Thromboelastography with Platelet Studies (TEG® with PlateletMapping®) After Rattlesnake Envenomation in the Southwestern United States Demonstrates Inhibition of ADP-Induced Platelet Activation As Well As Clot Lysis

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Abstract

Introduction Hematologic effects of North American rattlesnake envenomation can include fibrinogenolysis and thrombocytopenia, depending on species, geography, and other variables. During treatment, these effects are routinely monitored through assessment of fibrinogen concentrations and platelet counts. However, these tests provide no information about fibrinolysis or platelet dysfunction, both of which can also occur with venom from some species.

Methods This was a retrospective chart review of patients admitted to a quaternary care academic hospital (Banner – University Medical Center Phoenix) in the southwestern United States for treatment of rattlesnake envenomation, over an approximately 1-year period from March 2017 through April 2018. Patients who had thromboelastography with platelet studies (TEG® with PlateletMapping®) during their care were included.

Results Twelve patients were identified for this study. Four patients exhibited inhibition of ADP-induced platelet activation: one had normal fibrinogen and platelet count, two had concurrent hypofibrinogenemia, and one had concurrent thrombocytopenia. Crotalidae polyvalent immune Fab (ovine) reversed platelet inhibition in the single patient for whom serial thromboelastographs were available. Fibrinolysis was present in seven patients and resolved in the two patients with serial thromboelastographs.

Conclusions Inhibition of ADP-induced platelet aggregation and fibrinolysis occurred independent of hypofibrinogenemia and thrombocytopenia, indicating fibrinogen concentration (or protime) and platelet count monitoring alone is insufficient to assess the extent of hematologic toxicity in rattlesnake envenomation. Crotalidae polyvalent immune Fab (ovine) reversed platelet inhibition in one case, suggesting platelet inhibition could also be used in treatment decisions. Fibrinolysis could also be reversed, although the timing to antivenom administration was less clear.

Keywords Thromboelastography (TEG) with PlateletMapping · Platelet activation · Rattlesnake envenomation · Antivenom · Fibrinolysis

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Introduction

Envenomation by North American rattlesnakes can cause a range of clinical effects affecting tissue and blood. One hematologic effect is defibrination (fibrinogenolysis) from the action of thrombin-like enzymes. The resulting hypofibrinogenemia is thought to primarily explain the prolongation of coagulation tests such as protime (PT) and activated partial thromboplastin time (aPTT), because levels of most other coagulation factors remain normal [1–3]. Neither PT nor aPTT are sensitive to decreasing fibrinogen until levels are relatively low, since these tests only need enough fibrinogen for clot initiation. Tests for PT, aPTT, and fibrinogen also use platelet-poor plasma, which does not reflect the physiologic clotting process.

A second hematologic effect is venom-induced thrombocytopenia. Recent data from the North American Snakebite Registry showed 16.4% of rattlesnake envenomation patients developed early thrombocytopenia (defined in that study as platelets $\leq 120,000/\text{mm}^3$ occurring during initial treatment) and 24.2% developed late thrombocytopenia (defined as occurring after treatment completion) [4]. The mechanisms of thrombocytopenia from rattlesnake venom have not been fully elucidated but, depending on species, may include platelet aggregation and lysis [5].

Venom components can not only reduce platelet counts, but can also affect platelet function by inhibiting glycoprotein Ib, adhesion to collagen [6], and ADP-induced platelet aggregation [7]. One in vitro study of *Crotalus scutulatus* venom demonstrated that antivenom can reverse platelet inhibition, as measured by platelet aggregometry [8], although it should be noted that normal aggregometry does not necessarily indicate normal clot strength [9]. Conversely, venom from *C. atrox* has been reported to promote platelet aggregation [5]. Despite these potential effects on platelet function, patients being treated for rattlesnake envenomation are typically only monitored for their platelet count and fibrinogen concentration [4, 10]. That is, routine testing of platelet function is not performed. Consequently, it is not well studied whether platelet inhibition occurs in vivo and if it does, how it responds to antivenom.

One method of measuring platelet function is through thromboelastography (TEG®). This assay has several useful features when used for rattlesnake envenomation. Since it uses whole blood to assess coagulation, it can evaluate the effects of both defibrination and thrombocytopenia in a single test. Moreover, certain variations (i.e., TEG® with PlateletMapping®) can independently assess the fibrinogen and platelet contributions to a clot by testing the ability to activate platelets with arachidonic acid (AA) or adenosine diphosphate (ADP). The thromboelastograph can be monitored in real-time for rapid results (minutes for some parameters) and provides information about time to clot (*R*), clotting velocity (α angle), clot strength (MA), and lysis [11].

Although thromboelastography has been available for many decades, and is used commonly in liver transplant, cardiovascular surgery, and trauma, there has been no systematic study of its performance in actual rattlesnake envenomation patients. This lack of baseline data is a major barrier to studying thromboelastography for this application. There have been case reports or small case series of thromboelastography in rattlesnake envenomation but many have been from outside of North America [12–15] and details about methodology were not always included (e.g., citrated versus whole blood, which activator used, etc.). Moreover, all studies, whether from North America [16–18] or not, have reported only standard thromboelastography, which do not include platelet activation studies. More recent studies of various rattlesnake venoms added to human plasma have also used TEG [19] but these are not applicable for clinical use because of their in vitro nature, and because the platelet component of coagulation is absent.

To address this lack of data, this retrospective study was undertaken with the following aims: (1) to describe the thromboelastographic patterns (including platelet function) observed in patients admitted to a hospital for rattlesnake envenomation, with comparison to other laboratory parameters, (2) to investigate whether platelet inhibition occurs in vivo, and (3) assess whether this inhibition can be reversed by the antivenom available during the period of study, Crotalidae polyvalent immune Fab (ovine) (CroFab®; BTG International Inc., Conshohocken, PA, USA; hereafter Fab antivenom).

Methods

This was a retrospective chart review of rattlesnake envenomation patients admitted to the Medical Toxicology service at Banner – University Medical Center Phoenix (BUMCP), a quaternary care academic medical center affiliated with the University of Arizona College of Medicine – Phoenix (COMP). As a toxicology referral center, patients aged 15 years and over with rattlesnake envenomation are transferred to BUMCP for treatment from throughout Arizona. This chart review included all patients admitted for rattlesnake envenomation between March 15, 2017 and April 17, 2018, who had a TEG® with PlateletMapping® performed at some point during their course of treatment.

Thromboelastography was performed by the hospital hematology lab on Haemonetics TEG® 5000 Thrombelastograph® Hemostasis Analyzer instruments. Thromboelastographs were obtained using whole blood that is placed in a rotating cup. As a clot forms, the force produced on a pin within the cup is measured and plotted as a thromboelastograph. TEG® with PlateletMapping® is comprised of four assays, each performed with different reagents

to promote clotting. The first, or standard assay (TEG-CK), adds kaolin to citrated whole blood, in order to activate factor XII and the intrinsic pathway. This measures the contribution of both fibrinogen and platelets to clot formation. The second, or activator assay (TEG-A), isolates the fibrinogen/fibrin contribution. Reptilase is added to convert fibrinogen to fibrin, without activating platelets. Heparinized blood is used to prevent any generated thrombin from activating platelets. Since this also prevents endogenous factor XIII activation, “Activator F” (activated factor XIII) is also added to cross-link the fibrin. The third and fourth assays use heparinized blood along with Activator F and isolate the platelet contribution by activating platelets with either arachidonic acid (AA) or adenosine diphosphate (ADP), assessing the thromboxane A₂ (TXA₂) and ADP-receptor pathways, respectively. Thromboelastographs were reviewed using TEG® Analytical Software v4.2.3. Some of the important parameters are shown in Fig. 1 and include the reaction time (R , in seconds) to the beginning of clot formation, rate of clot formation (α angle, in degrees), clot strength (MA = maximum amplitude, in mm), and fibrinolysis measured at 30 min after the time of maximum amplitude ($LY30$, in %). The software also reports a percent inhibition for the AA and ADP reactions. However, this calculation depends on the MA_A , so if the activator assay does not clot, a value cannot be obtained. For this reason, we did not use this value in the current study.

Other collected data included medical histories, details of the rattlesnake bite, antivenom administered, and available hematologic labs (complete blood counts, fibrinogen, and coagulation assays). Hypofibrinogenemia was defined as fibrinogen activity ≤ 200 mg/dL and thrombocytopenia was defined as a platelet count $\leq 150,000/\text{mm}^3$.

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Arizona [20]. REDCap is a

secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

This study was approved by the institutional review board at the University of Arizona with consent waived.

Results

Twelve patients met inclusion criteria for this study (Table 1). Five of these patients (3, 7, 9, 11, and 12) had normal initial fibrinogen activity and platelet counts (group A). This group had normal TEG-CK and TEG-AA results, except for patient 12 who had a small degree of AA inhibition ($MA_{AA} = 38.9$ mm), consistent with reported use of low-dose aspirin (Fig. 2). Patient 7 exhibited severe inhibition on TEG-ADP, manifested by a large decrease in clot strength ($MA_{ADP} = 8.4$ mm; 12.8% of the MA_{CK} value), and a somewhat smaller decline in reaction rate ($\alpha_{ADP} = 46^\circ$; 72.1% of the α_{CK} value). Interestingly, this patient also appeared to have significant inhibition on the TEG-A, suggesting impaired fibrinogen function, with a very weak clot ($MA_A = 3.9$ mm) and low reaction rate ($\alpha_A = 12.8^\circ$), compared to others in group A; yet, the PT was normal (11.6 s). Three patients (9, 11, 12) also showed lysis with the TEG-CK assay (Fig. 2) and each of these had $LY30_{CK}$ greater than 8.0%, which is the upper limit of normal recommended by Haemonetics.

Three patients (1, 2, and 8) had hypofibrinogenemia with normal platelet counts (group B). Compared to group A, all of these patients had TEG-CK results indicating impaired hemostasis, with weak clot strengths, MA_{CK} , and decreased rates of clot formation α_{CK} (Table 1 and Fig. 3). The severity of impairment appeared to correspond to the degree of hypofibrinogenemia. TEG-A assays either did not clot or clotted slowly, with poor clot strength. The MA_{AA} values were even greater than MA_{CK} for each of these patients. Patient 8 had clear ADP inhibition, with $MA_{ADP} = 2.7$ mm (7.2% of MA_{CK}). The clot formation rates were low as well, with patient 2 most severely affected ($\alpha_{ADP} = 1.1^\circ$) indicating that the sample essentially did not clot. Patients 1 and 2 both had elevated $LY30_{CK}$ values over 8.0%.

Two patients (4, 10) had isolated thrombocytopenia with normal fibrinogen (group C). The range of TEG-CK values is similar to the group A patients (Table 1 and Fig. 4). The initial lab results for patient 10 were obtained prior to administration of any antivenom and indicated inhibition of both AA- and ADP-induced platelet activation ($MA = 9.0$ mm and 14.5 mm, respectively); this patient's results have been reported previously in abstract form [21]. Incidentally, this patient had taken a single dose of ibuprofen after envenomation, explaining the

Fig. 1 Stylized thromboelastograph showing the parameters reported in this study. R = reaction time (seconds), which is the time to clot formation; α = rate of clot formation ($^\circ$); MA = maximum amplitude (mm), which indicates clot strength; $LY30$ = fibrinolysis measured at 30 min after the time of maximum amplitude (%)

Table 1 Initial laboratory results, including TEG® with PlateletMapping®, for patients included in this study, grouped by fibrinogen and platelet patterns. * indicates patient was taking low-dose aspirin. † indicates patient took one dose of ibuprofen immediately after envenomation. Italicized MA_{ADP} indicates clear ADP inhibition on TEG®

Patient	Age (years)	Fibrinogen	Platelet	TEG-CK		TEG-A		TEG-AA		TEG-ADP		Comments					
				R (min)	α (°)	MA (mm)	LY30 (%)	R	α	MA	R		α	MA			
Group A: normal fibrinogen and platelet																	
3	19	324	251	5.6	65.4	66.8	1.0	0.4	44.8	31.4	0.8	64.9	62.7	0.5	49.0	49.3	Immediately after 4-vial loading dose
7	45	364	247	6.2	63.8	65.4	2.8	2.5	12.8	3.9	0.8	55.8	53.0	0.8	46.0	8.4	Prior to AV
9	72	323	234	4.9	72.0	67.6	10.7	0.8	58.5	17.4	0.8	69.6	65.9	0.8	63.4	53.0	Immediately after 4-vial loading dose
11	51	236	211	4.3	73.4	64.0	20.4	1.1	43.3	10.9	1.1	62.7	54.7	0.8	66.4	60.3	Immediately after 6 vials of AV, 10 vials total
12*	67	285	292	8.6	60.4	57.7	28.2	0.7	51.9	10.2	1.1	48.3	38.9	1.0	44.6	33.0	3.5 h after 4-vial loading dose
Group B: apparent isolated hypofibrinogenemia																	
1	38	98	207	6.1	47.7	30.0	19.2	Did not clot		2.0		46.9	37.1	3.1	17.4	17.4	3 h after 4-vial loading dose on readmission
2	72	<35	244	6.1	19.4	9.6	16.6	75.5	0.7	4.9	3.5	18.4	9.7	38.7	1.1	6.3	On readmission for hypofibrinogenemia, no AV given
8	66	114	228	6.8	51.9	37.6	5.3	2.8	11.2	2.5	2.3	38.0	38.2	2.2	15.1	2.7	3 h after 3 vials of AV, 6 vials total
Group C: apparent isolated thrombocytopenia																	
4	48	461	96	4.3	54.5	67.8	0.4	0.7	61.5	16.0	0.4	48.0	60.6	0.7	67.3	48.4	24 h after last dose of 2 vials of AV, 22 vials total
10†	38	238	125	4.4	63.3	58.2	1.1	0.4	64.0	14.1	0.4	51.2	9.0	0.2	68.6	14.5	Before AV
Group D: hypofibrinogenemia and thrombocytopenia																	
5	28	150	127	4.5	43.9	57.6	1.8	0.4	52.9	7.9	1.6	51.1	49.9	1.2	43.9	40.7	4 h after 4-vial loading dose
6	45	<35	115	11.3	9.8	7.5	30.9	Did not clot		5.9		12.4	4.5	Did not clot		Immediately after 4-vial loading dose; readmission	

Fig. 2 Thromboelastographs from patients in group A (normal fibrinogen and normal platelet count). Tracings from all four assays (TEG-CK, TEG-A, TEG-AA, and TEG-ADP) are superimposed for each patient

initial TEG-AA results, which quickly improved. Labs obtained shortly after a loading dose of Fab antivenom (sample 10–2 in Table 2) showed resolution of inhibition of ADP-induced

platelet activation, as well as improvement in the platelet count. Thrombocytopenia then recurred independent of ADP inhibition (10–4 in Table 2). On the other hand, antivenom did

Fig. 3 Thromboelastographs from patients in group B (decreased fibrinogen and normal platelet count). Tracings from all four assays (TEG-CK, TEG-A, TEG-AA, and TEG-ADP) are superimposed for each patient

Fig. 4 Thromboelastographs from patients in group C (normal fibrinogen and decreased platelet count). Tracings from all four assays (TEG-CK, TEG-A, TEG-AA, and TEG-ADP) are superimposed for each patient

not reverse ADP inhibition in patient 4, although it also did not reverse the thrombocytopenia in this patient (4–8 in Table 2). Neither patient in this group exhibited clot lysis on their initial thromboelastographs, but patient 10 had lysis on the second sample, which resolved on subsequent tests.

Two patients (5, 6) exhibited combined hypofibrinogenemia and thrombocytopenia (group D) on their initial results (Table 1 and Fig. 5). Similar to the group B patients, impaired hemostasis was observed on both TEG-CK and TEG-A. This was again prominent when fibrinogen was below the lower limit of detection (<35 mg/dL), with patient 6 having poor clot strength ($MA_{CK} = 7.5$ mm) and slowed formation rate ($\alpha_{CK} = 9.8^\circ$). Both the TEG-A and TEG-ADP did not clot. The impaired clotting with TEG-A and TEG-ADP did not resolve even after the fibrinogen concentration had recovered (sample 6–2 in Table 2), suggesting continued impaired fibrinogen function. Yet, the PT did show improvement from >150 s (at time of sample 6–1) to 11.6 s. Patient 6 also had lysis with the first sample ($LY30_{CK} = 30.9\%$), which resolved with the second sample ($LY30_{CK} = 5.9\%$).

The identity of the snake was known in only two cases, based on a herpetologist's review of photographs of the snakes: a Mojave rattlesnake (*C. scutulatus*) for patient 4 and a western diamondback rattlesnake (*C. atrox*) for patient 8.

None of the patients were taking serotonin-selective reuptake inhibitors (SSRIs), but patient 9 was taking venlafaxine. As was already mentioned, patient 10 took a single dose of ibuprofen prior to arrival in the emergency department and patient 12 was taking low-dose aspirin.

Discussion

Thromboelastography demonstrated inhibition of ADP-induced platelet activation in patients independent of hypofibrinogenemia and thrombocytopenia. Consequently,

monitoring solely fibrinogen concentration (or PT) and platelet count during treatment of rattlesnake envenomation would provide an incomplete picture of hematologic toxicity. Since this inhibition is similar to what would be seen in a patient being treated with a P2Y₁₂ receptor antagonist, such as clopidogrel, it is reasonable to assume an increased bleeding risk, particularly when combined with hypofibrinogenemia and/or thrombocytopenia. It would seem prudent then, to be aware of this potential hematologic toxicity and consider testing for it when possible.

The presence of platelet inhibition could also be an indicator of ongoing hematologic toxicity. For example, patient 4 began to show a trend of increasing ADP inhibition which preceded another decrease in platelet count. Since it was observed that the Fab antivenom in use at the time of this study reversed platelet inhibition in a patient for whom serial studies were available (patient 10, previously presented in abstract form [21]), it may be reasonable to consider platelet inhibition as an additional data point in decisions to administer antivenom, particularly for patients for whom the inhibition is seen to reverse with treatment. It is unknown if the recently introduced Crotalidae immune F(ab')₂ (equine) (Anavip®, Instituto Bioclon SA de CV, Mexico City, Mexico) will reverse this platelet inhibition, although there is no reason to assume it could not.

It is important to understand that there can be wide interindividual variability in TEG-ADP results. One study of healthy, unmedicated blood donors reported lower mean MA_{ADP} (51.1 mm) but with greater standard deviations (8.1 mm), compared to values for TEG-CK (60.9 [4.5]) or TEG-AA (64.6 [4.7]). Calculated % inhibition was as high as 58.1% in these normal individuals [22]. Consequently, a diagnosis of ADP inhibition should meet a relatively high threshold when using thromboelastography, and sequential testing to monitor trends may be informative.

Standard TEG-CK results were unaffected in group A patients (normal fibrinogen and platelet count) and fell within

Table 2 Sequential laboratory results for four patients with more than one TEG® performed. † indicates patient took one dose of ibuprofen immediately after envenomation. Italicized MA_{ADP} indicates clear ADP inhibition on TEG®

Patient/ sample	Fibrinogen	Platelet	TEG-CK		TEG-A			TEG-AA			TEG-ADP			Comments		
			R (min)	α (°)	MA (mm)	LY30 (%)	R		α		R		α			
3-1	324	251	5.6	65.4	66.8	1.9	0.4	44.8	31.4	0.8	64.9	62.7	0.5	49.0	49.3	Immediately after 4-vial loading dose
3-2	407	248	4.1	56.8	67.9	2.7	0.5	57.5	11.1	0.6	68.4	68.7	0.5	61.3	57.1	21 h after sample 3-1, no additional AV had been given
4-1	461	96	4.3	54.5	67.8	0.4	0.7	61.5	16.0	0.4	48.0	60.6	0.7	67.3	48.4	24 h after last dose of 2 vials of AV, 22 vials total
4-2	570	82	4.9	68.9	70.2	0.0	0.5	69.1	23.3	0.6	69.2	68.8	0.7	71.6	58.2	24 h after 4-2, 4 more vials given after this TEG
4-3	619	118	6.2	73.7	75.1	2.8	0.8	50.4	17.5	0.4	68.3	64.0	0.6	57.3	42.1	3 days after sample 4-2
4-4	619	89	6.4	68.7	76.2	0.1	0.6	54.6	20.1	0.6	61.2	64.5	0.6	63.8	27.7	5 days after sample 4-2
4-5	516	72	8.2	66.9	69.9	0.0	0.4	64.5	20.4	0.5	68.4	71.8	0.3	61.3	32.4	6 days after sample 4-2
4-6	415	78	3.6	78.7	78.4	0.1	0.6	66.7	20.0	0.7	65.8	73.4	0.5	67.0	42.3	8 days after sample 4-2, 1 day after 2 vials of AV, 24 vials total
6-1	<35	115	11.3	9.8	7.5	30.9	Did not clot			5.9	12.4	4.5	Did not clot			Immediately after 4-vial loading dose, readmission
6-2	197	179	7.5	36.6	39.1	5.9	Did not clot			2.9	28.8	27.3	4.0	8.9	3.3	24 h after sample 6-1, 8 vials total
10-1†	238	125	4.4	63.3	58.2	1.1	0.4	64.0	14.1	0.4	51.2	9.0	0.2	68.6	14.5	Before AV
10-2	277	424	5.3	67.6	47.2	18.2	0.6	57.2	10.8	0.8	57.5	49.9	0.7	63.3	53.0	6 h after 6 vials of AV
10-4	408	97	6.4	68.7	65.2	0.6	0.8	51.6	16.4	0.6	60.6	61.2	0.7	62.3	63.0	3 days after 2 vials of AV, 18 vials total

the range of MA values previously reported in healthy individuals [22]. The presence of hypofibrinogenemia (groups B and D) inhibited clot formation in the standard TEG® to varying degrees, depending on the amount of defibrination. MA_A showed large declines as well, with some samples never clotting. This is not surprising since the activator assay depends on fibrinogen, and a linear correlation with fibrinogen concentration has been reported in healthy subjects [23]. Although TEG-AA assays were not affected, TEG-ADP showed a decreasing α_{ADP} for all patients with hypofibrinogenemia. This appeared independent of declines in MA_{ADP}, suggesting it was related to the hypofibrinogenemia somehow, and was most severe with the two patients with fibrinogen concentrations below the lower limit of detection (patients 2 and 6). It is not clear why low fibrinogen activity would affect ADP activation but not AA activation of platelets so further study is needed to verify this pattern. Whatever the reason, extremely low fibrinogen appears to make it difficult to interpret TEG-ADP.

Fibrinolysis was also observed on TEG-CK from patients in several of the groups. It appeared independent of ADP inhibition and fibrinogen concentration and reversed on subsequent studies in the two patients who had multiple results available (patients 6 and 10). It is not clear why it developed after antivenom administration in patient 10, unless the antivenom quantity was insufficient, but the antivenom administration itself would not appear to be the etiology since it did not occur in other results obtained shortly after antivenom. Lysis is another effect that would not be measured through fibrinogen concentrations, PT, and platelet counts, and more study is needed to understand its role in guiding treatment.

The identity of the snake was definitively known in only two of the cases in this study. In Arizona, the geographic region for patients in this study, the western diamondback rattlesnake, *C. atrox*, is common, and both fibrinogenolytic [5] and fibrinolytic [24, 25] activity has been reported from proteins in its venom. Among the thirteen rattlesnake species found in the geographic area of this study, envenomations have also commonly been reported by the Mojave (*C. scutulatus*), Northern black-tailed (*C. molossus*), prairie (*C. viridis*), sidewinder (*C. cerastes*), and speckled (*C. mitchellii*). However, since venom composition has been reported to vary, even within a single species, due to factors such as age [26] and time of year [27], knowing the identity of the species would not be sufficient to predict hematologic effects, making more informative testing, such as thromboelastography with platelet studies, a potentially useful assay during treatment.

It has been reported that SSRIs decrease ADP-induced platelet aggregation, both in vitro [28] and in vivo [29]. There appear to be multiple mechanisms for this effect, different from how the thienopyridines act, including inhibition of signaling pathways downstream from the P2Y₁₂ receptors

Fig. 5 Thromboelastographs from patients in group D (decreased fibrinogen and decrease platelet count). Tracings from all four assays (TEG-CK, TEG-A, TEG-AA, and TEG-ADP) are superimposed for each patient

[28, 30]. None of the patients in this study with ADP inhibition reported taking SSRIs or other medications affecting serotonin transport, so this should not have played any role in the ADP inhibition observed. Interestingly, one patient (#9) did report taking venlafaxine, a serotonin-norepinephrine reuptake inhibitor, but did not have any inhibition noted on TEG-ADP. It would also be unexpected to see reversal after antivenom if unreported SSRI use was causing the platelet inhibition.

Limitations

This was a retrospective study that included only patients who had a TEG® with PlateletMapping® performed during their course of inpatient treatment. The sample size was small, since patients who had a TEG® without PlateletMapping® were not included, and many patients had only a single set of results so changes in response to treatment could not be assessed. The clinical significance of the thromboelastographic changes observed has not been studied. The snake species is not definitively known in most bites, although all were rattlesnakes native to Arizona.

Conclusions

Monitoring hemostatic parameters using TEG® with PlateletMapping® during treatment of a rattlesnake envenomation provides additional information about ADP-induced platelet aggregation and fibrinolysis that cannot be learned from simply measuring fibrinogen concentration, PT, and platelet count. Fab antivenom did show an ability to reverse platelet inhibition, although not in all cases. Fibrinolysis was also reversed, although the timing relative to antivenom administration was not as clear. In the setting of severe hypofibrinogenemia, it may be difficult to interpret the platelet studies of TEG®. More study is needed, particularly with sequential results during the course of treatment.

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Compliance with Ethical Standards

Conflicts of Interest None

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