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Research Article

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Cocaine Use is Associated with More Rapid Clot Formation and Weaker Clot Strength in Acute Stroke Patients

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Abstract

Introduction: Cocaine use is a known risk factor for stroke and has been associated with worse outcomes. Cocaine may cause an altered coagulable state by a number of different proposed mechanisms, including platelet activation, endothelial injury, and tissue factor expression. This study analyzes the effect of cocaine use on Thrombelastography (TEG) in acute stroke patients.

Patient and Methods: Patients presenting with Acute Ischemic Stroke (AIS) and spontaneous Intracerebral Hemorrhage (ICH) to a single academic center between 2009 and 2014 were prospectively enrolled. Blood was collected for TEG analysis at the time of presentation. Patient demographics and baseline TEG values were compared between two groups: cocaine and non-cocaine users. Multivariable Quantile regression models were used to compare the median TEG components between groups after controlling for the effect of confounders.

Results: 91 patients were included, 53 with AIS and 38 with ICH. 8 (8.8%) patients were positive for cocaine, 4 (50%) with AIS, and 4 (50%) with ICH. There were no significant differences in age, blood pressure, platelet count, or PT/PTT between the cocaine positive and cocaine negative group. Following multivariable analysis, and adjusting for factors known to influence TEG including stroke subtype, cocaine use was associated with shortened median R time (time to initiate clotting) of 3.8 minutes compared to 4.8 minutes in non-cocaine users (p=0.04). Delta (thrombin burst) was also earlier among cocaine users (0.4 minutes) compared with non-cocaine users (0.5 min, p=0.04). The median MA and G (measurements of final clot strength) were reduced in cocaine users (MA=62.5 mm, G=7.8 dynes/cm2) compared to non-cocaine users (MA=66.5 mm, G=10.1 dynes/cm2; p=0.047, p=0.04, respectively).

Conclusion: Cocaine users demonstrate more rapid clot formation but reduced overall clot strength based on admission TEG values.

Keywords: Coagulation; Cocaine; Intracerebral Hemorrhage; Ischemic Stroke; Thrombelastography

Introduction

Stroke is the third leading cause of death in the United States, and cocaine abuse is a prominent etiology of stroke in young adults [1-3]. Cocaine is associated with both ischemic and hemorrhagic strokes [4,5]. There are numerous mechanisms contributing to cocaine-induced stroke including vasospasm, vasculitis, blood pressure elevations, and cardiac arrhythmias [6,7]. Cocaine may cause a pro-coagulable state by a number of different proposed mechanisms, including platelet activation [8,9], endothelial dysfunction [10,11], and tissue factor expression [12].

Despite the association with hypercoagulability, cocaine use has also been associated with intracranial bleeding. Among patients with acute stroke, active cocaine users are more likely to have a hemorrhagic than ischemic stroke when compared with non-cocaine users [13]. Cocaine use is also associated with worse functional outcome and increased mortality among patients with Intracerebral Hemorrhage (ICH) [14].

Thromboelastography (TEG) is a hemostatic assay that measures the global viscoelastic properties of whole blood clot, and it demonstrates the interaction of platelets with the coagulation cascade. We examine the effect of cocaine use on TEG values in acute stroke patients.

Patients and Methods

We reviewed patients admitted to Memorial Hermann Hospital at Texas Medical Center with a diagnosis of Acute Ischemic Stroke (AIS) and spontaneous ICH between 2009 and 2014. Patients were prospectively enrolled and venous blood samples were collected at the time of presentation to the emergency department for TEG analysis. AIS patients were included if symptom onset was within 3 hours and they met eligibility criteria for treatment with intravenous tPA. Blood for TEG was drawn before the tPA bolus. ICH patients were included if presenting within 6 hours of symptom onset. ICH patients were excluded if baseline coagulopathy was present, hemostatic agents were administered, or ICH was thought to be secondary to an underlying lesion such as tumor, vascular malformation, or trauma. Detailed methods are described in previous publications [15,16]. TEG values were compared between two groups: cocaine and no cocaine users. Cocaine use was defined by positive urine toxicology at admission. Patients without a toxicology screen were excluded. Baseline demographics and clinical characteristics were compared between the two groups.

TEG Analysis

Blood was collected into citrated tube and refined in a computerized thrombelastography coagulation analyzer. The following TEG values were documented: R(minutes) is the time of latency from start of test to initial fibrin formation (amplitude of 2mm), δ (minutes) is the time to reach the maximum speed of initial clot formation, representing the thrombin burst, K (minutes) is the time taken to achieve a certain level of clot strength (amplitude of 20mm); α angle (Angle) measures the speed at which fibrin build up and cross linking takes place, hence assesses the rate of clot formation, MA = Maximum Amplitude (mm); represents the ultimate strength of the fibrin clot; i.e. overall stability of the clot; G (dynes/cm^2) measures clot firmness or strength (G=5000MA/(100-MA) and is higher in clots that are more platelet rich and held together by stronger fibrin matrices.

Statistical analysis

Continuous variables with normal distributions were summarized by mean ± standard deviation, and variables with skewed distributions were summarized by median and interquartile range. Categorical variables were described with frequency and percentages. The differences of demographics, medical history, home medications and baseline lab values between different cocaine use patients were compared using two sample t-test (or Wilcoxon rank sum test as appropriate) for continuous variables and Fisher's exact test for categorical variables. Multivariable quantile regression models were fitted to compare the median of TEG components between groups after controlling for the effect of confounders. The identification of confounders was based on both a priori and empirical considerations. First, variables shown previously to be correlated with TEG components (e.g., age, smoking status, platelet count, and stroke type AIS vs. ICH) were included in the analysis. Second, through a univariable analysis using p-value < 0.20, we identified the factors which both differed among drug use groups and also checked whether they were associated with TEG components. Lastly, the covariates were considered to be confounders if the regression coefficient of group indicator, varies by >20% when the covariate is added to or deleted from the multivariable model. All statistical analyses were performed using SAS 9.3 (SAS Institute. Inc., Cary, NC) and a p-value <0.05 was considered as significant.

This study was approved by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston and the Institutional Review Board (IRB) of Memorial Hermann Hospital.

Results

A total of 254 patients were enrolled, 174 AIS patients and 80 ICH patients. We excluded 163 patients who did not have a urine drug screen done at admission. Thus a total of 91 patients were included, 53 patients with AIS and 38 patients with ICH. Total of eight (8.8%) patients were positive for cocaine, four patients (50%)

with AIS and four patients (50%) with ICH. Patient demographics, clinical data, and baseline lab measurements are shown in (Table 1). There was no significant difference in age, blood pressure, platelet count, or PT/PTT between the two groups. However, smoking was significantly more prevalent among cocaine positive patients (75%) compared with cocaine negative patients (25.3%; p=0.01).

	Cocaine use		p value
	No (N=83)	Yes (N=8)	
Age (years), mean±SD	58.0±12.8	53.9±6.9	0.37*
Male, n(%)	54 (65.1)	5 (62.5)	1.0[1]
Race			
African American	25 (30.5)	6 (75.0)	
Caucasian	30 (36.6)	0 (0)	NR
Hispanic	19 (23.2)	2 (25.0)	
Other	8 (9.8)	0 (0)	
Hypertension, n(%)	57 (68.7)	6 (75.0)	1.0[1]
Hyperlipidemia, n(%)	17 (20.5)	1 (12.5)	1.0[1]
Diabetes Mellitus, n(%)	24 (28.9)	3 (37.5)	0.69[1]
Coronary artery disease, n(%)	7 (8.4)	0 (0)	NR
Smoking, n(%)	21 (25.3)	6 (75.0)	**0.01**[1]
Aspirin, n(%)	19 (22.9)	0 (0)	NR
Clopidogrel, n(%)	8 (9.6)	0 (0)	NR
Glucose (mg/L), median (Q1, Q3)	131.0 (110.0, 174.0)	114.5 (100.5, 249.0)	0.54**
Hemoglobin (g/dL), mean±SD	13.8±2.0	12.5±3.0	0.09*
Platelet count $x10^3$, mean±SD	220.1±60.4	185.5±72.4	0.13*
Partial thromboplastin time (seconds), mean±SD	30.8±17.4	30.5±5.9	0.91*
International normalized ratio, mean±SD	1.0±0.1	1.0±0.2	0.84*
National institutes of health stroke scale, median (Q1, Q3)	11 (5, 17)	10 (6, 16.5)	0.88**
Initial systolic blood pressure (mm Hg), mean±SD	176.6±38.6	181.6±41.0	0.73*
Initial diastolic blood pressure (mm Hg), mean±SD	96.0±21.4	89.6±35.3	0.63*
Stroke Type, n(%)			
Hemorrhagic	34 (41.0)	4 (50.0)	0.72[1]
Ischemic	49 (59.0)	4 (50.0)	

SD: Standard Deviation; Q1, 1st quartile; Q3, 3rd quartile; NR: Not Reported due to zero cells. *denotes p-values obtained by two sample t-test; ** denotes p-values obtained by Wilcoxon rank sum test; [1]denotes p-values obtained by Fisher's exact test.

Table 1: Comparison of baseline characteristics among cocaine and non-cocaine users.

Comparison of baseline TEG values between the two groups following multivariate analysis after controlling for the effect of potential confounders (age, smoking status, baseline platelet count, baseline hemoglobin and stroke type) is shown in (Table 2)**.** Following multivariable analysis, cocaine use was associated with shortened median R time (time to initiate clotting) of 3.8 minutes compared to 4.8 minutes in cocaine negative patients (p=0.04). Delta (thrombin burst) was also earlier among cocaine positive patients (0.4 minutes) compared with cocaine negative patients (0.5 min, p=0.04). The median MA and G (measurements of final clot strength) were reduced in cocaine positive patients (MA=62.5 mm, G=7.8 dynes/cm^2) compared cocaine negative patients (MA=66.5 mm, G=10.1 dynes/cm^2; p=0.047, p=0.04, respectively). Example TEG tracings from cocaine positive patient versus cocaine negative patient are shown in (Figure 1).

	Cocaine use		
	No (n=83)	Yes (n=8)	p value
R (minutes)	4.8 (3.3, 6.0)	3.8 (2.8, 4.1)	**0.04**
Delta (minutes)	0.5 (0.4, 0.8)	0.4 (0.3, 0.5)	**0.04**
K (minutes)	1.9 (1.6, 2.4)	1.8 (1.7, 2.6)	0.69
MA (mm)	66.5 (62.4, 69.5)	62.5 (58.9, 68.5)	**0.047**
Angle (degrees)	64.6 (59.7, 68.6)	67.3 (61.2, 71.1)	0.27
G (dynes/cm^2)	10.1 (9.0, 11.5)	7.8 (7.1, 10.7)	**0.04**
Data were reported as median (1st quartile, 3rd quartile). Quantile regression was performed for all baseline TEG values. P values were obtained to compare the median of baseline TEG values between different cocaine use groups by likelihood ratio test after adjusting for potential confounders: age, smoking status, baseline platelet count, baseline hemoglobin and stroke type.			

Table 2: Adjusted comparison of TEG parameters among cocaine and non-cocaine users.

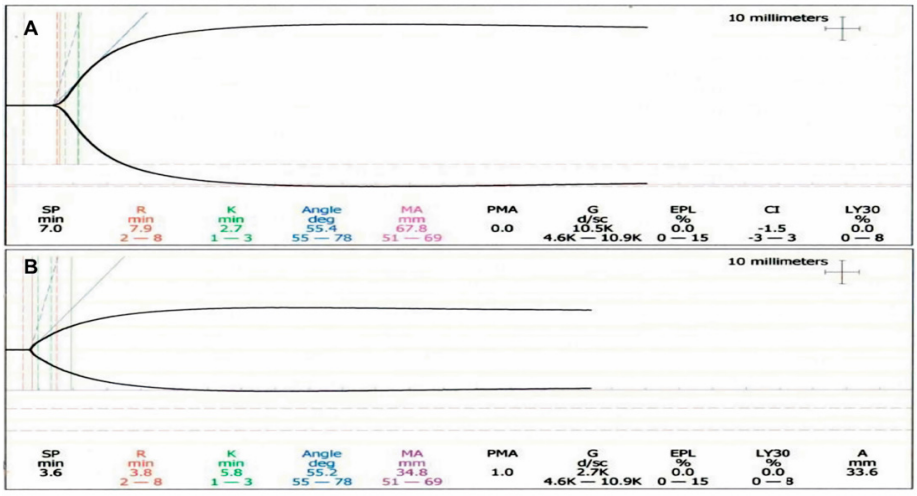

Figure 1: Example TEG tracings from A) cocaine negative and B) cocaine positive patients.

Discussion

To our knowledge this is the first study looking at the effect of cocaine on TEG values in acute stroke patients. Our study demonstrated that cocaine positive patients have more rapid clot formation but overall reduced clot strength. Cocaine use therefore appears to have a complex effect on coagulation, which may explain why previous studies have yielded conflicting results [17].

Our findings of faster clot formation (reduced R time) and earlier thrombin burst (reduced delta) in cocaine positive patients are suggestive of early activation of the extrinsic pathway and promotion of thrombin formation. Cocaine has been reported to promote the coagulation cascade. *In vitro* cocaine exposure increases tissue factor release, suppresses tissue factor pathway inhibitor, and induces von Willebrand Factor release from endothelium [12]. Cocaine use in healthy subjects induces

increased levels of plasminogen activator inhibitor-1, which may promote hypercoagulability by inhibiting fibrinolysis (inhibits tissue plasminogen activator and urokinase) [18].

Furthermore, numerous reports have identified cocaine as a promoter of platelet activation. In animals, daily administration of intravenous cocaine has been shown to increase vascular endothelium prostaglandin production [19]. *In vitro* studies using human plasma incubated with cocaine have identified increased platelet aggregation compared with controls [20,21]. Cocaine exposure also induces von Willebrand Factor release from endothelium, which promotes platelet adhesion [22]. Heesch et al. demonstrated in healthy volunteers that cocaine use, at doses comparable with recreational use, leads to platelet activation, increased platelet containing microaggregates, and a slight decrease in bleeding time [8]. Chronic cocaine users have also been demonstrated to have highly activated platelets; if followed over time, biomarkers of increased platelet activity return to normal levels after 4 weeks of abstinence [9].

However, the impact of cocaine on platelet aggregation does not appear to be consistent across all cocaine users and in all studies. Although mean platelet aggregation is increased after exposure to cocaine *in vitro*, Rezkalla et al. reported that only 5 of the 10 patients included in their study demonstrated a marked increase in aggregabililty in response to cocaine [20]. Rinder et al. reported that only a small group of chronic cocaine users (5/25) had significantly elevated levels of activated platelets 3 SD above the mean [21]. This suggests that cocaine may promote platelet aggregation in the setting of other stimuli or under certain conditions.

Our data finding reduced clot strength (decreased MA and G) suggests a net inhibition of platelet function with cocaine use. Jennings et al. reported that cocaine impaired aggregation *in vitro*, even in the setting of agonists adenosine diphosphate and collagen [23]. Furthermore, they found that cocaine prevented the binding of fibrinogen to agonist stimulated platelets and promoted the dissociation of platelet aggregates [23]. Their results suggest an overall impairment of platelet function and thrombus formation in the setting of acute cocaine exposure, similar to our findings. If our results are substantiated in larger numbers of patients, it might explain the increased propensity to brain bleeding in cocaine patients.

Our findings are limited by a small sample size and single center experience. Additionally, this study retrospectively analyzed prospectively obtained data. Potentially significant confounders including unknown medication history, blood pressure control, and cardiac function could not be adjusted for. Both AIS and ICH patients have been shown to be hypercoagulable at baseline [15,16,24]. In a prior study including the same patient population, we reported that AIS patients presented with shorter R time, greater angle, and shorter K when compared with normal controls [16]. We also previously reported that ICH patients were hypercoagulable at presentation as demonstrated by shorter R, shorter delta, and greater angle than controls [15]. We included all acute stroke patients, both AIS and ICH, in our analysis due to the small sample size. This could introduce heterogeneity into our patient population. However, stroke type was adjusted for in the multivariate analysis. Our results may not be applicable to populations presenting with other acute illnesses besides stroke.

The ability of standard TEG to detect the effects of cocaine on coagulation in acute stroke patients has important ramifications. In the setting of cocaine use, TEG demonstrates a mixed coagulation disturbance, which may affect patient management in the setting of acute stroke. For example, TEG might be used to help guide hemostatic therapy in ICH patients with normal conventional coagulation studies (PT/PTT), as they were in our patient population. As cocaine use may affect the coagulation profile differently among individual patients, it is important that we find a tool to quantify coagulation disturbances for risk stratification. If our results are corroborated, TEG profiles might be used to guide decision making regarding thrombolysis risk, antiplatelet therapy and/or response, bleeding tendency, and delayed thrombotic complications. These potential applications represent an area for future research.

Conclusions

Cocaine use is associated with rapid clot formation but overall weaker clot strength as demonstrated by TEG values in acute stroke patients. These findings suggest cocaine may induce thrombin generation and faster clotting due to tissue factor release or other mechanism, and platelet inhibition, resulting in a relatively weaker thrombin-rich clot leading to a propensity to bleeding. Further studies are needed to examine the impact on both clot formation and bleeding risk in acute stroke.

Disclosures

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Conflicts of Interest

The authors declare no conflicts of interest.

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