without any further administration of FabAV.

This small titered-to-effect dose appears safe, especially when compared to the previously used method which reflects "starting over" using large and frequently administered bolus therapy with FabAV. Thus we have saved an estimated 20-40 extra vials of FabAV per patient, as well as an uncertain amount of blood products,particularly FFP and cryoprecipitate, which we did not employ in any of these patients for this late recurrence syndrome. We agree with Bush et al (10) that we cannot claimsuperiority or even causation in an evidence-based manner without a randomized controlled trial. Reports of further experience in this area by othertreaters are warranted.

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