Impact of Acute Cocaine Use on Aneurysmal Subarachnoid Hemorrhage

Tiffany R. Chang, MD; Robert G. Kowalski, MBCh, MS; Filissa Caserta, MSN, ACNP-BC; Juan Ricardo Carhuapoma, MD; Rafael J. Tamargo, MD; Neeraj S. Naval, MD

Background and Purpose—Acute cocaine use has been temporally associated with aneurysmal subarachnoid hemorrhage (aSAH). This study analyzes the impact of cocaine use on patient presentation, complications, and outcomes.

Methods—Data of patients admitted with aSAH between 1991 and 2009 were reviewed to determine impact of acute cocaine use (C). These patients were compared with aSAH patients without recent cocaine exposure (NC) in relation to their presentation, complications such as aneurysmal rerupture and delayed cerebral ischemia, and outcomes including hospital mortality and functional outcome.

Results—Data of 1134 aSAH patients were reviewed; 142 patients (12.5%) had associated cocaine use. Cocaine users were more likely to be younger (mean age: C, 49±11; NC, 53±14; P<0.001). There were no differences in rates of poor-grade Hunt and Hess (4–5); (C, 21%; NC, 26%; P>0.05), associated intraventricular hemorrhage (C, 56%; NC, 51%; P>0.05), or hydrocephalus on admission Head CT (C, 49%; NC, 52%; P>0.05). Aneurysm rerupture incidence was higher among cocaine users (C, 7.7%; NC, 2.7%; P<0.05). The association of cocaine use with higher risk of delayed cerebral ischemia (C, 22%; NC, 16%; P<0.05) was not significant after correcting for other factors. Cocaine users were less likely to survive hospitalization compared with nonusers (mortality: C, 26%; NC, 17%; P<0.05); the adjusted odds of hospital mortality were 2.9 times higher among cocaine users (P<0.001). There were no differences in functional outcomes between the 2 groups.

Conclusions—Acute cocaine use was associated with a higher risk of aneurysm rerupture and hospital mortality after aSAH. (Stroke. 2013;44:00-00.)

Key Words: aneurysm | cocaine | mortality | outcome | subarachnoid hemorrhage | vasospasm

Subarachnoid hemorrhage comprises ≈5% of all strokes, with an incidence of ≈30,000 per year in the United States. Illicit drug use is a major health hazard, with each drug having unique interactions with the brain and vasculature, predisposing even healthy people to ischemic or hemorrhagic stroke. Cocaine and amphetamines have been found to have the strongest association with stroke. Recent cocaine use has been reported in ≤33% of cases of aneurysmal subarachnoid hemorrhage (aSAH). Cocaine use is widespread and increasingly more common, especially in younger patients. A recent survey reported there are ≈1.9 million cocaine users nationwide. Cocaine users may be younger and more frequently have anterior circulation aneurysms compared with noncocaine users. Although cocaine use has been associated with aSAH, the effect of cocaine on aSAH outcomes remains unclear.

Vasospasm is one proposed mechanism by which cocaine use may directly affect outcome from aSAH. Patients with active cocaine use have been reported to have higher rates of clinically significant or angiographically confirmed vasospasm. Other studies, however, have failed to demonstrate this association. There have also been conflicting reports of the association between cocaine use and clinical presentation as well as functional outcome and mortality from aSAH.

In an earlier analysis of 440 patients who had presented with aSAH at our institution, we had reported an increased prevalence of vasospasm in aSAH patients with recent cocaine exposure, but there was no difference in clinical outcome. With a greater sample size available for review with increasing rates of cocaine use over time, our study now aims to clarify the relationship between cocaine use and aSAH by reviewing the data of patients admitted to our institution over ≈2 decades. We examine whether cocaine use impacts clinical and radiological presentation, complications, such as aneurysm rerupture and cerebral infarction, and ultimately outcomes including hospital mortality.

Materials and Methods

We reviewed data of patients admitted to the Johns Hopkins Medical Institutions with a diagnosis of aSAH between 1991 and 2009, which were incorporated into an institutional review board-approved database. For the purpose of our analysis, we excluded patients with SAH related either to trauma or secondary to other causes such as

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arteriovenous malformation, dural arteriovenous fistulas, and brain tumors or angiogram-negative SAH of uncertain pathogenesis. Patients with recent cocaine exposure were identified based on positive urine toxicology or a history of cocaine use in the past 72 hours. Because of the fact that 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 a negative urine drug screen in such cases. Baseline demographic and radiological data were examined in patients with (C) and without (NC) recent cocaine exposure.

Outcome measures studied included (1) hospital mortality, (2) functional status at and after discharge, using Glasgow Outcome Scale (evaluated by a neurosurgeon both at discharge and at first clinic appointment postdischarge), and (3) complications related to aSAH, including aneurysm rerupture and delayed cerebral ischemia (DCI). Good functional outcome was defined as Glasgow Outcome Scale 4 to 5. The impact of other factors that could affect outcomes such as age, admission Glasgow Coma Scale (GCS), Hunt and Hess grade, World Federation of Neurological Societies scale, cocaine use, intraventricular hemorrhage (IVH), and hydrocephalus was analyzed as well.

We also compared complications associated with SAH, including incidence of aneurysmal rerupture and DCI. Aneurysm rerupture was determined based on CT confirmation of new SAH, IVH, or intracerebral hemorrhage after a neurological deterioration that prompted the CT in the first place or identified on institutional CT after interhospital transfer. To define DCI, we included patients who had new clinical deterioration >48 hours post-SAH and >24 hours after surgical clipping or endovascular coiling and (1) radiological confirmation of cerebral infarction, (2) angiographic confirmation of vasospasm, or (3) clinical responsiveness (transient or sustained) to hemodynamic augmentation with transcranial doppler correlation. The impact of these complications as well as the method of securing aneurysm (surgical clipping or endovascular coiling) on hospital mortality and functional outcomes was also assessed.

Statistical Analysis
The unpaired t test was used when data were normally distributed, and nonparametric tests (Mann–Whitney U test, Kruskal–Wallis test) used when data were not normally distributed. Dichotomous variables were compared with outcome using the χ² test. The Fisher exact test result was reported where appropriate. The SPSS (version 18.0; SPSS Statistics, Chicago, IL) was used to assess the potential impact of these complications as well as the method of securing aneurysm (surgical clipping or endovascular coiling) on hospital mortality and functional outcomes was also assessed.

Results
One thousand one hundred thirty-four patients with aSAH were included in the analysis. Recent cocaine use was present in 142 patients (12.5%). Baseline patient characteristics are shown in Table 1. Cocaine users were more likely to be younger (mean age: C, 49; NC, 53; P<0.001). Clinical presentation on admission was similar between the 2 groups, using admission GCS, Hunt and Hess grades, and World Federation of Neurological Societies scale. There were no significant differences in rates of poor-grade Hunt and Hess (4–5), World Federation of Neurological Societies scale, IVH, hydrocephalus, and cocaine use. Age, grade on admission based on admission GCS, Hunt and Hess grade, or World Federation of Neurological Societies scale, IVH, hydrocephalus, and cocaine use were predictors of hospital mortality. Multivariate analysis showed that the adjusted odds of hospital mortality were 2.9× higher among cocaine users (odds ratio [OR], 2.857; 95% confidence interval [CI], 1.761–4.630; P<0.001; Table 1). Age (OR, 1.034; 95% CI, 1.020–1.047; P<0.010) and clinical status at admission were the only other independent predictors of mortality, with Hunt and Hess grade being the strongest clinical predictor (OR, 2.336; 95% CI, 2.020–2.695; P<0.010).

Surgical clipping, which accounted for 84% of aneurysm securing procedures, was associated with lower mortality than endovascular clipping. However, because the latter was performed in a generally older and higher-grade population, this difference was not observed after correction for other admission factors impacting outcomes.

Aneurysm Rerupture
Aneurysm rerupture occurred in 11 patients (7.7%) with cocaine use and 27 patients (2.7%) without cocaine use; this difference was statistically significant (P<0.05). Aneurysm

<table>
<thead>
<tr>
<th>Table 1. Baseline Patient Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Cocaine Use (n=142)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Age &gt;70</td>
</tr>
<tr>
<td>Grade 4/5 H/H</td>
</tr>
<tr>
<td>WFNS 1 (1–5)</td>
</tr>
<tr>
<td>GCS 15 (3–15)</td>
</tr>
<tr>
<td>GCS&lt;8</td>
</tr>
<tr>
<td>Associated IVH</td>
</tr>
<tr>
<td>Hydrocephalus</td>
</tr>
</tbody>
</table>

Data are: n (%), mean±SD, median (range). GCS indicates Glasgow Coma Scale; H/H, Hunt and Hess grade; IVH, intraventricular hemorrhage; and WFNS, World Federation of Neurosurgical Societies subarachnoid hemorrhage grading scale.

Figure 1. Relationship between cocaine use, hospital mortality, and vasospasm-mediated cerebral infarction after aneurysmal subarachnoid hemorrhage.
 Delayed Cerebral Ischemia

Cocaine users were more likely to have DCI (C, 22%; NC, 16%; P=0.041); however, after multivariate analysis, this association was not found to be statistically significant. Age (OR, 1.029; 95% CI, 1.016; P=0.001), Hunt and Hess grade at admission (OR, 1.218; 95% CI, 1.072–1.383; P=0.002), and IVH (OR, 1.696; 95% CI, 1.019–2.546; P=0.003) remained independent predictors of vasospasm-mediated cerebral infarction. DCI was not independently associated with age (OR, 1.029; 95% CI, 1.016–1.042; P<0.001) and Hunt and Hess grade at admission (OR, 2.188; 95% CI, 1.934–2.469; P<0.001).

Functional Outcomes

There was no significant difference in functional outcome at discharge or postdischarge between the 2 groups. Favorable functional outcome at discharge was also independently associated with age (OR, 1.066; 95% CI, 1.054–1.080; P<0.001) and Hunt and Hess grade at admission (OR, 2.188; 95% CI, 1.934–2.469; P<0.001).

Discussion

We found recent cocaine use to be an independent predictor of in-hospital mortality in patients with aSAH. To our knowledge, this is the first report of this association in a study of this size. A recent study by Alaraj et al examined the effect of cocaine use on outcomes from aSAH. They found no differences in clinical vasospasm, functional outcome, or mortality in cocaine users. However, recent cocaine use was present in 25% of patients with cocaine use (25%) compared with those without (16%; P=0.019).

We did find higher incidence of aneurysm rupture after SAH among cocaine users in our patient population, which has historically been linked to higher case-fatality rates. Cocaine use is associated with hypertension, which may play a key role in aneurysm rupture in cocaine users,9,10 with cocaine-mediated sympathetic hyperstimulation causing transient, profound hypertension. This is potentially mediated by inhibition of reuptake of dopamine and norepinephrine from the synaptic cleft, which in turn stimulates the release of adrenal catecholamines and increases postsynaptic catecholamine and dopamine-receptor sensitivity.11 A limitation of our analysis is the lack of reliable relevant blood pressure data which would have helped clarify if the mechanism of increased aneurysm rupture was associated with a hospital mortality rate of 39.5% compared with 17.5% in patients without aneurysm rupture (P=0.002). After the exclusion of patients who had aneurysm rupture from both cohorts, hospital mortality remained elevated in patients with cocaine use (25%) compared with those without (16%; P=0.019).

Table 2. Impact of Admission Characteristics on Mortality, Functional Outcome, and Delayed Cerebral Ischemia (Univariate Analysis)

<table>
<thead>
<tr>
<th>Admission Variables</th>
<th>In-Hospital Mortality</th>
<th>Hospital Discharge Status</th>
<th>Delayed Cerebral Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dead (n=207)</td>
<td>Alive (n=927)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Value</td>
<td>Value</td>
<td>Value</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>95% Confidence Interval</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Hunt and Hess</td>
<td>4 (1–5)</td>
<td>2 (1–5)</td>
<td>4 (1–5)</td>
</tr>
<tr>
<td>Poor-grade H/H (4–5)</td>
<td>125 (60)</td>
<td>163 (18)</td>
<td>182 (51)</td>
</tr>
<tr>
<td>WFNS</td>
<td>4 (1–5)</td>
<td>1 (1–5)</td>
<td>4 (1–5)</td>
</tr>
<tr>
<td>Age</td>
<td>58.4±14.3</td>
<td>51.2±13.6</td>
<td>60.6±13.9</td>
</tr>
<tr>
<td>IVH</td>
<td>147 (71)</td>
<td>439 (47)</td>
<td>245 (69)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>142 (69)</td>
<td>447 (48)</td>
<td>241 (68)</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>37 (18)</td>
<td>105 (11)</td>
<td>39 (11)</td>
</tr>
</tbody>
</table>

Data are: n (%), mean±SD, median (range). GCS indicates Glasgow Coma Scale; GOS, Glasgow Outcome Scale; H/H, Hunt and Hess grade; IVH, intraventricular hemorrhage; and WFNS, World Federation of Neurosurgical Societies subarachnoid hemorrhage grading scale.

Table 3. Factors Impacting Mortality, Functional Outcomes, and Delayed Cerebral Ischemia (Multivariate Analysis)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds Ratio</th>
<th>P Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (higher)</td>
<td>1.034</td>
<td>&lt;0.001</td>
<td>1.020–1.047</td>
</tr>
<tr>
<td>Admission H/H</td>
<td>2.336</td>
<td>&lt;0.001</td>
<td>2.020–2.695</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>2.857</td>
<td>&lt;0.001</td>
<td>1.761–4.630</td>
</tr>
<tr>
<td>Good discharge status (GOS 4, 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (lower)</td>
<td>1.066</td>
<td>&lt;0.001</td>
<td>1.054–1.080</td>
</tr>
<tr>
<td>Admission H/H</td>
<td>2.188</td>
<td>&lt;0.001</td>
<td>1.934–2.469</td>
</tr>
<tr>
<td>Delayed cerebral ischemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (lower)</td>
<td>1.029</td>
<td>&lt;0.001</td>
<td>1.016–1.042</td>
</tr>
<tr>
<td>Admission H/H</td>
<td>1.218</td>
<td>0.002</td>
<td>1.072–1.383</td>
</tr>
<tr>
<td>IVH</td>
<td>1.696</td>
<td>0.003</td>
<td>0.193–2.412</td>
</tr>
</tbody>
</table>

GOS indicates Glasgow Outcome Scale; H/H, Hunt and Hess grade; and IVH, intraventricular hemorrhage.
rerupture was secondary to uncontrolled hypertension in cocaine users.

It must be noted that examination of our aSAH database after exclusion of all patients who had rerupture of the aneurysm revealed a persistent impact of cocaine use on mortality. This suggests that other factors may also have contributed to higher mortality observed in patients with cocaine use as well. We could not reliably examine the concurrent use of alcohol, cigarettes, or other illicit substances, because some of these data had not been consistently collected. We also reviewed the database for do not resuscitate/do not intubate status, and did not find a higher association of do not resuscitate/do not intubate status or early withdrawal of technological support in patients in the cocaine cohort.

Another potential factor is the effect cocaine and hypertension may have on cardiac function after subarachnoid hemorrhage. Kothavale et al.12 prospectively studied the echocardiograms of 300 patients. They found cocaine use to be an independent predictor of regional wall motion abnormalities after subarachnoid hemorrhage. We could not reliably examine cardiac function in cocaine users in the present study because obtaining echocardiograms was not part of the routine management protocol for all SAH patients but rather driven by clinical indication. Myocardial stunning has been associated with vasospasm-mediated infarction but has not generally been found to impact outcome independently from aSAH.2,3,4 Further research to examine this relationship is warranted.

Previous case series have reported an independent association between cocaine use and symptomatic vasospasm.2,3,5 Cocaine may potentially cause vasospasm by several mechanisms: (1) inhibition of serotonin reuptake,15 (2) potentiation of norepinephrine-induced vasoconstriction,16 (3) increasing calcium flux into vascular smooth muscle,17 (4) through active metabolites benzoylecgonine and ecgonine,18 and (5) endothelin-1–mediated endothelial activation.2 We elected to use DCI as our end point defined by a constellation of clinical deterioration, timing of deterioration consistent with natural history of vasospasm, radiological confirmation of cerebral infarction, and either angiographic vasospasm or high clinical index of suspicion based on clinical response to therapy with transcranial doppler corroboration. Selection of this end point was based on data from a large case series of 580 patients, suggesting that angiographic and transcranial Doppler vasospasm in isolation are not associated with any differences in meaningful clinical outcomes, whereas symptomatic vasospasm in the absence of cerebral infarction is associated with poor cognitive outcomes but not death or severe disability.19 Only DCI incorporating both cerebral infarction and symptomatic vasospasm in that case series was found to be associated with higher rates of death and severe disability at 3 months.

Although we found that cocaine users were more likely to have DCI, this association was not statistically significant after controlling for other confounding factors. Cerebral vasospasm has been associated with younger age,20 although not consistently,21 and SAH patients associated with cocaine use were younger in our analysis. IVH was another factor associated with higher risk of cerebral infarction secondary to vasospasm. It has been reported that cocaine-associated intracerebral hemorrhage has an association with higher rates of IVH compared with patients with cocaine-negative intracerebral hemorrhage.22 The underlying mechanisms that predispose cocaine exposure to cause IVH in adults remains unclear, but if in fact a cause–effect relationship between cocaine use and IVH does exist, one could argue that the observed trends toward a higher incidence of IVH in the setting of SAH in our analysis (C, 56%; NC, 51%) may represent one mechanism by which exposure to cocaine predisposes to a higher risk of cerebral vasospasm. Therefore, the inclusion of IVH in the multivariate analysis model may potentially mask the true impact of cocaine exposure on DCI.

Despite an independent association with lower rates of survival, we did not demonstrate any difference in functional outcomes in cocaine users. This could have been driven by the significant differences in age between the 2 groups, with younger patients much more likely to recover from neurological injury. Previous studies have reported worse functional outcomes in cocaine users, but these studies have also reported higher Hunt and Hess grades among cocaine users.2,3,5 Long-term functional outcomes studies are lacking. The lack of a standardized time for follow-up appointment postdischarge renders our functional status evaluation suboptimal.

Our study has several limitations including the lack of standardized care given the different neurosurgical and neurocritical care providers managing these patients and changes in patient management and practice guidelines over time. Despite the fact that all data were collected prospectively, our retrospective review of this data limits our ability to obtain information that we now deem clinically relevant such as (1) trends in systolic and mean arterial blood pressure and correlation of suboptimal blood pressure control with aneurysm rerupture rates, (2) information regarding cardiac status and presence of myocardial stunning based on echocardiograms, which are not available for all patients because this was not considered routine standard of care for SAH admissions, and (3) Fisher grade, which we did not adjust for with regard to DCI. However, we adjusted for radiological factors that impacted DCI and found IVH to be the most strongly predictive factor, which was included in multivariate analysis. An important limitation may be the potential usefulness of the results of our analysis, because there are limited therapeutic implications. Closer monitoring may be indicated, given the higher risk for mortality and aneurysm rerupture among cocaine users. Perhaps further research that focuses on interventions that could decrease the risk of aneurysm rerupture (eg, strict blood pressure control, antifibrinolytic therapy) may be warranted in this population. A safety end point as it relates to DCI would also be required, given the correlation of cocaine use with DCI on univariate (but not multivariate) analysis.

**Conclusions**

Acute cocaine use was associated with a higher risk of hospital mortality after aSAH. Because mortality remained higher in the cocaine group after the exclusion of patients with aneurysm rerupture, it is unlikely that rerupture represents the only mechanism for the nearly 3-fold increased odds of death associated with cocaine use. The relationships between age, cocaine use, cerebral vasospasm, and cardiac function warrant further investigation. Long-term functional outcomes from
subarachnoid hemorrhage in cocaine users represent an area of future research.

Disclosures
Dr Naval has received honoraria as a speaker for Cornerstone Therapeutics. The other authors have no conflict to report.

References
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