Cocaine use as an independent predictor of seizures after aneurysmal subarachnoid hemorrhage

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OBJECTIVE Seizures are relatively common after aneurysmal subarachnoid hemorrhage (aSAH). Seizure prophylaxis is controversial and is often based on risk stratification; middle cerebral artery (MCA) aneurysms, associated intracerebral hemorrhage (ICH), poor neurological grade, increased clot thickness, and cerebral infarction are considered highest risk for seizures. The purpose of this study was to evaluate the impact of recent cocaine use on seizure incidence following aSAH.

METHODS Prospectively collected data from aSAH patients admitted to 2 institutional neuroscience critical care units between 1991 and 2009 were reviewed. The authors analyzed factors that potentially affected the incidence of seizures, including patient demographic characteristics, poor clinical grade (Hunt and Hess Grade IV or V), medical comorbidities, associated ICH, intraventricular hemorrhage (IVH), hydrocephalus, aneurysm location, surgical clipping and cocaine use. They further studied the impact of these factors on “early” and “late” seizures (defined, respectively, as occurring before and after clipping/coiling).

RESULTS Of 1134 aSAH patients studied, 182 (16%) had seizures; 81 patients (7.1%) had early and 127 (11.2%) late seizures, with 26 having both. The seizure rate was significantly higher in cocaine users (37 [26%] of 142 patients) than in non–cocaine users (151 [15.2%] of 992 patients, p = 0.001). Eighteen cocaine-positive patients (12.7%) had early seizures compared with 6.6% of cocaine-negative patients (p = 0.003); 27 cocaine users (19%) had late seizures compared with 10.5% non–cocaine users (p = 0.001). Factors that showed a significant association with increased risk for seizure (early or late) on univariate analysis included younger age (< 40 years) (p = 0.009), poor clinical grade (p = 0.029), associated ICH (p = 0.007), and MCA aneurysm location (p < 0.001); surgical clipping was associated with late seizures (p = 0.004). Following multivariate analysis, age < 40 years (OR 2.04, 95% CI 1.355–3.058, p = 0.001), poor clinical grade (OR 1.62, 95% CI 1.124–2.336, p = 0.001), ICH (OR 1.95, 95% CI 1.164–3.273, p = 0.011), MCA aneurysm location (OR 3.3, 95% CI 2.237–4.854, p < 0.001), and cocaine use (OR 2.06, 95% CI 1.330–3.175, p = 0.001) independently predicted seizures.

CONCLUSIONS Cocaine use confers a higher seizure risk following aSAH and should be considered during risk stratification for seizure prophylaxis and close neuromonitoring.

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KEY WORDS subarachnoid hemorrhage; aneurysm; cocaine; seizure; seizure prophylaxis; antiepileptic medication; vascular disorders

Cocaine abuse is a significant public health issue in the United States. There are approximately 1.6 million cocaine users in the US, with 639,000 new users per year.27 Cocaine use is a known risk factor for stroke, particularly among young patients without other vascular risk factors.4,13,14 While subarachnoid hemorrhage (SAH) comprises only 5% of all strokes in the general population,7 SAH accounts for roughly 20%–30% of strokes among cocaine users.13,14,28 Among patients with aneurysmal SAH (aSAH), recent cocaine use has been reported in up to 33% of cases.20 Cocaine users with aSAH tend to be younger than other aSAH patients, and their aneurysms are more often located in the anterior circulation.3,5,9 Recent cocaine use is independently associated with higher rates of aneurysm rerupture and a nearly 3-fold increase in hospital mortality following aSAH.2
Cocaine abuse has also been historically associated with seizures. Seizures have been reported in 1%–10% of patients with acute cocaine use, but there have been conflicting reports regarding the true impact on seizure incidence compared with the incidence in non–cocaine users. In general, seizures are a relatively frequent occurrence after aSAH and may occur in up to 20% of patients. In the International Subarachnoid Aneurysm Trial (ISAT), seizures were found to be more common following surgical clipping (14%) than after endovascular coiling (8%). Other reported risk factors for seizure following aSAH include middle cerebral artery (MCA) aneurysm location, younger age, worse clinical grade, delayed cerebral ischemia, subarachnoid clot burden, and subdural hematoma. The relationship between cocaine use and seizures following aSAH has been poorly studied.

We sought to further investigate the relationship between cocaine use and seizures following aSAH by reviewing prospectively collected data from our institution between 1991 and 2009. We examined the impact of cocaine use and other potential seizure risk factors on the incidence and timing of seizures after aSAH.

Methods

Cases involving patients admitted to the 2 neuroscience critical care units (NCCUs) at Johns Hopkins Medical Institutions with a diagnosis of aSAH between 1991 and 2009 were reviewed. Vascular neurosurgeons, neurointerventional faculty, and neurointensivists with specialized qualifications in the care of patients with SAH are common across both the campuses, located at Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center. Treatment protocols for aSAH are similar between the 2 units. Data were collected prospectively in an institutional review board–approved database. Patients with SAH due to trauma, angiogram-negative SAH of uncertain etiology, or SAH secondary to other causes such as arteriovenous malformations, dural arteriovenous fistulas, and brain tumors were excluded from our analysis. The Johns Hopkins University institutional review board approved the database collection and waived the need for informed consent.

Patients were divided into 2 groups—those with any seizure at initial presentation and/or during their hospitalization and those without. Seizure was defined based on 1) a clinical diagnosis of seizure by the treating physician, or 2) an electroencephalogram reading confirming seizure. Seizures were also categorized as early (before clipping or coiling) or late (after clipping or coiling). Electroencephalographic (EEG) studies were obtained on an individual basis based on the clinical assessment of the treatment team; routine EEG monitoring was not performed. Continuous EEG monitoring was available if clinically indicated. All patients received antiepileptic prophylaxis with phenytoin and/or levetiracetam. This treatment was continued for a minimum of 7 days, or longer at the discretion of the treating physician. Seizures, if they occurred, were managed by the neurocritical care team.

We analyzed factors that potentially affected the overall incidence of seizures, including patient demographic characteristics, poor clinical Hunt and Hess grade (Grade IV or V), medical comorbidities, associated intracerebral hemorrhage (ICH) or intraventricular hemorrhage (IVH), hydrocephalus, aneurysm location, surgical clipping, and cocaine use. Furthermore, we investigated whether modification of the seizure prophylaxis regimen over the past 2 decades—from phenytoin (1991–2006) to levetiracetam and/or phenytoin (2006–2009)—had any impact on seizure occurrence. Our methods for identifying cocaine-positive versus cocaine-negative patients have been described in detail in previous publications. Acute cocaine use was identified based on positive urine toxicology or a history of cocaine use in the past 72 hours. As some patients presented a few days after the initial onset of headache, when the urine toxicology findings may have been falsely negative, a positive history of cocaine use within 72 hours took precedence over negative results on urine drug screening in those cases. We further studied the impact of each of these factors on early and late seizures.

Statistical Analysis

The unpaired t-test was used when data were normally distributed, and nonparametric tests (Mann-Whitney U-test, Kruskal-Wallis test) were used when data were not normally distributed or categorical. Dichotomous variables were compared with outcome using the chi-square test. The Fisher exact test result was reported where appropriate. Data were analyzed with SPSS version 22.0 (IBM Inc.) to assess the potential impact of each of the admission factors on seizure incidence. The impact of various factors was assessed using multiple logistic regression analysis, excluding factors that were deemed to be collinear.

Results

Data from 1134 patients with aSAH were included in the analysis. A total of 182 (16%) of these patients had seizures. Of these, 81 (7.1%) had early seizures and 127 (11.2%) had late seizures; 26 patients had both early and late seizures. Patient characteristics are shown in Table 1. Patients who had seizures were significantly younger (mean age 50 ± 14.7 years) than patients without seizures (mean age 53 ± 13.8 years, p = 0.009). Compared with those without seizures, patients with seizures had a higher rate of cocaine use (20% vs 11%, p = 0.001), poor Hunt and Hess grade at admission (32% vs 24%, p = 0.029), associated ICH (13% vs 7%, p = 0.007), and MCA aneurysm location (30% vs 11%, p < 0.001). The two groups had similar median GCS scores and rates of medical comorbidities, IVH, and hydrocephalus.

Characteristics of patients with early and late seizures are shown in Table 2. Patients with early seizures had a higher incidence of associated ICH (16% vs 7%, p = 0.005) and higher frequency of poor Hunt and Hess grade at admission (35% vs 24%, p = 0.038) than those without early seizures. Among patients with late seizures, the incidence of ICH (11% vs 7%, p = 0.134) and frequency of poor Hunt and Hess grade (31% vs 24%, p = 0.073) were not significantly different between the 2 groups. Based on our definition, surgical clipping should only be expected to alter the incidence of late (postprocedural) seizures. Surgical
clipping was not significantly more frequent among patients with any seizure (83%) compared with seizure-free patients (79%, p = 0.288); however, clipping was used significantly more often in patients with late seizures (91%) than in those with no seizures (79%, p = 0.004). There was no significant difference in seizure incidence in the 2 NCCUs (15.9% vs 16.5%, p > 0.05). Also, rates of seizures were not significantly different when comparing the “phenytoin era” (15.9%) with the levetiracetam and/or phenytoin prophylaxis regimens used for the last 3 years of the studied database (16.6%, p > 0.05).

Multivariate analysis was performed using factors found to be associated with seizures in univariate analyses (Table 3). Following multivariate analysis, age < 40 years (OR 2.04, 95% CI 1.355–3.058, p = 0.001), poor clinical grade (OR 1.62, 95% CI 1.124–2.336, p = 0.01), ICH (OR 1.95, 95% CI 1.164–3.273, p = 0.011), MCA location (OR 3.3, 95% CI 2.237–4.854, p < 0.001) and cocaine use (OR 2.06, 95% CI 1.330–3.175, p = 0.001) independently predicted seizures after aSAH.

### Cocaine Use

The incidence of seizures following aSAH in patients with and without cocaine use is shown in Fig. 1. Cocaine use was significantly associated with higher rates of overall, early, and late seizures. Of 142 cocaine users, 37 (26%) had seizures compared with 151 (15.2%) of 992 non–cocaine users (p = 0.001). Eighteen cocaine-positive patients (12.7%) had early seizures compared with 6.6% cocaine-negative patients (p = 0.003); 27 cocaine users (19%) had late seizures compared with 10.5% non–cocaine users (p = 0.001). Aneurysm rerupture occurred in 11 patients (7.7%) with cocaine use and 27 patients (2.7%) without cocaine use. As there is a potential interaction between aneurysm rerupture and seizures, we further investigated this by excluding all patients with aneurysm rerupture and repeating our analysis. Cocaine users still had a higher incidence of overall seizures (25.2%) compared with non–cocaine users (14.4%) after excluding those patients with rerupture (p = 0.003).

### Discussion

We found that acute cocaine use is independently associated with seizures after aSAH. This is consistent with the results of a recent retrospective review from the Nationwide Inpatient Sample. Murthy et al.18 reported a seizure incidence of 16.2% in cocaine users compared with 11.1% in non–cocaine users following aSAH.18 Due to the nature of the database, seizure was poorly defined and subject to errors in reporting and coding. Our current study confirms that prospectively identified seizures after aSAH occur more commonly among cocaine users than in non–cocaine users at our institution.

Cocaine use is traditionally thought to increase the risk of seizures.24,25 There are a number of proposed mechanisms by which cocaine may induce seizures. Cocaine decreases GABA activity through alternations in the function of ion channels, in particular sodium and calcium channels, leading to an increase in excitatory neurotransmission.2,22,29 Increased serotonin neurotransmission due to decreased serotonin reuptake has also been implicated in cocaine-induced seizures.37 The 5-HT2 receptors appear to play a significant role in this effect. 5-HT2 receptor agonists and serotonin reuptake inhibitors have been shown to increase cocaine-induced seizures in animal models, while 5-HT2 antagonists appear to increase the seizure threshold.16,17,2 The 5-HT2 receptors and serotonin reuptake inhibitors have been shown to increase cocaine-induced seizures in animal models, while 5-HT2 antagonists appear to increase the seizure threshold.16,17,2 Lastly, chronic cocaine use may increase the body’s sensitivity to the convulsant effects of cocaine.
The underlying mechanism behind seizures after SAH remains unclear and is possibly multifactorial. Potential contributing factors include direct toxicity of the blood itself, inflammation, increased intracranial pressure, vasospasm, and cortical spreading depolarization.\textsuperscript{5,8,11} Regardless of the etiology, SAH patients appear to have a lowered seizure threshold. It is plausible the cocaine-induced alterations in neuronal activity previously discussed have an additive or synergistic effect on the proconvulsive state seen after SAH. For example, spreading convulsions have been identified in patients with SAH and are attributed to reduced GABA activity.\textsuperscript{6} This would be further exacerbated by both the GABA suppression and NMDA receptor–mediated excitatory effects of cocaine.

In a previous publication involving the same patient population, we reported that cocaine users have significantly higher rates of aneurysm rerupture.\textsuperscript{2} After excluding the patients with rerupture, we were able to exclude this as the possible mechanism underlying the higher incidence

\begin{table}
\centering
\caption{Patient characteristics affecting early and late seizures after aSAH\textsuperscript{*}}
\begin{tabular}{|l|c|c|c|c|c|}
\hline
Characteristic & No Seizure & Early Seizure & \textit{p} Value & No Seizure & Late Seizure \\
 & (n = 952) & (n = 81) & & (n = 952) & (n = 127) \\
\hline
Female sex & 688 (72) & 59 (73) & 0.912 & 688 (72) & 84 (66) \\
Race & & & & & 0.151 \\
White & 559 (59) & 48 (59) & 0.534 & 559 (59) & 71 (56) \\
Black & 358 (38) & 29 (36) & & 358 (38) & 51 (40) \\
Hispanic & 13 (1) & 3 (4) & & 13 (1) & 3 (2) \\
Asian & 2 (1) & 0 (0) & & 2 (1) & 0 (0) \\
Other & 20 (2) & 1 (1) & & 20 (2) & 2 (2) \\
Mean age in yrs & 53.0 ± 13.8 & 49.5 ± 14.0 & 0.028 & 53.0 ± 13.8 & 50.5 ± 15.5 \\
Age <40 yrs & 139 (15) & 20 (25) & 0.016 & 139 (15) & 31 (24) \\
Cocaine use & 105 (11) & 18 (22) & 0.003 & 105 (11) & 27 (21) \\
GCS score at admission & & & & & 0.001 \\
Median & 14 & 13 & 0.592 & 14 & 14 \\
Poor admission HH grade & 230 (24) & 28 (35) & 0.038 & 230 (24) & 40 (31) \\
Comorbid condition & & & & & 0.073 \\
No risk factors & 339 (36) & 32 (39) & 0.653 & 339 (36) & 45 (35) \\
1 risk factor & 353 (37) & 26 (32) & & 353 (37) & 44 (35) \\
2 or more risk factors & 260 (27) & 23 (28) & & 260 (27) & 38 (30) \\
IVH & 494 (52) & 36 (44) & 0.198 & 494 (52) & 69 (54) \\
ICH & 69 (7) & 13 (16) & 0.005 & 69 (7) & 14 (11) \\
Hydrocephalus & 503 (53) & 38 (47) & 0.306 & 503 (53) & 60 (47) \\
Aneurysm location & & & & & 0.236 \\
ACoA/ACA & 358 (38) & 28 (35) & <0.001 & 358 (38) & 45 (35) \\
MCA & 106 (11) & 32 (39) & & 106 (11) & 38 (30) \\
ICA & 98 (10) & 10 (12) & & 98 (10) & 11 (9) \\
VB/AICA/PICA/SCA & 162 (17) & 4 (5) & & 162 (17) & 4 (3) \\
PCoA & 228 (24) & 7 (9) & & 228 (24) & 29 (23) \\
MCA vs other & 106 (11) & 32 (39) & <0.001 & 106 (11) & 38 (30) \\
Surgical intervention & & & & & <0.001 \\
Clipped & 748 (79) & 60 (74) & 0.309 & 748 (79) & 115 (91) \\
Coiled & 132 (14) & 11 (14) & & 132 (14) & 10 (8) \\
None & 72 (8) & 10 (12) & & 72 (8) & 2 (2) \\
\hline
\end{tabular}
\textsuperscript{*} Data are numbers of patients (%) unless otherwise indicated. Mean values are presented ± SD.
\end{table}

\section*{TABLE 3. Multivariate analysis of factors impacting seizures after aneurysmal SAH}

\begin{table}
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\begin{tabular}{|l|c|c|}
\hline
Factor & OR & \textit{p} Value \\
\hline
Age <40 yrs & 2.037 & 0.001 \\
Cocaine & 2.055 & 0.001 \\
Poor admission HH grade & 1.620 & 0.010 \\
ICH & 1.952 & 0.011 \\
MCA aneurysm & 3.300 & <0.001 \\
\hline
\end{tabular}
\end{table}
of seizures in the cocaine population. Another potential confounding factor is the concurrent use of alcohol, other illicit substances, or centrally acting medications that could impact the seizure threshold. Other substances have the potential to either augment or diminish the convulsive effect of cocaine, depending on the substance and dose.16 Unfortunately, we had insufficient data to control for this effect.

Surgical clipping was noted to be the modality used to secure the aneurysm in 91% of the patients who had late seizures; this was higher than the overall 84% surgical clipping rate for this aSAH population who had their aneurysms secured. This suggests a likely impact of the choice of procedure on subsequent risk of seizures. The fact that surgical clipping did not have a significant impact on the overall incidence of seizures was a surprising finding at first review of the results; however on further reflection, given that a significant number of seizures occurred prior to securing the aneurysm, the choice of procedure could not be held accountable for this early seizure incidence given our definition for timing of seizures. The true impact of the procedure was really only seen in late seizures (Table 3), which was significant (p = 0.004).

Our study is limited by its retrospective nature and the single academic institution experience. The patient population included in our analysis may not be representative of other centers around the country. A notable difference is the high rate of surgical clipping at our institution (over 80%), which is disparate from what is practiced across most centers in the country. Given that craniotomy was not performed more often in the cocaine cohort than in the non–cocaine group, we do not believe that craniotomy in itself invalidates our findings as it relates to epileptogenic impact of cocaine. Our analysis also did hold true when only coil-treated patients were evaluated. Within the subgroup of patients treated with coiling, cocaine use was associated with a higher incidence of late seizures (12.5%) compared with the incidence in patients without cocaine use (6.3%); however, due to the relatively small number of aneurysms that were treated by this modality, this difference did not meet statistical significance. All patients were admitted to a specialized NCCU, which is not available at many centers in the United States. According to our institutional protocol, all patients with aSAH are started on prophylactic antiepileptic therapy with phenytoin or levetiracetam at the time of admission, and this is not universal practice across the country. This could impact our overall seizure rates, as could the availability and utilization of EEG monitoring in more recent years. We did not, however, note a change in the reported rate of seizures over time with the availability of more frequent long-term EEG monitoring or with the use of newer antiepileptic drugs for seizure prophylaxis as reported above.

Although there are many limitations, we believe our results identify cocaine use as an independent risk factor for seizures following aSAH. Cocaine use should be taken into consideration during risk stratification for seizure prophylaxis. A careful history of substance use should be obtained whenever possible, and it is reasonable to consider toxicology screening in all patients presenting with aSAH. In addition, a higher level of suspicion for seizures should be maintained in patients identified to be cocaine positive at admission. Cocaine-positive patients may warrant more frequent or continuous EEG monitoring, particularly patients with a poor and hence unreliable neurological examination. Further studies are needed to determine whether cocaine users should receive a different prophylactic agent, dose, or duration of treatment and whether different EEG monitoring practices should be adopted in this population.

Conclusions

Acute cocaine use confers a higher risk of seizures following aSAH. Cocaine use should be considered during risk stratification for seizure prophylaxis and neuromonitoring in aSAH patients.

References

Cocaine and seizures after subarachnoid hemorrhage


Disclosure
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: all authors. Acquisition of data: Chang, Tamargo, Naval. Analysis and interpretation of data: all authors. Drafting the article: Chang, Naval. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chang. Statistical analysis: Kowalski. Study supervision: Naval.

Supplemental Information
Previous Presentation
Portions of this work were presented in poster form at the 12th Annual Meeting of the Neurocritical Care Society, Seattle, Washington, September 11, 2014.

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