Influence of cocaine on ruptured intracranial aneurysms: a case control study of poor prognostic indicators

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Object. The purpose of this study was to determine whether cocaine use is a significant prognostic factor for outcome measures such as Hunt and Hess grade and Glasgow Outcome Scale (GOS) score among patients presenting with ruptured intracranial aneurysms (IAs).

Methods. The authors performed a MEDLINE/PubMed search for cases of ruptured IAs associated with cocaine use. Fourteen cases from the authors’ experience were combined with 50 from a literature review, for a total of 64 cases associated with cocaine use. These 64 cases were compared with 65 cases without cocaine use (controls), which had been obtained from an aneurysm database. Logistic regression analysis was performed to determine significant prognostic factors for a poor Hunt and Hess grade and a poor GOS score, and a general linear model was applied to identify significant factors for these measures among cocaine users.

Results. There were 40 women in each group. The mean age was 32.3 ± 8.1 years in the cocaine group and 49.7 ± 10.6 years in the control group; thus, patients in the cocaine group were significantly younger (p < 0.01). Cocaine was snorted in 21% of cases, smoked in 55%, and intravenously injected or taken in through a combination of routes in 24%. Fifty-one percent of cocaine users and 7.7% of nonusers presented with a poor GOS score (p < 0.01). Fifty-six percent had ictus during cocaine abuse. At the end of a 30-day follow-up, 51% of the patients in the cocaine group had a good GOS score compared with 92% in the control group (p < 0.01). Controlling for the effects of other significant factors, cocaine use had a significant effect on Hunt and Hess grade (p < 0.03) and GOS score (p < 0.01). The odds of having a poor Hunt and Hess grade among cocaine users were 4.2 times greater than those in nonusers, and the odds of having a poor GOS score among cocaine users were 38.8 times greater.

Conclusions. Aneurysms were significantly smaller and ruptured at a younger age among cocaine users compared with nonusers. Although the poor clinical grade was not significantly different between the 2 groups, outcome was significantly worse in cocaine users. (DOI: 10.3171/JNS/2008/108/3/0470)

Key Words • aneurysm • cerebral ischemia • cocaine • intracranial aneurysm

The Substance Abuse and Mental Health Administration has reported that nearly 2.5 million Americans admitted to occasional and 600,000 to frequent cocaine use in 1995 (US Department of Health and Human Services). These statistics indicate that a large number of individuals are exposing themselves to the potentially adverse health consequences associated with cocaine use, and the most commonly affected system is the cardiovascular system. The rate of major cerebrovascular abnormalities in hospital admissions associated with cocaine abuse has been < 3%; however, recent case reports illustrate that the incidence of cocaine-related cerebrovascular disease is rapidly increasing. The relative likelihood of a stroke in cocaine users may be as much as 14 times greater than in age-matched nonusers, and 25–60% of these strokes are attributable to cerebral ischemia. The cause of cocaine-induced brain ischemia may be multifactorial and involves vasospasm, platelet aggregation, pathological changes in cerebral vasculature, and impaired cellular oxygenation. Ruptured IAs or arteriovenous malformations have been detected in nearly half of the hemorrhagic strokes due to cocaine abuse. There is a marked temporal association between cocaine administration and the onset of hemorrhagic and ischemic strokes, with the majority developing within 1 hour.

Cocaine is a highly lipid-soluble alkaloid that reaches a brain/plasma ratio of 5:1 with a half-life of ~1 hour. It potentiates the effects of monoamines by blocking the reuptake of norepinephrine and thus increasing the bioavailability of the catecholamines. This effect combined with the increased sensitivity of catecholamine receptors leads to sympathetic hyperactivity and transient hypertension. Hypertension is a significant risk factor for a cerebrovascular accident as well as aneurysm formation and/or rupture. In a susceptible patient, cocaine probably would produce an intracranial hemorrhage by repeatedly inducing transient bouts of hypertension.

We aimed to determine whether cocaine use is a significant prognostic factor of outcome, as measured by Hunt and Hess grade and GOS score, among patients with IAs.

Clinical Material and Methods

We have published data on our earlier experience with IAs in patients actively using cocaine. During that time...
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we reviewed the literature for studies focused on the same topic and obtained information on the required variables for a metaanalysis. We found 17 reports (Table 1), most of which had small numbers of patients with IAs who had also used cocaine (range 1–6 patients). Two reports had 12 cases each. There were 64 cases involving cocaine use among these reports, which we studied for details regarding patient age, sex, route of cocaine administration, Hunt and Hess grade, interval between substance abuse and icterus, size of aneurysm, and GOS score. Six of the 64 cases had missing information with regard to Hunt and Hess grade or GOS score (3 each).

We picked the initial 65 entries with ruptured aneurysms from our aneurysm database as the control group. The 2 groups were compared for differences on observed variables and the effect of cocaine abuse on clinical grade and outcome.

Given the observed nonnormality of the quantitative variables of Hunt and Hess grade, GOS score, patient age, and aneurysm size in both groups, a nonparametric test such as the Wilcoxon rank-sum test was used to compare the 2 groups on these factors. The 2 groups were evaluated on the categorical variables as well (Hunt and Hess Grade III, IV, or V; GOS Score 3, 4, or 5; and male sex) by using either a chi-square or Fisher exact test. A multiple logistic regression analysis was performed to compare the 2 groups on poor Hunt and Hess grade (III, IV, or V) and poor GOS score (3, 4, or 5), adjusted for significant differences in patient age and aneurysm size. A GLM was used to determine significant effects on Hunt and Hess grade and GOS score among cocaine users.

Results

Patients in the cocaine group, consisting of 40 women and 24 men, had a mean age of 32.3 ± 8.1 years (mean ± standard deviation, range 21–62 years). In contrast, the non–cocaine users comprised 65 patients with a mean age of 49.7 ± 10.6 years (range 32–73 years) and a female preponderance of 40 patients. All aneurysms except 1 were located on the carotid artery circulation in patients in the cocaine group, whereas 23% of the control group had posterior circulation aneurysms. The cocaine group aneurysms were more proximal than those in the control group. The mean aneurysm size in the cocaine group was 7.5 mm, whereas the mean size in the other group was 12.5 mm. Figures 1 and 2 show the distributions of Hunt and Hess grades and GOS scores among patients in the 2 groups, which correspond with those in Table 2.

Table 3 shows the comparison between cocaine users and nonusers with regard to outcome (as reflected by Hunt and Hess grades and GOS scores), patient age, and sex by using separate univariate analyses. The cocaine users were significantly younger, had a significantly higher average GOS score, and harbored a significantly smaller aneurysm on average. There was a significantly higher proportion of cocaine users with a GOS score of 3, 4, or 5, compared with nonusers. Although the proportion of patients with a Hunt and Hess grade of III, IV, or V was not statistically different between the 2 groups (2.3 ± 1.4 for users versus 1.9 ± 1.1 for nonusers, p = 0.06) at the 5% level on univariate analysis, it was close to being significant. Moreover, on multivariate analysis with a multiple logistic regression model (that is, controlling for the effects of age and aneurysm size; Table 4), the proportion of patients with Hunt and Hess grades of III, IV, or V was significantly higher for cocaine users, as shown in Table 5.

Tables 4 and 5 show the probability values of cocaine use, patient age, and aneurysm size as effects on higher Hunt and Hess grades and GOS scores (that is, III/3, IV/4, or V/5). Adjusted for the effects of age and aneurysm size, cocaine use had a significant effect on higher Hunt and Hess grades and GOS scores. The odds of having a high Hunt and Hess grade were 4.2 times greater in cocaine users than in nonusers. Adjusted for the effect of cocaine use and patient age, the larger the aneurysm, the greater the odds for a higher Hunt and Hess grade. There was a significant 1% increase in the odds for a higher Hunt and Hess grade for every unit increase in aneurysm size. Cocaine use and aneurysm size were the significant independent prognostic factors for a higher Hunt and Hess grade (III, IV, or V).

Adjusted for the effects of patient age, aneurysm size, and high Hunt and Hess grade, the odds of having a GOS score of 3, 4, or 5 among cocaine users were 38.8 times greater than those in nonusers (Table 5). The larger the aneurysm, the greater the odds for a higher GOS score. There was a significant 14% increase in the odds for a higher GOS score for every unit increase in aneurysm size. The odds for a high GOS score among patients with a high Hunt and Hess grade were 9.8 times greater than in patients with a low grade. Cocaine use, aneurysm size, and a high Hunt and Hess grade were the significant independent factors for a higher GOS score.

Although there was no significant difference in the average Hunt and Hess grade between the 2 groups, the groups differed significantly in average GOS score. As shown in Table 2, the mortality rate was 44.3% (27 of 61 patients) and 1.5% (1 of 65 patients) in the cocaine and control groups, respectively (p < 0.01). As shown in Table 5, a poor Hunt and Hess grade had a significant effect (p = 0.005) on a GOS score in the combined groups; that is, a poor Hunt and Hess grade would predict a poor GOS score.
Table 6 shows the effects of patient characteristics on Hunt and Hess grade and GOS scores among drug users according to GLM. There were no significant factors for Hunt and Hess grade and GOS score among the cocaine users. To provide the information shown in Fig. 3, we used GLM analysis to show that Hunt and Hess grade is indeed a significant predictor of GOS score among cocaine users. Based on GLM analysis, Hunt and Hess grade is a significant predictor of the GOS score among cocaine users ($p < 0.01$).

![Graph demonstrating the distribution of Hunt and Hess grades among cocaine users and nonusers (control).](image1)

![Graph depicting the significant difference in GOS scores between the cocaine users and nonusers ($p < 0.01$).](image2)

**Discussion**

Cocaine-induced hemodynamic changes may play a vital role in the formation and rupture of IAs. Van de Bor and colleagues’ transcranial Doppler ultrasonography study in infants exposed to cocaine in utero strongly supports the hypothesis that aneurysm rupture is a direct consequence of the hemodynamic effects of cocaine; the transient but repeated bouts of hypertension are transmitted, almost unchanged, to saccular aneurysms and result in exceeding-
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**TABLE 2**
Distribution of clinical and outcome scores in 61 cocaine users and 65 nonusers*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cocaine Users</th>
<th>Nonusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>H &amp; H grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>22 (36.1)</td>
<td>33 (50.8)</td>
</tr>
<tr>
<td>II</td>
<td>17 (27.8)</td>
<td>15 (23)</td>
</tr>
<tr>
<td>III</td>
<td>9 (14.7)</td>
<td>9 (13.8)</td>
</tr>
<tr>
<td>IV</td>
<td>5 (8.2)</td>
<td>8 (12.3)</td>
</tr>
<tr>
<td>V</td>
<td>8 (13.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>GOS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24 (39.3)</td>
<td>47 (72.3)</td>
</tr>
<tr>
<td>2</td>
<td>6 (9.8)</td>
<td>13 (20)</td>
</tr>
<tr>
<td>3</td>
<td>4 (6.5)</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>5</td>
<td>27 (44.3)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

* Overall difference in grade distribution and severity of Hunt and Hess grade had no statistical significance; however, outcome differences between the 2 groups were significant. There were more deaths among cocaine users with aneurysmal SAH. Although clinical status was not a significant variable influencing outcome, cocaine use itself had an effect on outcome (recall that the 2 groups did not differ significantly in the number of patients with a poor clinical grade. p = 0.23). Abbreviation: H & H = Hunt and Hess.

ly high intraneurysm wall tension that increases the risk of rupture. Because of the relative nondistensibility of the aneurysm sac, which is deficient in functional elastin and collagen, the intraluminal stress within the lesion can be nearly 10 times that of cerebral arteries at a particular pressure. Frequent bursts of hypertension thus can induce injury to the arterial wall, the formation and enlargement of an aneurysm, and even subsequent lesion rupture. In both the formation and growth of an aneurysm, this vessel narrowing has a direct mechanism. The major metabolites of cocaine appeared to have no detectable effects on neurons, indicating that a similar phenomenon has been demonstrated in human volunteers by Kaufman et al., whose findings have also suggested a dose-related cumulative residual effect in which repeated cocaine exposure produces delayed and/or prolonged vasoconstriction. In both the formation and growth of an aneurysm, this vessel narrowing has a direct influence (that is, the nozzle effect of a jet of blood emerging from a constricted area) resulting in turbulence that induces damage to the vessel wall. Note, however, that the in vivo duration of cocaine-induced vasoconstriction is unclear. The active metabolites benzoylecgonine and ecgonine are known to remain in the brain long after exposure to the drug, and the defective areas of cerebral blood flow can remain 10 days after intake. The smaller size of aneurysms at the time of rupture (p < 0.01) and the young age of patients (p < 0.01) may be indicators of these vasoactive properties of cocaine and its resultant damage to the cerebral vasculature. In the present study population a larger aneurysm size had directly proportionate worsening in clinical grades and outcome (Tables 4 and 5). This result is similar to the experience published in the literature on aneurysms, including ours. Only the cocaine users were much younger and had significantly smaller aneurysms at the time of rupture. However, our results do not indicate that smaller aneurysms were associated with worse clinical grades and poorer outcomes. In Table 4, the OR for aneurysm size is 1.07, which means that for every increase in aneurysm size—controlling for cocaine use and patient age—there is a 7% increase in the odds for a Hunt and Hess grade of III, IV, or V. Similarly, in Table 5, the OR for aneurysm size is 1.14, which means that for every increase in aneurysm size—controlling for cocaine use, age, and Hunt and Hess grade—there is a 14% increase in the odds for a GOS score of 3, 4, or 5.

A recent study by Su et al. has shown that cerebral vascular smooth muscle can undergo rapid apoptosis in response to cocaine in a concentration-dependent manner. These authors postulated that cocaine-induced apoptosis plays a major role in brain microvascular damage, cerebral vascular toxicity, and stroke.

Most patients with a poor clinical grade succumb to the intracranial pathological entity. The manner in which cocaine can induce cerebrovascular disease is multifactorial.

Nassogne and colleagues have shown that exposure of fetal mouse brain cocultures to cocaine does not affect the viability of glial cells but selectively inhibits neurite outgrowth, followed by a loss of neurons through an unknown mechanism. The major metabolites of cocaine appeared to have no detectable effects on neurons, indicating that apoptosis could be due to the cocaine itself. Inappropriate neuronal apoptosis in cocaine-exposed fetal brain could perturb the neurodevelopment program and contribute to quantitative neuronal defects. Similar laboratory data suggest that cocaine induces apoptosis in the smooth muscle.

**TABLE 3**
Comparison between cocaine users and nonusers with regard to Hunt and Hess grade, GOS score, and patient characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cocaine Users</th>
<th>Nonusers</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>64</td>
<td>65</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>mean age</td>
<td>32.3 ± 8.1</td>
<td>49.7 ± 10.6</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>mean GOS score</td>
<td>3.0 ± 1.9</td>
<td>1.4 ± 0.8</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>mean H &amp; H grade</td>
<td>2.3 ± 1.4</td>
<td>1.9 ± 1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>mean size of aneurysm (mm)</td>
<td>7.8 ± 5.9</td>
<td>12.5 ± 7.2</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>no. male sex (%)</td>
<td>24 (37.5)</td>
<td>25 (38.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>no. w/ H &amp; H grade of III, IV, or V (%)</td>
<td>22/61 (36.1)</td>
<td>17/65 (26.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>no. w/ GOS score of 3, 4, or 5 (%)</td>
<td>31/61 (50.8)</td>
<td>5/65 (7.7)</td>
<td>&lt;0.01†</td>
</tr>
</tbody>
</table>

* Values represent the means ± standard deviations, unless indicated otherwise.
† Significant at p < 0.01.

**TABLE 4**
Effect of cocaine use on Hunt and Hess Grade III, IV, or V among patients with IAs, adjusted for age and aneurysm size*

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cocaine use</td>
<td>4.22 (1.14–15.56)</td>
<td>&lt;0.03†</td>
</tr>
<tr>
<td>age</td>
<td>1.04 (0.99–1.09)</td>
<td>0.12</td>
</tr>
<tr>
<td>aneurysm size</td>
<td>1.07 (1.002–1.145)</td>
<td>0.04†</td>
</tr>
</tbody>
</table>

* CI = confidence interval.
† Significant at p < 0.05.
of cerebral vasculature, predisposing the brain to multiple cerebrovascular diseases. Kaufman and associates\textsuperscript{23} study also confirmed the findings of Su et al.,\textsuperscript{18} suggesting that cocaine has a cumulative effect in producing cerebrovascular dysfunction in addition to its acute vasoconstrictive effect. If the clinical grades of cocaine users at the time of presentation were not very different from those of nonusers and yet they had a significantly worse outcome, the cocaine itself might be playing a crucial role through a variety of its injury mechanisms damaging cerebral vasculature and neurons. The odds of having a poor outcome were as high as 38.8 times greater with cocaine use, and patients with a poor clinical grade had 9.8 times higher odds for a worse GOS score (Table 5).

In a previously published study we showed that a large number of patients presented with hemorrhage (intracerebral hemorrhage, SAH, or both) with either aneurysmal or nonaneurysmal stroke.\textsuperscript{29} There is a cause and effect relationship between a cerebrovascular event and cocaine use, as shown by the present study in which the majority of aneurysms bled during drug abuse. A similar observation has been made in other clinical studies.\textsuperscript{16,24,28} Apart from spasm, other possible mechanisms for an increased stroke risk include emboli from drug impurities,\textsuperscript{9} paradoxical fat embolism,\textsuperscript{8} infectious emboli from the heart,\textsuperscript{22} acute severe increase in blood pressure,\textsuperscript{46} cardiomyopathy-induced emboli,\textsuperscript{32} hypoxia during a drug overdose,\textsuperscript{48} and allergic reactions to the drug or its additives.\textsuperscript{8} Cocaine also enhances the response of platelets to arachidonic acid in vitro and thus promotes thrombus formation.\textsuperscript{40} Chronic cocaine use increases platelet levels, enhances adenosine diphosphate platelet activation, and augments sporadic release of platelet-bound alpha granules. These activities may be mediated by cocaine-induced increases in monoamine levels, particularly of 5-hydroxytryptamine.\textsuperscript{25}

The increased mortality and morbidity rates in cocaine users (38.8 times higher odds) could be attributed to these various mechanics of hemodynamics and cocaine properties. The outcome as well as the poor clinical status in cocaine users (4.2 times worse) may in part be due to the susceptibility of the neurons as well as the vascular endothelium with increased risks for hypoxia and vasospasm. The neurogenic cardiac dysfunction and the neurological injury and cardiac dysfunction combined may also be at play in these individuals.

Vascular changes described histologically in cocaine abuse include abnormal internal elastic lamina infolding and tunica media disruption in cerebral infarction,\textsuperscript{25} arteriolar and periarteriolar fibrosis in nasal mucosa of cocaine snorters,\textsuperscript{46} elastic disruption and subendothelial edema in submucosal intestinal arterioles in cases of intestinal ischemia,\textsuperscript{12} and coronary artery intimal hyperplasia with platelet thrombi in ischemic heart disease.\textsuperscript{25} These vascular changes can appear as spasms on angiography, and the beaded appearance of vessels sometimes accompanies vasculitis. Large arteries also can go into spasm and produce infarction. In some instances, platelet activation and subsequent thrombus formation can induce vascular occlusion. The role of vasospasm in a poor outcome following SAH has been documented in several studies.\textsuperscript{1,14,22}

The biological half-life of cocaine in the blood is \(\sim 1\) hour, with \(< 5\%\) of cocaine appearing unchanged in urine. Most urine excretion of cocaine and its metabolites occurs within the first 24 hours after administration regardless of the route. The duration of detection of urinary cocaine metabolites depends on 2 factors: the amount of cocaine absorbed or injected and the sensitivity of the drug test used. Smoking cocaine provides the fastest route of entry into the cerebral circulation (6–8 seconds), and an intravenous route takes twice as long; nasal insufflations produce peak levels in 30–60 minutes.\textsuperscript{19,64} The approximate time window for the detection of cocaine metabolites is 1–2 days if using the enzyme-linked immunosorbent assay and 5–6 days if using gas chromatography with mass spectrometry.\textsuperscript{21}

With advances in diagnostics, cocaine and benzoylecgonine deposited in the hair shaft can be detected for several months. The identification of the cocaine-abuse population with an aneurysmal SAH (or brain attack) background has several implications. It would give us the cause–effect relationship between cocaine and SAH, enabling us to create a model for studying aneurysm formation and rupture. It would also offer some ideas about the mechanisms responsible for a poor prognosis in cocaine-related SAH (or brain attack), and treatment methods can be directed to effectively reduce poor outcome.

For example, cerebrovascular accident (stroke, both hemorrhagic and nonhemorrhagic) has a reported rate of 0.2% (200 per 100,000 persons) in the general population. Cocaine users were estimated to have a 14 times greater risk of stroke,\textsuperscript{48} which means that stroke would occur in 2800 per 100,000 persons or in 70,000 among 2.5 million cocaine users. The annual new admissions for stroke have been reported to be 750,000, and approximately \(> 10\%\) would be cocaine users if one applied the statistics provided by the Substance Abuse and Mental Health Administration, 1995. However, the identification of drug abuse in hospital admissions remains very low. Peterson and associates\textsuperscript{47} have reported that 0.1% of in-patient admissions involved a cerebrovascular event temporarily related to co-
Cocaine use. Even by low estimates we had 15 cocaine users among 640 cases of IAs, meaning that 2.3% of our patients were identified as cocaine users (and another 1.35% of stroke registry patients). On the other hand, in a prospective autopsy series Nolte et al. reported that 60% of the fatal intracranial hemorrhages were associated with cocaine use.

Conclusions

If patients in the cocaine group had 4.2 times higher odds of having a poor Hunt and Hess grade and 38.8 times higher odds of a poor GOS score compared with nonusers, it is imperative that we consider better medical implications and applications than those that currently exist for this social problem.

References


Fig. 3. Graph revealing the significant influence of Hunt and Hess grade on GOS score in cocaine users.


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