High mortality of cocaine-related ischemic colitis: a hybrid cohort/case-control study

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Background: Isolated case reports describe bowel ischemia in cocaine users, and the optimal management of these patients remains uncertain.

Design: Case-control study.

Setting: Teaching hospitals.

Patients: Patients hospitalized for colonic ischemia related to cocaine compared with noncocaine-related ischemic colitis. Cases were identified by using ICD-9 codes and laboratory urine toxicology tests. Patients were included if they had a confirmed diagnosis of bowel ischemia by CT, colonoscopy, angiography, or, in the case of emergency exploration, a pathology report showing bowel ischemia and a urine toxicology test that was positive for cocaine. Controls were individuals who met the same criteria but had no history of cocaine use and a urine test negative for cocaine. Charts were individually audited for accuracy of coding.

Main Outcome Measurements: Mortality and its risk factors.

Results: Patients with cocaine-related ischemia were significantly younger and had a significantly ($P < .05$) higher mortality rate than patients with ischemic colitis unrelated to cocaine (cocaine: 5/19 [26%] and noncocaine: 6/78 [7.7%]). The cause of death in all cases was septic shock caused by extensive bowel ischemia. Multivariate logistic regression analysis showed that cocaine-related ischemic colitis was a significant risk factor for mortality (odds ratio 5.77; 95% CI, 1.37-24.39) as was the need for surgical intervention (odds ratio 4.95; 95% CI, 1.22-20.12).

Limitations: Retrospective design.

Conclusions: Cocaine-related ischemic colitis has a high mortality. In young patients presenting with acute abdominal pain and/or rectal bleeding with evidence of bowel wall thickening or pneumatosis on imaging studies or colonoscopy, cocaine-related ischemia should be considered. Testing for cocaine use may help identify patients at high risk of sepsis and death. (Gastrointest Endosc 2012;75:1226-32.)

Cocaine is a commonly used illicit central nervous system stimulant in the United States. The National Survey on Drug Use and Health estimated that 5.9 million Americans used cocaine in 2002 and 2003.[1] Ten percent to 14% of the U.S. population report using cocaine at least once; of these, nearly half are long-term users. Cocaine-related complications are therefore of are clinical importance. Other than alcohol, cocaine is the most common cause of acute drug-related emergency department visits in the United States.[1]

Among GI complications, bowel ischemia and perforation are the most common; gastric ulcerations, retroperitoneal fibrosis, and visceral infarctions have also been reported. The clinical presentation is typically abdominal pain or rectal bleeding, but some patients may present with chest and abdominal pain caused by concurrent car-

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diac and abdominal ischemia. Although the mechanism of cocaine-induced ischemia is not completely defined, it is suggested that there may be 3 causal factors involved in bowel ischemia: (1) arteriolar vasospasm, (2) platelet activation, and (3) accelerated atherosclerosis.[2-4]

Most of the data in literature on cocaine-related bowel ischemia is in the form of case reports and small case series, which suggest that the mortality of cocaine-induced ischemia may be high. There are, however, no controls in these studies, and the size of the case series are too small to draw conclusions. The aim of our study was to compare the presentation and clinical outcome (mortality) of patients with cocaine-related ischemic colitis with patients with other forms of ischemic colitis.

Take-home Message

- Young patients presenting with acute abdominal pain, colonic thickening, and pneumatosis intestinalis on CT and colonoscopy should be suspected of having cocaine-related ischemic colitis, which is associated with a substantial risk of death from septic shock.

METHODS

Study population and case identification

This was a retrospective review of medical records at 2 affiliated teaching hospitals located in a downtown area of Milwaukee that extended over 9 years. Patients were initially identified by using ICD-9 codes for vascular insufficiency of the small intestine or colon. Initially, 208 patients were identified by using the ICD-9 codes. Charts were then audited. Inclusion criteria for both cases and controls included a confirmed diagnosis of bowel ischemia by either CT (bowel wall thickening, pneumatosis intestinalis, and portal venous air), findings on colonoscopic examination compatible with bowel ischemia, angiographic findings of intestinal ischemia, or a resection specimen that confirmed ischemia. The cases (cocaine-related ischemia) were identified by either (1) self-report of recent cocaine use or (2) positive urine toxicology screen for cocaine within 6 months of the hospital admission for ischemia. The human subjects committee governing both institutions approved the study protocol. Because of the sensitive nature of the information (drug use data), the human subjects committee required data extraction from the individual patient record be performed through an "honest broker" who had no further part in the conduct or analysis of the study and would be the only person who had the name and personal data of the patient. Information on the patient was turned over in a coded format to the investigators.

Cocaine testing was performed at a centralized laboratory for both hospitals by using an immunoassay for cocaine as the initial screen. If the urine screen was positive, another aliquot of the sample was used to confirm the findings by gas chromatography–mass spectrometry.

Statistical analysis

Statistical analysis was performed by using the Wilcoxon rank sum test and χ^2/Fisher exact tests (2 tailed) to compare 2 groups with reference to demographic and clinical characteristics. An independent-group t test and 1-way analysis of variance were used to compare the difference in the mean between 2 or more independent groups. To analyze risk factors for death, univariate logistic regression analysis was first used. Multivariate logistic regression analysis was used to evaluate the independent association of each risk factor for mortality. Results are reported as mean and standard deviation. The final multivariate logistic regression derived in stepwise analysis was considered the main definitive result because it determined those variables independently associated with mortality, after adjusting for the contributions of the other variables. Other P values are not corrected for multiple testing because those tests are taken as exploratory.

RESULTS

The initial screen yielded 208 patients with a diagnostic code for intestinal ischemia. Of these, 97 patients met our criteria for inclusion in this study. Nineteen patients had used cocaine immediately before admission; 15 were confirmed by positive toxicology results at the time of admission and 4 by self-report. The remaining 78 patients had ischemic colitis but no history of cocaine use and/or negative findings on a urine screen.

Clinical presentation

All patients presented with acute abdominal pain and diarrhea or rectal bleeding. One patient in the cocaine group presented with severe acute abdominal pain, rigidity, and a silent abdomen. The baseline characteristics and outcomes of the 2 groups are shown in Table 1. Compared with noncocaine users, those with cocaine-induced bowel ischemia were more likely to be nonwhite, younger, and male; have ischemia in the right side of the colon and small bowel; and were less likely to be diabetic.

Diagnostic studies

Seventy-two patients in the cohort underwent CT, 60 underwent colonoscopy, and 9 underwent angiography. The diagnostic studies performed in the cocaine-related ischemia group were angiography in 1 patient, CT in 12 patients, and colonoscopy in 12 patients. In the control group, angiography was performed in 8 patients, CT in 58, and colonoscopy in 48. Eight of the 9 angiograms revealed no abnormalities; 1 angiogram in the control group revealed superior mesenteric stenosis and ischemia. The principal findings at endoscopy in cocaine-induced isch-

TABLE 1. Baseline characteristics of the patients

Characteristic	Overall	No cocaine	Cocaine	*P* value
No. (%) of patients	97	78 (80.4)	19 (19.6)	
Demographics				
Age, y (range)	59 (50-71)	62 (53-74)	46 (44-56)	<.001
Age >60 y, no. (%)	46 (47.4)	44 (5.4)	2 (10.5)	<.001
Sex, no. (%)				
Male	39 (40.2)	25 (32.1)	14 (73.7)	<.001
Female	58 (59.8)	53 (67.9)	5 (26.3)	
Race, no. (%)				
White	73 (75.3)	67 (85.9)	6 (31.6)	<.001
Other	24 (24.7)	11 (14.1)	13 (68.4)	
Comorbidities, no. (%)				
Coronary artery disease	19 (19.6)	15 (19.2)	4 (21.1)	1.000
Peripheral vascular disease	9 (9.3)	8 (10.3)	1 (5.3)	.684
Diabetes mellitus	59 (60.8)	52 (66.7)	7 (36.8)	.017
Atrial fibrillation	19 (19.6)	18 (23.1)	1 (5.3)	.109
Hypercoagulable state	6 (6.2)	6 (7.7)	0 (0)	.594
Any of 3	27 (27.8)	23 (29.5)	4 (21.1)	
Endpoint				
Length of stay, d	6 (3-10)	6 (3-11)	4 (2-9)	.299
In-hospital mortality, no. (%)	11 (11.3)	6 (7.7)	5 (26)	.022

Continuous variables are shown with median and interquartile range. Differences in patient demographic and clinical characteristics were compared with Wilcoxon rank sum test and χ^2/Fisher exact tests (2 tailed).

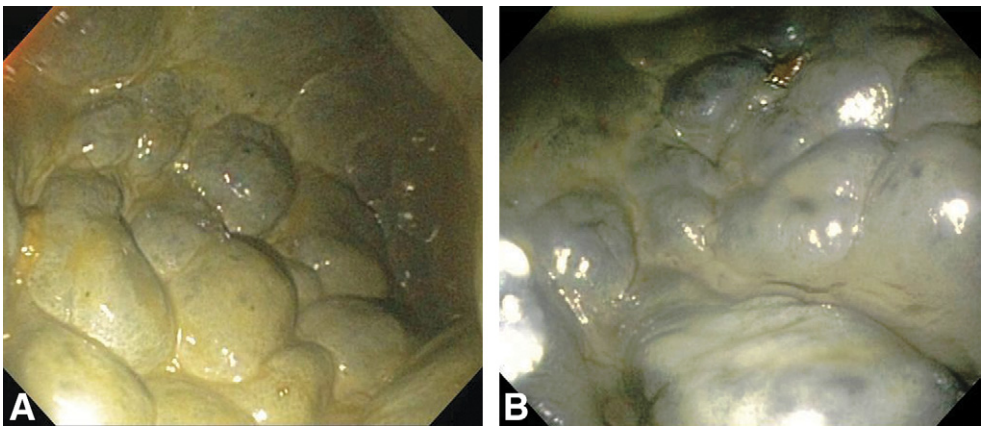

Figure 1. A and **B**, Colonoscopic findings in ischemic colitis. **A,** Bowel wall pallor, edema, and **(B)** pneumatosis are common findings. Bowel preparation is often limited because of the acute nature of the illness and the urgency with which a diagnosis is required.

emia were mucosal edema, pallor, and pneumatosis of the colonic wall (Fig. 1). On CT, bowel wall thickening was the most common finding (Fig. 2). The prevalence of ischemia in different segments of the colon was as follows. Ischemia of the left side of the colon was noted in 46 of 78 patients (59%) with ischemia unrelated to cocaine and 7 of 19 patients (37%) with cocaine-related ischemia. Right-sided colon ischemia was seen in 24 of 78 patients (31%)

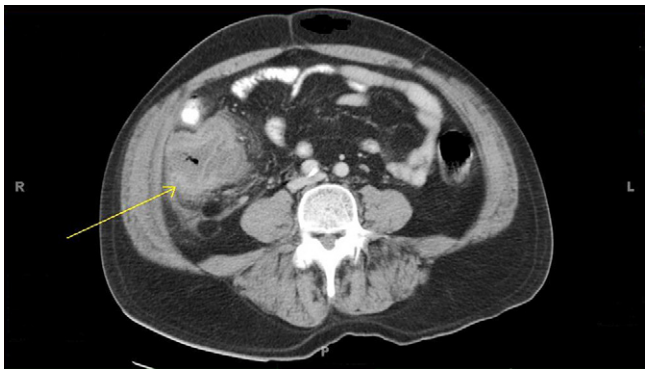

Figure 2. CT in a patient with cocaine-related ischemic colitis. Note the bowel wall thickening (*arrow*).

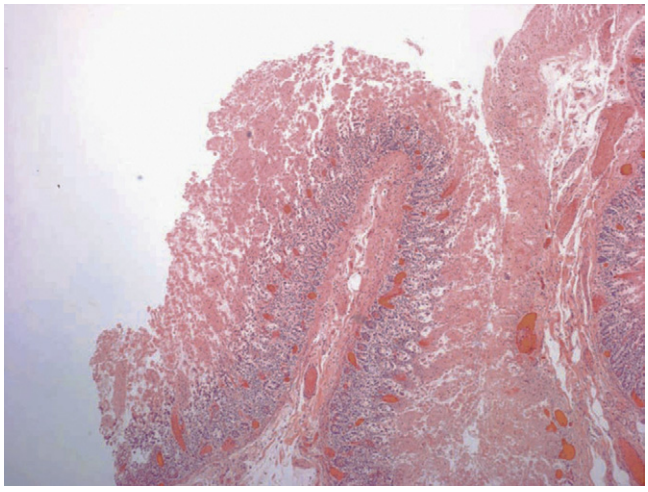

Figure 3. Resected specimen in ischemic colitis (same patient as in Figure 2). Note the hemorrhagic necrosis of the mucosa.

with ischemia unrelated to cocaine and 7 of 19 patients (37%) with cocaine-related ischemia. Small-bowel ischemia was present in 7 of 78 patients with cocaine-unrelated ischemia (9%) and 3 of 19 patients (16%) with cocaine-related ischemia. In patients with cocaine-induced ischemia, the findings at surgery ranged from frank gangrene of the small or large bowel to dusky ischemia of the mucosa with pneumatosis of the intestine. Pathological specimens in all patients showed extensive ulceration of the mucosa with arteriolar and venous thrombosis and hemorrhage in the wall of the intestine (Fig. 3). In other patients, there was transmural ischemia and gangrene of the small bowel with perforation of the intestine.

Surgery

Of the entire cohort, 27 patients underwent surgery; 13 patients (43%) underwent hemicolectomy, 1 underwent a total colectomy (3%), and 16 (53%) underwent small-bowel resection (3 of whom also had a hemicolectomy).

Outcome

The in-hospital mortality was 5 patients (26%) in the cocaine-related intestinal ischemia group compared with 6 patients (7.7%) in the noncocaine intestinal ischemia group ($P = .0366$). The cause of death was progressive bowel ischemia and septic shock and its complications (multiorgan failure) in all patients in both groups. Two patients in the cocaine-induced ischemia group died in the first 24 hours after admission. One patient presenting with acute abdominal pain, rigidity, and a silent abdomen had evidence of small-bowel ischemia on CT and underwent emergent exploration. Extensive small-bowel gangrene was found, and the patient did not survive surgery. One patient with cocaine-related ischemic colitis successfully underwent hemicolectomy but died of sepsis 3 days after admission. One patient survived surgery and stayed in the hospital for 27 days and eventually died of multiorgan failure. The mean length of stay was 9 ± 11 days in the cocaine-related ischemia group and 8.9 ± 9.9 days in the control group.

Risk of death

Table 2 shows univariate logistic regression analysis, and Tables 3 and 4 show multivariate regression analysis. In a stepwise multiple logistic regression analysis, cocaine use was an independent risk factor for mortality (odds ratio 5.77; 95% CI, 1.37-24.39) as was the need for surgery (odds ratio 4.95; 95% CI, 1.22-20.12). We were not able to show an effect for comorbid illnesses, but the prevalence of comorbid illnesses with the exception of diabetes was low in the cohort. The effect of age on mortality is shown in Table 2.

DISCUSSION

The increasing use of low-cost crack cocaine has led to a significant increase in cocaine-related ischemic injury. Cocaine has been associated with an array of acute medical complications, including myocardial ischemia and infarction, cerebral ischemia, and renal infarction. Long-term intravenous and crack cocaine abuse is also associated with a wide spectrum of GI disturbances ranging from diarrhea to frank ischemia with extensive bowel necrosis and intestinal perforation.

The results of our study are consistent with national statistics on cocaine use. The National Survey on Drug Use and Health reported that men were more than twice as likely as women to have met the criteria for cocaine abuse or dependence and that blacks and Hispanics had higher rates of cocaine abuse or dependence than whites and Asians.[1] In Wisconsin, the primary drug threats are the availability of low-cost Mexican cocaine from Chicago.[1] Both powdered cocaine and crack cocaine are drugs of abuse in Milwaukee. Our study was performed in downtown Milwaukee where the Federal Bureau of Investigation field office reports that the use of cocaine affects

TABLE 2. Univariate logistic regression analysis

Characteristic	In-hospital mortality				
	Overall	Alive	Death	OR (95% CI)	*P* value
No. (%) of patients	97	86 (88.7)	11 (11.3)		
Demographics					
Cocaine use, no. (%)	19 (19.6)	14 (16.3)	5 (45.5)	4.29 (1.15-16.01)	.030
Age, y (range)	59 (50-71)	59 (51-71)	54 (42-73)	0.99 (0.94-1.03)	.498
Age >60 y, no. (%)	46 (47.4)	41 (47.7)	5 (45.5)	0.92 (0.26-3.22)	.890
Sex, no. (%)					
Male	39 (40.2)	34 (39.5)	5 (45.5)	0.79 (0.22-2.78)	.707
Female	58 (59.8)	52 (60.5)	6 (54.5)		
Race, no. (%)					
White	73 (75.3)	66 (76.7)	7 (63.6)	0.53 (0.14-2.00)	.349
Other	24 (24.7)	20 (23.3)	4 (36.4%)		
Comorbidities, no. (%)					
Coronary artery disease	19 (19.6)	18 (20.9)	1 (9.1)	0.38 (0.05-3.15)	.368
Diabetes mellitus	59 (60.8)	54 (62.8)	5 (45.5)	0.49 (0.14-1.75)	.274
Atrial fibrillation	19 (19.6)	15 (17.4)	4 (36.4)	2.71 (0.70-10.42)	.148
Hypercoagulable state	6 (6.2)	5 (5.8)	1 (9.1)	1.62 (0.17-15.30)	.674
Surgery	27 (27.8)	21 (24.4)	6 (54.6)	3.71 (1.03-13.42)	.036

Differences in patient demographic and clinical characteristics were compared by using univariate logistic regression analysis (2 tailed).
OR, Odds ratio; *CI,* confidence interval.

primarily lower income and black families.[5] A survey at Aurora Sinai Medical Center, one of the major metropolitan hospitals in Milwaukee and one of the sites where this study was performed, showed that 1 in 6 women giving birth used drugs—usually cocaine—compared with a national average of 1 in 20, indicating a high prevalence of cocaine use in this study population.[5] We did not encounter any "mules" with rupture or leakage of ingested bags of cocaine. This may be attributed to the lack of direct commercial flights to Milwaukee from Latin America.

Animal models suggest possible mechanisms for the effect of cocaine on the mesenteric circulation. In a neonatal swine model, Hebra et al[6] showed significant and prolonged increases in systemic vascular resistance and mesenteric vascular resistance with decreased mesenteric flow after intravenous infusion of cocaine. Cocaine acts at the presynaptic nerve ending by blocking the reuptake of norepinephrine.[2] The intestinal vasculature contains α-adrenergic receptors, which are stimulated by norepinephrine, leading to intense mesenteric vasoconstriction and focal tissue ischemia that is prone to perforation.[6-9] Cocaine may cause thrombus formation and platelet aggregation.[2] It also decreases fibrinolytic activity by stimulating plasminogen activator inhibitor activity.[3] Cocaine may have a direct vascular constrictive effect mediated by enhancement of the flux of calcium across the endothelial cell membranes.[4]

A review article published in 2000 reviewed the available literature and found 28 cases of cocaine-induced ischemia in the literature and suggested that the mortality may be high.[4] We believe that this is the largest series of patients with documented ischemic colitis related to cocaine use. The strength of our study is the size of the cocaine-related ischemia cohort, contemporaneous controls, and evaluation of other risk factors related to ischemia. Records of patients were individually audited for accuracy. As with all retrospective studies, our data are limited by the database descriptors. Patients who arrived in septic shock and died before diagnostic tests or surgery could be performed may have been missed. A history of cocaine use was obtained in all patients, but urine testing was not uniformly performed in all patients in the control group and the time interval between cocaine use and the development of abdominal pain could not be determined. However, misclassification of significant numbers of patients who had cocaine-induced ischemia but did not volunteer a history of drug use would tend to bias the results toward showing a similar mortality between the groups.

TABLE 3. Multivariate logistic regression analysis

Characteristic	In-hospital mortality				
	Overall	Alive	Death	OR (95% CI)	*P* value
No. (%) of patients	97	86 (88.7)	11 (11.3)		
Demographics					
Cocaine use, no. (%)	19 (19.6)	14 (16.3)	5 (45.5)	5.21 (0.63-42.8)	.125
Age, y (range)	59 (50-71)	59 (51-71)	54 (42-73)	1.03 (0.93-1.14)	.583
Age >60 y, no. (%)	46 (47.4)	41 (47.7)	5 (45.5)	0.27 (0.01-8.02)	.447
Sex, no.(%)					
Male	39 (40.2)	34 (39.5)	5 (45.5)	1.84 (0.33-10.19)	.485
Female	58 (59.8)	52 (60.5)	6 (54.5)		
Race, no. (%)					
White	73 (75.3)	66 (76.7)	7 (63.6)	0.30 (0.40-2.24)	.242
Other	24 (24.7)	20 (23.3)	4 (36.4)		
Comorbidities, no. (%)					
Coronary artery disease	19 (19.6)	18 (20.9)	1 (9.1)	1.25 (0.16-9.89)	.836
Diabetes mellitus	59 (60.8)	54 (62.8)	5 (45.5)	0.53 (0.10-2.98)	.474
Atrial fibrillation	19 (19.6)	15 (17.4)	4 (36.4)	5.05 (0.54-47.55)	.157
Hypercoagulable state	6 (6.2)	5 (5.8)	1 (9.1)	4.30 (0.19-96.76)	.359
Surgery	27 (27.8)	21 (24.4)	6 (54.6)	9.83 (1.26-76.62)	.036

Differences in patient demographic and clinical characteristics were compared by using multivariate logistic regression analysis (2 tailed).
OR, Odds ratio; *CI,* confidence interval.

TABLE 4. Multivariate logistic regression analysis (stepwise)

Characteristic	In-hospital mortality				
	Overall	Alive	Death	OR (95% CI)	*P* value
No. (%) of patients	97	86 (88.7)	11 (11.3)		
Risk factors, no. (%)					
Cocaine use	19 (19.6)	14 (16.3)	5 (45.5)	5.77 (1.37-24.39)	.017
Surgery	27 (27.8)	21 (24.4)	6 (54.6)	4.95 (1.22-20.12)	.026

Differences in patient demographic and clinical characteristics were compared by using multivariate logistic regression analysis (2 tailed).
OR, Odds ratio; *CI,* confidence interval.

In many parts of the United States and the world, cocaine-induced bowel ischemia may be an uncommon event in an average gastroenterologist's clinical practice. The clinical messages of our study are that cocaine-induced ischemia should be suspected in patients presenting to emergency departments with acute abdominal pain with or without rectal bleeding. Pneumatosis intestinalis on seen abdominal radiographs, CT, or colonoscopy is another indication of possible ischemic colitis related to cocaine. At endoscopy, the key findings are pneumatosis of the colon with a marked pallor of the mucosa. The deaths in our series were all related to overwhelming sepsis likely related to necrotic bowel. Although our study was designed to demonstrate this, it is intuitive that early identification and resection of necrotic bowel may improve the outcome. Our study cannot determine whether primary anastomosis of the bowel is appropriate or whether an ileostomy or colostomy should be performed as the initial surgical procedure. Further study is needed in this regard.

Hybrid case-control/cohort studies are studies that have features of both these study designs.[10] In a traditional cohort study, all patients have the disease, whereas in a traditional case-control study, controls without disease are compared with cases with the disease in question. In our study, the controls are not without the disease, but have ischemia related to causes other than cocaine. Our study is therefore a hybrid study with features of both a case-control study and a cohort study. Another interesting aspect of our study is the use of an honest broker to extract the data. To our knowledge, this is the first use of an honest broker in endoscopic research. Honest brokers are used when sensitive information is being accessed (such as a history of drug use) to provide a firewall between the patient's medical record and the academic researcher.[11] An honest broker is an individual who has the authority to act on behalf of an organization to provide data, biological specimens, or images to researchers. The honest broker system has an organizational set of policies, procedures, and a certification process that enables honest brokers to perform their function, and the individual is appointed by the board that oversees the protection of human subjects.[6]

In summary, acute abdominal pain with or without diarrhea or rectal bleeding with bowel wall thickening on CT and/or severe edema with pneumatosis at colonoscopy should raise the question of cocaine-induced ischemic colitis. Ischemic colitis may be a greater problem in areas where cocaine use is highly prevalent, and further study of the prevalence of cocaine-related bowel ischemia is necessary. The optimal treatment of this condition is unknown, and further research is necessary to determine the criteria for early surgical intervention and the type of surgical procedure that should be performed.

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