BRIEF REPORT

Rebound Coagulopathy in Patients With Snakebite Presenting With Marked Initial Coagulopathy

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Objective.—An estimated 70% of patients with pit viper snakebites require antivenom to treat serious complications such as coagulopathy. Evidence-based guidance is limited for the appropriate administration of Crotalinae Polyvalent Immune Fab (FabAV) and the duration of laboratory follow-up. The objective of our study was to assess the incidence of marked and recurrent envenomation coagulopathy at our trauma center and identify practice patterns that may prevent serious complications.

Methods.—A retrospective case review was conducted over a 3-year period on patients treated for symptomatic snakebite injury. Case records were reviewed for the inclusion criteria of international normalized ratio (INR) greater than 2.0. The exclusion criterion was limited to patients receiving anticoagulant therapy.

Results.—In all, 61 patients were identified on retrospective chart review and 3 patients (4.9%) met inclusion criteria. Two of the 3 patients had marked rebound coagulopathy requiring readmission and additional treatment. In our small series, 2 patients presenting after crotaline envenomation with increased INR (>6.0), decreased fibrinogen (<60 mg/dL), and decreased platelet count ($<100,000$ /mL) had recurrent coagulopathy and were asymptomatic, and recurrence was noted only with follow-up laboratory testing. All patients responded positively within a matter of hours to repeat FabAV administration, with resolution of rebound coagulopathy.

Conclusions.—We recommend periodic monitoring of patients with increased INR, decreased fibrinogen, and decreased platelet count. Patients should be monitored for 10 to 14 days after envenomation to identify asymptomatic rebound coagulopathy. Prompt readministration of FabAV appears to correct the coagulopathy.

Key words: coagulopathy, Crotalinae, envenomation, FabAV, hypersensitivity

Introduction

Most venomous snakebites in North America are inflicted by the Crotalinae subfamily of Viperidae, or vipers. The Crotalinae (crotalines) are commonly known as pit vipers and include species of rattlesnakes, copperheads, and cottonmouths.¹ Roughly 4000 to 6000 venomous snakebites occur each year in the United States. Although few are fatal, approximately 70% of victims require administration of antivenom.² Antivenom probably arrests the progression of some of the local effects of envenomation (eg, swelling, pain, ecchymosis, bruising), as well as the potentially serious systemic effects such as coagulopathy.³

Pit viper envenomation often results in coagulopathy owing to disseminated intravascular coagulation (DIC), also referred to as consumptive coagulopathy.^{4–6} Disseminated intravascular coagulation is a pathologic activation of coagulation mechanisms leading to the development of thrombocytopenia and prolongation of both prothrombin time (PT) and partial thromboplastin time (PTT), thus resulting in abnormal bleeding and usually accompanied by low fibrinogen levels.⁷ Disseminated intravascular coagulation is associated with significant morbidity and can lead to end-organ damage.^{4–6}

In a postmarketing, multicenter, retrospective chart review, 100% of 28 patients with severe envenomation showed improved severity scores for all venom effects, including coagulopathy/defibrination syndrome, thrombocytopenia, and significant/spontaneous bleeding.^{3,5}

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These same studies also showed that platelet counts may return to normal within hours after an initial control dose of Crotalinae Polyvalent Immune Fab (FabAV).⁴ A significant number of patients did not normalize platelets 1 to 2 weeks after envenomation. None of these studies, however, have addressed the long-term consequences associated with snakebite envenomation. There is a paucity of data on the use of FabAV in the management of rebound coagulation, and there are few evidence-based protocols and algorithms available.^{2,6} In a study by Seifert⁷ in 2011, patients with normal hematology studies (fibrinogen, D-dimer, international normalized ratio [INR], PTT, and <20% increase in platelet counts) did not have late hematologic effects.

The development of recurrent coagulopathy or thrombocytopenia, which usually occurs after the patient has been stabilized and discharged, is recognized in the literature.⁴ The underlying mechanism of recurrence remains to be fully elucidated; nonetheless, we have found that with modern therapies, control of envenomation is achieved earlier and hospitalization times have been shortened.⁶ Unfortunately, we have learned that there is the potential that patients are not being monitored long enough to detect signs of rebound coagulopathy.

The objective of the present study was to determine the incidence of marked and recurrent envenomation coagulopathy at our trauma center with the intention of assessing the extent of the problem and identifying practice patterns that may improve outcomes for patients who receive a snakebite.

Methods

CLINICAL SETTING

Our facility at Texas Health Harris Methodist Hospital Fort Worth is a Level II Trauma Center. With an average of 3000 trauma admissions a year, approximately 20 patients are seen annually because of a snakebite injury. The majority of snakebite injury patients come from rural areas outside the suburban area of Fort Worth, Texas, and are transferred to our trauma center. All patients returned to the clinic 10 to 14 days after envenomation for laboratory testing of PT, INR, and platelet count to ensure there was no evidence of rebound coagulopathy.

STUDY DESIGN

A retrospective case review was conducted. This study was submitted to the Texas Health Institutional Review Board, which conducted an expedited review and assigned a status of exempt.

INCLUSION CRITERIA

All patient records over a 3-year period were searched for a diagnosis of snakebite. Case records were reviewed for the following: diagnosis, laboratory reports, procedures/treatments received, discharge summaries, dates related to course of treatment, and names of drugs and devices used as a part of treatment. Of all patient records identified, only patients with an INR greater than 2.0 were included in this study.

EXCLUSION CRITERION

Patients receiving anticoagulant therapy at presentation were excluded from this study.

PROTECTION OF PATIENT CONFIDENTIALITY

Appropriate steps were taken to ensure no breach of confidentiality. All identifying data were kept in the research coordinator's locked office, data were deidentified, and all computer files were password protected.

LABORATORY VALUES

The hospital's laboratory normal range values and a description of the scenario when a value is unable to be calculated are as follows: INR less than 1.2 normal; INR is a calculation based on the PT, and if the PT is beyond the measurable limit, the INR cannot be calculated (INR >22/PT >140 seconds); fibrinogen, 204 to 488 mg/dL (undetectable <60 mg/dL) by Clauss assay; PT, 11.9 to 14.7 seconds.

Case Reports

In all, 61 patients were identified on the initial chart review, and 4 met the inclusion criteria, with an INR greater than 2.0. One patient was receiving warfarin on admission and was excluded from further analysis. One patient did not have rebound coagulopathy and was not readmitted or retreated, and was also excluded from further analysis. The total patient cohort consisted of 2 patients presumed to have been bitten who presented with marked thrombocytopenia and clinical evidence of DIC. All patients underwent postdischarge laboratory evaluations 10 to 14 days after envenomation. The 2 patients had marked rebound coagulopathy requiring readmission and retreatment (Table 1). Neither patient had evidence of bleeding. The other 59 patients did not have rebound coagulopathy and did not require readmission and retreatment.

Table 1. Laboratory Results

	Patient 1	Patient 2
Treatment	6 vials FabAV 4 units FFP 1 unit platelets	2 units FabAV 2 units of FFP
Labs On Admission	PT unmeasurable > 140 PTT unmeasurable > 250 Fibrinogen unmeasurable < 60 mg/dL Platelet count 4,000/ μ L	Platelet count 63,000/ μ L PT and INR unmeasurable
Labs During Admission	Platelet 3,000/ μ L PT unmeasurable at > 140	INR 2.27 corrected to 1.36 Fibrinogen 60 mg/dL Platelet count 275,000/ μ L
Labs During Admission	INR normalized @ 1.7 Fibrinogen $\downarrow$ 48 hours Platelet count 150,000/ μ L range (post platelet transfusion)	Platelet count 225,000/ μ L
Labs 4 Days Post Discharge	Platelet count 75,000/ μ L INR 4.0.	INR 5.91 PT 50.7
Labs on Final Discharge	Fibrinogen Level $\downarrow$ for 48 Hours then normalized Platelet Count 110,000 after 2 Vials FabAV; remained 124,000/ μ L	Coagulation Time /Platelet Count remained normal
Labs on Follow-up 1 Week Later	PT/INR Normalized	NA

Patient 1**PREADMISSION**

The patient was a 65-year-old woman bitten on the finger by what she believed to be a rattlesnake. She was initially evaluated at an outside facility and was transferred to our trauma center secondary to clinical and laboratory evidence of DIC. She presented with mild swelling of the forearm and the following outside hospital laboratory assessment: PT unmeasurable at greater than 140 seconds, PTT unmeasurable at more than 250 seconds, and fibrinogen unmeasurable at < 60 mg/dL. The platelet count was 4000/ μ L, with no previous history of coagulopathy or thrombocytopenia. Before transfer, she had received 6 vials FabAV, 4 units fresh frozen plasma (FFP), and 1 unit platelets.

INITIAL ADMISSION

On arrival, the patient's platelet count had further decreased to 3000/ μ L, and her PT remained unmeasurable at > 140 seconds. She was transferred to the intensive care unit and administered 9 additional units of FabAV. Subsequently, the INR normalized, with almost immediate correction to 1.7. Although the fibrinogen level remained low for approximately 48 hours, the platelet count rebounded promptly with platelet transfusion, then stabilized in the 150,000/ μ L range. The patient was discharged 5 days later in good health, with a platelet count of 143,000/ μ L, INR of 1.0, and

fibrinogen level of 248 mg/dL, all of which were within normal range.

READMISSION

The patient visited the clinic 4 days later for outpatient PT and INR assessment and platelet count. The INR had increased to 4.0, and the platelet count had decreased to 75,000/ μ L. Although the patient was clinically asymptomatic, she was readmitted to the hospital and administered 2 vials FabAV, with prompt correction of coagulation markers. The fibrinogen level remained low for approximately 48 hours, at which time it normalized. The platelet count increased to 110,000/ μ L after the 2 vials of FabAV but remained below normal levels, at 123,000/ μ L, throughout the hospital stay.

DISCHARGE AND FOLLOW-UP

The patient was discharged again and followed up approximately 1 week later in the office, at which time the PT and INR were normal. The patient had no residual effects with respect to clinical or laboratory assessments.

Patient 2**PREADMISSION**

The patient was a 63-year-old woman believed to have been bitten on the foot by a copperhead snake. On

presentation at an outside hospital, her laboratory results showed a platelet count of 63,000/ μ L. The PT and INR were unmeasurable. The patient was administered 2 units FabAV and 2 units FFP and was transferred to our facility by emergency air transport.

INITIAL ADMISSION

On arrival at our trauma center, the patient showed mild clinical DIC with petechial hemorrhaging and bruising at contact points. The INR had corrected to 2.27. Fibrinogen was 60 mg/dL, and the platelet count was 275,000/ μ L. She was administered another 2 vials FabAV, and the INR corrected to 1.36. The platelet count remained approximately 250,000/ μ L, and she was discharged on hospital day 3.

READMISSION

The patient returned to the clinic on postdischarge day 4 for PT and INR assessment and a platelet check. At that time, the INR had rebounded to 5.91, with a PT of 50.7 seconds. On readmission, the fibrinogen level was less than 60 mg/dL, but the platelet count remained normal. She showed no evidence of recurrent petechial hemorrhage and was administered 2 vials FabAV and 4 units FFP. She was observed for 4 more days, showing stabilization of coagulation time, and the platelet count remained normal.

DISCHARGE AND FOLLOW-UP

The patient was discharged, and laboratory results 1 week later were normal.

Discussion

This retrospective study assessed 3 patients, from a population of 61, who presented initially with marked coagulopathy. Two of the 3 had marked recurrent coagulopathy 4 days after hospitalization (which was, on average, 9 days after envenomation). Both of these patients presented with a triad of markedly abnormal laboratory results: INR greater than 6, fibrinogen less than 60 mg/dL, and platelet count less than 100,000/ μ L.

It is evident from this small series that FabAV had a profound effect on the resolution of recurrent coagulopathy, minimizing the need for FFP. The 2 patients did not have significant sequelae from their rebound coagulopathy, and they were clinically asymptomatic. Given that these patients who presented originally with marked coagulopathy were discharged early and were then readmitted with marked rebound coagulopathy, and given that rebound coagulopathy is often asymptomatic, we suggest that envenomated patients who present with

marked coagulopathy be followed up periodically for as long as 10 to 14 days after envenomation. This suggestion is based on the findings of this case series, which identified potentially life-threatening recurrent coagulopathy whose presentation was delayed until after patient discharge.

In one study of 209 evaluable patients from 17 large US hospitals, only 28 were deemed to have severe envenomation, and of those, 11 showed signs of recurrent asymptomatic coagulopathy.⁴ The relatively small number of patients with recurrent asymptomatic coagulopathy will make it difficult to perform large randomized trials of FabAV, which is currently the only available Crotaline antivenom. Brown et al⁸ reported that there is earlier improvement of coagulopathy with early factor placement after the administration of antivenom. A retrospective observational case series reported late abnormalities in hematology results, including complication of bleeding with the use of continuous intravenous FabAV.⁹ The present study documents the effectiveness of FabAV in resolving recurrent delayed coagulopathy beyond 72 hours in 2 patients after receipt of antivenom and substantiates the need for follow-up strategies. The small patient population prevents the drawing of definitive conclusions regarding the effectiveness of FabAV, however, and is therefore a limitation. Additional research with a larger patient population is warranted to further define criteria for follow-up of envenomated patients who present with marked coagulopathy.

Conclusion

Patients presenting after Crotalinae envenomation with a triad of symptoms comprising increased INR (>6.0), decreased fibrinogen (<60 mg/dL), and decreased platelet count ($<100,000$ /mL) may be at risk for the development of recurrent coagulopathy. Therefore, based on our small number of cases, we suggest continued periodic laboratory monitoring of these patients for 10 to 14 days after envenomation.

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