Cocaine Use Is an Independent Risk Factor for Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

James E. Conway, BS; Rafael J. Tamargo, MD

Background and Purpose—Although acute cocaine use has been temporally associated with aneurysmal subarachnoid hemorrhage (aSAH), the prevalence of vasospasm and the clinical outcome of patients experiencing aSAH associated with cocaine exposure are unclear. We have analyzed this patient population in our institution to address these issues.

Methods—Between 1992 and 1999, 440 patients presented to our institution with aSAH. This sample was retrospectively analyzed to determine which patients had used cocaine within 72 hours of aSAH as documented by urine toxicology studies or patient history. These patients were then compared with control aSAH patients without recent cocaine exposure through univariable and multivariable analyses.

Results—Twenty-seven aSAH patients (6.1% of total) had either urine toxicology positive for cocaine metabolites (20 patients, 74%) or a history of cocaine use within 72 hours of aSAH (7 patients, 26%). Cocaine users were more likely to experience cerebral vasospasm defined as a delayed clinical deficit (from 3 to 16 days after aSAH) unexplained by concurrent CT scan and either responsive to hypervolemic and/or hypertensive therapy or accompanied by angiographic confirmation of vessel narrowing than control subjects (63% versus 30%; odds ratio [OR], 3.90; 95% confidence interval [CI], 1.77 to 8.62; \( P<0.0001 \)). Patients using cocaine were younger than control subjects (mean age, 36 versus 52 years; \( P<0.0001 \)). Aneurysms of the anterior circulation were observed more frequently in cocaine users than in control subjects (97% versus 84%; OR, 6.89; 95% CI, 1.18 to 47.47; \( P=0.029 \)). A significant difference was not observed, however, in the discharge Glasgow Outcome Scale (GOS) scores between the 2 groups (\( P=0.73 \)). Differences were not observed between the 2 groups when the distributions of sex, hypertension, admission Glasgow Coma Scale subarachnoid hemorrhage grade, and multiple aneurysms were analyzed. Logistic regression models identified variables independently associated with vasospasm and discharge GOS score. Only a thick blood clot on the admission CT (OR, 7.46; 95% CI, 3.95 to 14.08; \( P<0.0001 \)) and recent cocaine use (OR, 6.41; 95% CI, 2.14 to 19.23; \( P=0.0009 \)) were independently associated with vasospasm. Cocaine use was not independently associated with the discharge GOS score.

Conclusions—We conclude that there is an increased prevalence of vasospasm in aSAH patients with recent cocaine exposure but no difference in clinical outcome. In addition, these patients are younger and more likely to have anterior circulation aneurysms. (Stroke. 2001;32:2338-2343.)

Key Words: cocaine ■ subarachnoid hemorrhage ■ vasospasm
To address these issues, we have analyzed patients who presented to our institution with aSAH. A retrospective analysis of these patients was completed to determine which patients experienced aSAH associated with documented cocaine exposure. Univariable and multivariable statistical models were then evaluated to determine whether recent cocaine exposure was independently associated with cerebral vasospasm and clinical outcome in aSAH patients.

Subjects and Methods

Patient Selection Criteria

Patients admitted to the neurosurgical service of The Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center (both in Baltimore, Md) between January 1992 and July 1999 with an angiographically or autopsy-proven diagnosis of aSAH were included in the study. Unruptured aneurysm patients were excluded. The medical, toxicology, radiology, and autopsy records for all patients were reviewed retrospectively. The diagnosis of SAH was confirmed by either CT scan or lumbar puncture. The diagnosis of cerebral aneurysm was confirmed by either angiography or autopsy. Patients with SAH from causes other than cerebral aneurysm or from unidentifiable causes were excluded from the study. A total of 440 patients with aSAH were the study subjects.

Clinical and Radiological Features

Medical records of all aSAH patients were reviewed to determine which patients had a history of cocaine use within 72 hours of symptom onset. Admission urine toxicology analyses were reviewed to determine which patients had toxicology evidence of cocaine exposure. Generally, the limit of detection for cocaine and its metabolites is <72 hours after administration. Of 440 patients, 32 had toxicology tests. Twenty patients tested positive for cocaine or its metabolites; 12 patients tested negative. A history of additional drug use, including heroin, barbiturate, benzodiazepine, marijuana, amphetamine, or alcohol, was recorded, as well as urine toxicology evidence of heroin, barbiturate, benzodiazepine, marijuana, or amphetamine administration. The type of cocaine administered (alkaloid or cocaine hydrochloride) was determined from the history.

Additional clinical features recorded for each patient included the patient’s admission Glasgow Coma Scale (GCS) SAH grade, discharge Glasgow Outcome Scale (GOS) score, occurrence of vasospasm, age, race, sex, number of aneurysms, location of aneurysms, and preexisting medical conditions.

At admission to medical care, each patient was evaluated by the house staff and faculty of the Department of Neurosurgery, who assigned GCS scores to each patient. The admission GCS score for each patient was converted to a GCS SAH grade with the use of a 5-level GCS SAH grading system that we have previously shown to have greater predictive value than other SAH grading systems in a logistic regression model. Briefly, in the GCS SAH grading system, an admission GCS score of 15 corresponds to grade of I; a GCS score of 12 to 14, a grade of II; a GCS score of 9 to 11, a grade of III; a GCS score of 6 to 8, a grade of IV; and a GCS score of 3 to 5, a grade of V.

At discharge from short-term hospitalization, each patient was given a GOS rating based on the written evaluations of either the rehabilitation medicine physicians or the physical, occupational, or speech therapists involved in the outcome assessment of the patient. As originally presented, a GOS score of 1 describes death; a GOS score of 2, persistent vegetative state; a GOS score of 3, severe disability (conscious but disabled); a GOS score of 4, moderate disability (disabled but independent); and a GOS score of 5, good recovery with resumption of normal life. The GOS is recommended as the preferred outcome measure after aSAH by the World Federation of Neurological Surgeons. The GOS has a high interobserver reproducibility and good association with neuropsychological outcome.

The diagnosis of symptomatic vasospasm was based on documentation of a delayed clinical deficit (from 3 to 16 days after aSAH) unexplained by concurrent CT scan and either responsive to hypervolemic and/or hypertensive therapy or accompanied by angiographic confirmation of vessel narrowing. All patients were prophylactically treated for vasospasm with hypervolemic therapy and nimodipine. Fourteen aSAH patients without cocaine exposure died before cerebral vasospasm could occur. The 14 early deaths in the nonexposure group (3.4% of patients not exposed to cocaine) was not statistically different from 0 deaths in the cocaine group (P=0.33, Fisher’s exact test).

Age was stratified by decade. Race was categorized into white, black, and other (including Asian and Hispanic). Cerebral aneurysm number and location were determined by angiography. For statistical analysis, aneurysm location was dichotomized into anterior cerebral artery (ACA) and internal carotid artery (ICA) aneurysms or middle cerebral artery and posterior circulation aneurysms, as suggested by Qureshi et al. Preexisting medical conditions such as a history of treated hypertension were recorded. Intravenous drug use–associated medical complications, including hepatitis B or C infection, HIV infection, endocarditis, or abscess, were noted.

Admission head CT scans obtained within 72 hours of symptom onset were reviewed when available. Subarachnoid clot thickness was determined manually with the centimeter scale printed on each CT scan and was stratified into 2 groups based on thickness (≤5 mm = thin clot or >5 mm = thick clot) as previously described. The thickness of the subarachnoid clot on CT scan was used in the analysis because the location and extent of subarachnoid blood found on the CT scan have been shown to be related to the development of cerebral vasospasm. Head CT scans obtained >72 hours after symptom onset were not included in the analysis because it has been demonstrated that the sensitivity of CT for detecting SAH falls to <70% at this point secondary to elimination of blood from the subarachnoid space.

Statistical Analysis

Patients presenting with aSAH associated with cocaine use were compared with control aSAH patients without cocaine exposure. Univariable comparisons of the distributions of sex, age, presence of multiple aneurysms, aneurysm location, history of treated hypertension, admission GCS SAH grade, discharge GOS score, and symptomatic vasospasm in the 2 groups were completed. Dichotomous variables were analyzed by use of 2-sided Fisher’s exact test. The odds ratio (OR) and 95% confidence interval (CI) were calculated. Ordinal variables were analyzed by use of the Wilcoxon rank-sums test. A value of P<0.05 was considered significant.

Admission CT scans were available for 240 patients, 17 of whom were cocaine users. Primary reasons for CT unavailability were that the CT was not transferred with the patient, the CT was not present in the patient’s radiology file, and the patient was admitted >72 hours after aSAH. To determine whether those patients with admission head CTs were representative of the total aSAH sample, a comparison of the distributions of age, recent cocaine use, symptomatic vasospasm, and discharge GOS score between the 2 groups was completed. A difference was not observed in any distribution (P=0.48, P=0.56, P=0.83, and P=0.62, respectively). Dichotomous variables were analyzed by use of 2-sided Fisher’s exact test. Ordinal variables were analyzed by use of the Wilcoxon rank-sums test. A value of P<0.05 was considered significant.

Multivariable analysis using stepwise logistic regression analysis with backward elimination was used to determine which admission clinical and radiological variables were independent predictors of vasospasm and discharge GOS score. In the first model, the variables of age, sex, race, admission GCS SAH grade, hypertension, aneurysm location, and recent cocaine exposure were treated as independent variables, and symptomatic vasospasm was treated as the dependent variable. Next, for patients with an admission head CT, SAH clot thickness on the admission head CT and all other clinical and radiological variables were analyzed to identify those variables independently associated with symptomatic vasospasm. In another model, possible independent predictors of the discharge GOS score,
including age, sex, race, admission GCS SAH grade, hypertension, aneurysm location, acute cocaine exposure, and symptomatic vasospasm, were analyzed. Finally, for patients with an admission head CT, SAH clot thickness and all other features were analyzed to identify variables independently associated with discharge GOS score. In all multivariable analyses, a value of $P<0.05$ was required for retention of the independent variable in the final model.

Statistical Analysis Software (version 6.12, SAS Institute) and Stata statistical software (version 6.0, Stata Corp) were used for these analyses.

Results

Characteristics of Patients With aSAH Associated With Cocaine Use

Of the 440 patients who presented with aSAH, 27 patients (6.1%) had evidence of recent cocaine exposure. Of these 27 patients, 20 (74%) had urine toxicology positive for cocaine or its metabolites. Seven patients (26%) in whom urine toxicology was not performed provided a history of cocaine use $<72$ hours before symptom onset. The type of cocaine administered before aSAH was known from the patient’s history for 26 of the 27 patients (96%). Thirteen aSAH patients (48%) administered cocaine hydrochloride, and 13 patients (48%) administered the alkaloid form of the drug. The cocaine formulation used was not known for 1 patient (4.0%).

Many patients with cocaine-associated aSAH had a significant history or toxicology evidence of polysubstance abuse. Additional drug use occurred in 22 patients (81%). Alcohol was used by 16 patients (59%), heroin by 14 patients (52%), and marijuana by 4 patients (15%). Additionally, 10 patients (37%) with cocaine-associated aSAH had a history of medical problems acquired from drug use. Five patients (18%) had serological evidence of hepatitis C infection, 4 (15%) were infected with HIV, 3 (11%) had abscesses, 3 had endocarditis (11%), and 1 was infected by hepatitis B virus (3.7%).

Univariable Comparison Between Cocaine Users and Control Subjects

Patients with cocaine-associated aSAH were compared with control aSAH patients (Table 1). Patients with cocaine-associated aSAH experienced symptomatic vasospasm more frequently than control aSAH patients, were younger, and had a greater proportion of anterior cerebral circulation aneurysms. Of 27 cocaine-exposed patients, 17 (63%) experienced vasospasm, but only 30% of nonusers experienced vasospasm (OR, 3.90; 95% CI, 1.77 to 8.62; $P=0.001$). The mean age of cocaine-associated aSAH patients was 36 years compared with 52 years in the control group ($P<0.0001$). Aneurysms of the anterior circulation made up 97% of aneurysms in the cocaine group but only 84% in the control group (OR, 6.89; 95% CI, 1.18 to 47.47; $P=0.03$). Differences were not observed between the 2 groups for sex, percentage of patients with a history of treated hypertension, or frequency of multiple aneurysms.

The distributions of the admission GCS SAH grades and discharge GOS scores for patients with cocaine-associated aSAH and control aSAH patients were analyzed (the Figure). A statistically significant difference was not observed in the distributions of admission SAH GCS grades between the 2 groups ($P=0.88$). In addition, there was no detectable difference between the groups in discharge outcomes as assessed by GOS scores ($P=0.73$).

Independent Predictors of Vasospasm After aSAH

To identify clinical and radiological variables independently associated with vasospasm, statistical models using logistic regression were constructed. In the first model, the association between the dependent variable vasospasm and the independent variables age, sex, race, admission GCS SAH grade, hypertension, aneurysm location, and recent cocaine use was analyzed (Table 2). In this model, recent cocaine use (OR, 4.06; 95% CI, 1.78 to 9.26; $P=0.0009$), ACA and ICA aneurysms (OR, 1.77; 95% CI, 1.16 to 2.69; $P=0.0075$), and higher admission GCS SAH grade (OR, 1.25; 95% CI, 1.05 to 1.49; $P=0.012$) were independently associated with vasospasm. The patient’s age, sex, race, and history of hypertension were not independently associated with vasospasm ($P=0.12$, $P=0.14$, $P=0.075$, and $P=0.061$, respectively).

An analysis of factors independently associated with vasospasm was also completed with SAH clot thickness on the
admission CT used as an additional independent variable (Table 3). In this analysis, only a thick SAH clot (OR, 7.46; 95% CI, 3.95 to 14.08; \( P < 0.0001 \)) and recent cocaine use (OR, 6.41; 95% CI, 2.14 to 19.23; \( P < 0.0009 \)) were independently associated with the development of vasospasm. The patient’s age, sex, race, admission GCS SAH grade, hypertension, aneurysm location, and recent cocaine use were not independently associated with vasospasm (\( P = 0.32, P = 0.31, P = 0.32, P = 0.89, P = 0.77, \) and \( P = 0.14 \), respectively).

### Discussion

Cocaine use has been temporally associated with aSAH in previous reports.\(^1-4,6-10,12\) Although cocaine is a vasoactive drug, these studies did not specifically investigate any potential association between cocaine-related aSAH and delayed symptomatic cerebral vasospasm. In addition, the studies that have specifically analyzed cocaine-related aSAH have reached opposite conclusions regarding the clinical outcome of these patients.\(^1,3,8\)

In this study, we compared clinical and radiological features of 27 patients with documented cocaine use before aSAH to those of 413 control aSAH patients. As in previous reports, patients who presented with cocaine-associated aSAH were younger than control aSAH patients and had a greater proportion of anterior circulation aneurysms.\(^1,3,8\) Unique to our analysis is the observation that patients with clot thickness as an independent variable. In 1 model, the association between discharge GOS score and age, sex, race, admission GCS SAH grade, hypertension, aneurysm location, and recent cocaine use was determined (Table 4). In this analysis, higher admission GCS SAH grade (OR, 2.76; 95% CI, 1.65 to 4.63; \( P < 0.0001 \)), and increased age (OR, 1.39; 95% CI, 1.16 to 1.65; \( P = 0.0001 \)) were independently associated with worse outcome. Sex, race, hypertension, recent cocaine use, and aneurysm location were not independently related to outcome (\( P = 0.84, P = 0.55, P = 0.73, P = 0.51, P = 0.29, \) and \( P = 0.14 \), respectively).

### Independent Predictors of Discharge GOS Score After aSAH.

Analyses of variables independently associated with worse discharge GOS scores were completed with and without SAH clot thickness as an independent variable. In 1 model, the association between discharge GOS score and age, sex, race, admission GCS SAH grade, hypertension, aneurysm location, recent cocaine use, and aneurysm location were not independently related to outcome (\( P = 0.69, P = 0.89, P = 0.14, P = 0.44, \) and \( P = 0.79 \), respectively).

Analysis of factors independently associated with discharge GOS scores was also completed with SAH clot thickness used as an additional independent variable. Again, only higher admission GCS SAH grade (OR, 2.76; 95% CI, 1.65 to 4.63; \( P < 0.0001 \)), and increased age (OR, 1.39; 95% CI, 1.16 to 1.65; \( P = 0.0001 \)) were independently associated with worse outcome. Sex, race, hypertension, recent cocaine use, and aneurysm location and SAH clot thickness were not independently related to outcome (\( P = 0.84, P = 0.55, P = 0.73, P = 0.51, P = 0.29, \) and \( P = 0.14 \), respectively).

### Table 2: Multivariable Analysis of Features That Independently Predicted Symptomatic Vasospasm in Patients With aSAH

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine use</td>
<td>4.06</td>
<td>1.78–9.26</td>
<td>0.0009</td>
</tr>
<tr>
<td>ACA and ICA aneurysms</td>
<td>1.77</td>
<td>1.16–2.69</td>
<td>0.0075</td>
</tr>
<tr>
<td>GCS SAH grade</td>
<td>1.25</td>
<td>1.05–1.49</td>
<td>0.012</td>
</tr>
</tbody>
</table>

### Table 3: Multivariable Analysis of Features That Independently Predicted Symptomatic Vasospasm in Patients With aSAH When Blood Clot Thickness on the Admission CT Is Also Considered

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thick SAH clot</td>
<td>7.46</td>
<td>3.95–14.08</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>6.41</td>
<td>2.14–19.23</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

### Table 4: Multivariable Analysis of Features That Independently Predicted a Worse Discharge GOS Score in Patients With aSAH

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS SAH grade</td>
<td>2.41</td>
<td>2.01–2.88</td>
<td>0.0001</td>
</tr>
<tr>
<td>Vasospasm</td>
<td>2.99</td>
<td>2.02–4.43</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.49</td>
<td>1.31–1.70</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
cocaine-related aSAH were more likely to experience vasospasm (OR, 3.90) than other aSAH patients.

In this study, recent cocaine use was an independent risk factor strongly associated with the development of vasospasm in 2 multivariable logistic regression models. In 1 statistical model, recent cocaine use (OR, 4.06), higher admission GCS SAH grade (OR, 1.25), and a ruptured ACA or ICA aneurysm (OR, 1.77) were related to the development of vasospasm. When SAH clot thickness was considered in the statistical model, only a thick SAH clot (OR, 7.46) and cocaine use (OR, 6.41) were independent risk factors for the development of vasospasm.

Previous studies have analyzed the association of risk factors with the development of symptomatic vasospasm after aSAH.13,28,30–34 Fisher et al30 and Kistler and colleagues31 were the first to demonstrate that SAH clot thickness was predictive of vasospasm. Ohman et al15 reported that SAH clot thickness, the timing of surgery, and a history of hypertension were related to the development of vasospasm. Rabb et al32 demonstrated that in addition to SAH clot thickness, cerebral vasospasm was also associated with clinical grade and age. Lasner et al33 and Weir et al34 reported that cigarette smoking was a risk factor for the development of vasospasm, although Weir and colleagues found that the relationship was not very strong. Qureshi et al28 recently reported that transcranial Doppler results and ruptured ACA and ICA aneurysms could also be associated with the development of vasospasm.

Cocaine is highly lipophilic and readily crosses the blood-brain barrier.35 Although cocaine has a relatively short half-life of ~1 hour, the major cocaine metabolite benzoylecgonine is still eliminated up to 10 days after administration in long-term cocaine users.18–20 Cocaine and its metabolites have been shown to potently induce cerebral artery vasoconstriction and cause chronic cerebral hypoperfusion in both animal models and human clinical studies.36–41 Cocaine may directly predispose patients suffering from aSAH to symptomatic vasospasm by increasing the reactivity of cerebral vessels to vasoconstrictive factors present in the SAH clot and indirectly by decreasing cerebral blood flow reserves through chronic hypoperfusion.

The primary screening tool used to identify cocaine-exposed patients was history and physical examination. It is likely, however, that the history and physical examination did not identify every patient with recent cocaine exposure, particularly occasional cocaine users. Urine and blood toxicology tests were usually performed on patients only if there was historical evidence of drug use, a previous medical illness that would be consistent with drug use (history of hepatitis C infection, HIV infection, bacterial endocarditis, etc), or physical signs (abscesses or injection marks) suggesting drug use. Thus, the patients identified in this study were generally long-term drug users, as evidenced by the large number of patients with drug use–acquired medical problems (35% of cocaine-exposed patients) and polysubstance abuse (81% of cocaine-exposed patients). The results of this study may therefore be most applicable to long-term cocaine users. A prospective trial that uses toxicology screening to evaluate all patients presenting with aSAH for cocaine exposure will more thoroughly address this issue.

In this study, aneurysms of the anterior circulation occurred more frequently in cocaine users compared with control subjects (97% versus 84%; OR, 6.89). This observation has been previously reported by Nanda et al.1 In their report, Nanda and colleagues have suggested that hemodynamic alterations arising from cocaine use preferentially cause anterior circulation aneurysms to form and rupture. An alternative explanation is that long-term cocaine users suffering ruptured anterior circulation aneurysms are more likely to survive to the hospital than those with ruptured posterior circulation aneurysms. Unfortunately, it is impossible to definitely explain the observed difference in aneurysm distribution on the basis of these studies because aneurysm location was not determined for cocaine users who did not survive to the hospital.

Earlier studies analyzing the association between cocaine and aSAH reported that clinical outcomes for these patients were poor.3,8 A recent study by Nanda et al,1 however, reported that aSAH patients had similar clinical outcomes regardless of cocaine exposure. The results of our study are in concordance with the report by Nanda and colleagues. In our analysis, a difference was not observed in the distributions of clinical outcomes between the 2 groups. In addition, cocaine was not independently related to clinical outcome in 2 multivariable statistical models. In these multivariable analyses, only higher admission GCS SAH grade, the occurrence of vasospasm, and increased age were independent risk factors of poor clinical outcome. These variables have consistently been shown to be associated with poor outcome.13,14,42,43 Thus, although patients with cocaine-associated aSAH were more likely to experience vasospasm, they were also significantly younger and in total not more likely to experience increased morbidity or mortality.

In conclusion, patients with cocaine-associated aSAH tend to be younger, have a higher proportion of anterior circulation aneurysms, and experience symptomatic vasospasm more frequently than other aSAH patients but do not have a worse prognosis.

References


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