Randomized, Double-blind, Placebo-controlled Trial of Diazepam, Nitroglycerin, or Both for Treatment of Patients with Potential Cocaine-associated Acute Coronary Syndromes

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Abstract. **Introduction:** To the authors' knowledge, treatment of patients with cocaine-associated acute coronary syndromes has not been rigorously investigated in symptomatic patients. **Objective:** To perform a randomized double-blind trial of diazepam, nitroglycerin, or both for treatment of patients with potential cocaine-associated acute coronary syndromes. **Methods:** Patients with potential cocaine-associated acute coronary syndromes were randomized to treatment with either diazepam, nitroglycerin, or both every 5 minutes or until symptom resolution. Outcomes were chest pain resolution (measured by visual analog scale), and changes in blood pressure, pulse rate, cardiac output (L/min), cardiac index (L/min/m^2), stroke volume (mL/beat), and stroke index (mL/beat/m^2) over the 15-minute treatment period. To adjust for seven outcomes using the Bonferroni correction, alpha was set at 0.007. **Results:** Forty patients were enrolled (diazepam, 12; nitroglycerin, 13; both, 15). Patients had a mean age (±SD) of 35.4 (±7.5) years; 75% were male. They presented a mean of 5 hours and 37 minutes after cocaine use. Baseline demographics, cocaine use patterns, chest pain characteristics, and initial electrocardiograms were similar for all groups. Chest pain severity improved similarly in the three groups [−33.3 mm (±8.0); −30.7 mm (±7.1); −33.0 mm (±7.9); p = 0.6]. The stroke index decreased during the 15-minute treatment period for all groups (diazepam, −8.7 (±3.3); nitroglycerin, −3.1 ± 2.8; both, −1.8 (±3.1) mL/beat/m^2; p = 0.03). After adjustment for differences between baseline hemodynamic and cardiac profiles and multiple comparisons, there was no difference in any response to therapy over time for the different treatments. **Conclusions:** For treatment of patients with potential cocaine-associated acute coronary syndromes, chest pain resolutions and changes in cardiac performance are not different in patients treated with diazepam or nitroglycerin. In this study, the use of both agents did not offer any advantage over either agent alone. **Key words:** cocaine; myocardial infarction; acute coronary syndrome; benzodiazepines; nitroglycerin. ACADEMIC EMERGENCY MEDICINE 2000; 7:878–885

THE pathophysiology of cocaine-associated myocardial ischemia is complex.[1] The sympathomimetic effects of cocaine (tachycardia and hypertension) increase the myocardial oxygen demand,[2] while reducing coronary artery blood flow through alpha-adrenergic-mediated coronary artery vasoconstriction.[3] Additionally, cocaine increases thrombogenicity, enhances platelet aggregation, and decreases fibrinolysis by increasing levels of endogenous tissue plasminogen activator inhibitor.[4–7] Chronic cocaine users often develop left ventricular hypertrophy and premature coronary atherosclerosis.[1,8–10]

Current recommendations for the treatment of patients with cocaine-associated myocardial acute coronary syndromes differ from those standard recommendations for patients with acute coronary syndromes unrelated to cocaine.[1] The Goldfrank-Hoffman model of cocaine toxicity states that central nervous system stimulation may result in central nervous system toxicity (such as seizures), as well as exacerbate the peripheral effects of cocaine.[11] Suppression of the central nervous system effects may prevent that part of the peripheral sympathomimetic effects due to central excitation. Blockade of the peripheral manifestations of cocaine toxicity (for example, the cardiovascular effects) may not be beneficial to the central nervous system toxicity.

In addition, the treatment of the cardiovascular

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effects must ensure that the central nervous system effects are not enhanced.[1,11] Reversal of coronary vasoconstriction, hypertension, tachycardia, and predisposition to thrombus formation are the main methods to decrease myocardial oxygen demand and improve coronary artery perfusion and oxygen delivery.[1] To this end, central nervous system protection and decreased sympathetic outflow may be accomplished with the administration of benzodiazepines. Multiple animal experiments and anecdotal experience in humans support the use of benzodiazepines as the initial agent for the management of cocaine-intoxicated patients.[1,12–15] Benzodiazepines alone may calm the agitated patient and return abnormal vital signs to the normal range. Reduction in hypertension and/or tachycardia (which is present in more than 30% of patients with cocaine-associated chest pain)[16] will decrease the myocardial oxygen demand.

Specific anti-ischemic therapy begins with nitroglycerin.[1] In traditional patients with acute infarction, nitroglycerin reduces infarct size, cardiovascular complications, and mortality.[17,18] Nitroglycerin reverses cocaine-induced coronary artery vasoconstriction,[19] and relieves cocaine-associated chest pain.[20] Although infarct size reduction or mortality benefits have not been assessed, based on direct vasodilatory effects of nitroglycerin, experimental reversal of coronary vasoconstriction, and clinical relief of chest pain, it is recommended.[1] Sublingual nitroglycerin has more rapid relief of chest pain, and can be followed with either topical or intravenous nitroglycerin as dictated by the clinical situation.[20]

To the best of our knowledge, there have not been well-designed, randomized, prospective clinical trials to compare treatment strategies for patients with potential cocaine-induced acute coronary syndromes.[1] In fact, few studies have assessed the efficacy of any treatment modalities in patients with active cocaine-associated symptoms. The currently noted treatment recommendations are based primarily on well-controlled trials with animals, cardiac catheterization trials, case series, observational studies, and case reports. We conducted a randomized controlled clinical trial to compare the effects of nitroglycerin, diazepam, and both agents on chest pain resolution and cardiac profiles of patients with cocaine-associated chest pain.

METHODS

Study Design. We conducted a prospective, randomized, double-blind clinical trial comparing the efficacies of diazepam, diazepam with nitroglycerin, and nitroglycerin alone in the management of patients with potential cocaine-associated acute coronary syndromes. Our main outcomes were the hemodynamic (heart rate, blood pressure) and cardiac (chest pain resolution and cardiac performance) profiles over the first 15 minutes of treatment. The institutional review board at the University of Pennsylvania approved the study. All patients provided written informed consent.

Study Setting and Population. All emergency department (ED) patients with a chief complaint of chest pain were screened for study eligibility. Inclusion criteria included 1) age $\geq$18 years and $\leq$60 years, 2) cocaine use within 24 hours, 3) a history suggestive of ischemic chest pain, and 4) the ability to provide informed consent. The upper age limit is based on the fact that patients 61 years and older rarely use cocaine.[21] Patients presenting only with anginal equivalents in the absence of chest pain, patients unable to provide informed consent, and those outlying the inclusion age group were excluded.

Patients were identified by trained research assistants present in the ED between 8 AM and midnight, seven days per week.[22] All patients received an intravenous line and oxygen, and were placed on a cardiac monitor, pulse oximeter, and transthoracic cardiac output monitor. An electrocardiogram (ECG), blood pressure, heart rate, oxygen saturation, and chest pain score were obtained from all patients. Serum was drawn for determination of cardiac markers. Patients were then randomly assigned to one of the three study groups.

Study Protocol. Randomization codes were generated by the Hospital of the University of Pennsylvania pharmacy using a computer-generated random number scheme based on individual assignment. Active drugs and/or placebo were packaged together based on study group assignment. These study packages were stored in the ED and were made available for use after informed consent and initial history and physical were obtained. Study group assignment was maintained only in the pharmacy until after study completion. Both diazepam and its placebo were packaged in a syringe having the same volume and color. Nitroglycerin tablets and its placebo were identical in terms of shape, color, and time until dissolution, when used sublingually.

Enrolled subjects received either diazepam along with placebo nitroglycerin, nitroglycerin along with placebo diazepam, or both active drugs based on study group assignment. We did not include a two-placebo group for ethical reasons. Diazepam was administered 5 mg intravenously every 5 minutes for a total dose of 15 mg. Nitroglycerin, 0.4 mg, was administered sublingually every 5 minutes for up to a total of 3 doses.

Criteria for termination of study drug administration were the presence of standard contraindications for treatment with nitroglycerin or diazepam. They included a systolic blood pressure <90 mm Hg, orthostatic symptoms unresponsive to saline bolus, respiratory depression, and lethargy necessitating withholding of benzodiazepines. In addition, resolution of symptoms was an indication to withhold further treatment. After completion of study protocol, further management was at the discretion of the treating physician.

Measurements. All patients had a structured history and physical examination performed. Historical and demographic data were recorded on a standardized data collection form that included: patient age and gender; cardiac risk factors (hypertension, hypercholesterolemia, tobacco use, diabetes mellitus, and family history of premature atherosclerotic heart disease); and cocaine use details (length of time used, frequency of use, route of administration, estimated quantity used in the preceding 24 hours, and time of most recent use). Mandatory urine testing was not part of the treatment protocol. Patients who self-report cocaine use are usually correct. Patients who deny cocaine use would need to be treated before results of urine testing were available.

The duration, location, and quality of pain (pressure/tightness, aching/dull, burning/indigestion, sharp/stabbing or other) and the presence of associated cardiac symptoms (nausea, emesis, dyspnea, diaphoresis, syncope, lightheadedness, and palpitations) were recorded. Current medications and past medical history, with an emphasis on chest-pain syndromes and heart disease, were sought. The recorded physical examination included vital signs and the presence or absence of jugular venous distension, rales, abnormal heart sounds, and pedal edema.

After each treatment (every 5, 10, and 15 minutes after enrollment) and again 30 minutes after enrollment, blood pressure, pulse, cardiac output, and the patient's perception of pain per visual analog scale was obtained.

Cardiac Performance. All patients enrolled in the study had cardiac output, cardiac index, and stroke volume measured via the IQ System (Renaissance Technologies, Newtown, PA).[23] This system provides continuous, noninvasive measurements of a patient's hemodynamic condition and left ventricular performance through electrical bioimpedance technology. Body mass index was calculated by the IQ System using patient reports of height and weight. Cardiac output values obtained through thoracic impedance closely approximate those obtained with thermodilution techniques with r values of 0.81–0.86 and mean differences between these two methods relative to their average of 16.6%.[23–25]

Cardiac Enzymes. Creatine kinase–MB (CK-MB) was analyzed on the Dade Stratus immunoassay analyzer (Dade International Inc., Miami, FL) utilizing a rapid two-site sandwich monoclonal assay. This assay measures immunologic activity rather than enzymatic activity. The within-run coefficient of variation ranges from 2.5% to 3.8% and the between-run coefficient of variation ranges between 3.0% and 3.7%. The reference range for CK-MB was defined by the manufacturer as less than 5 ng/mL.

Diagnosis of Myocardial Infarction and Unstable Angina. The final diagnosis of myocardial infarction was based on the clinical presentation, serial ECGs, and a serial in-hospital biochemical marker analysis in the hospital clinical laboratory using World Health Organization criteria.[26] Unstable angina was classified according to the Agency for Health Care Policy and Research risk stratification scheme.[27]

Electrocardiogram Interpretation. The ECGs were interpreted blinded to the patients' serum results and clinical outcome. Each ECG was classified using a previously validated closed-question format.[28]

Follow-up. All patients were followed for final diagnosis, length of stay, cardiovascular complications, and interventions such as angioplasty, coronary bypass grafting, intraaortic balloon pump, intubation, pressor support, pacemaker placement, or thrombolysis.

Data Analysis. Data were entered into a Microsoft Access 97 database (Microsoft, Inc., Redmond, WA) and transferred into SAS (Version 6.12, SAS Institute, Cary, NC) for statistical analysis. Baseline characteristics are reported as summary data with means ± standard deviations. Baseline characteristics of the patients in each of the three study groups were compared using analysis of variance for continuous variables and the chi-square tests for categorical variables. A one-way analysis of variance in repeated measures over time was performed where the grouping factor was the treatment group. Variables analyzed in this manner included heart rate, mean arterial pressure, cardiac output, cardiac index, stroke volume, stroke index, and chest pain visual analog score. Means adjusted for baseline values at each time point were obtained using SAS software.[29] Overall analysis of covariance (covariate equals baseline values) was performed using BMDP software.[30] To

adjust for multiple comparisons, statistical significance was set at 0.007 by using the Bonferroni correction.

In order to detect the minimum clinically significant differences in chest pain score and cardiac output at a power of 0.8 and an alpha of 0.05, the study required a minimum sample size of 14 patients per group (total of 42 patients).

RESULTS

Forty-three patients consented to study enrollment. Three patients were excluded from study participation because the IQ monitor system failed to record their data. Forty patients completed the study protocol. There were 12 patients in the diazepam alone group, 13 patients in the nitroglycerin alone group, and 15 patients who received both medications. The mean age (±SD) was 35.4 (±7.5) years, with a range of 23 to 54 years. Overall, 75% of patients were male. Chest pain most often occurred at rest (85%), was described as pressure or tightness (58%), and was located substernally or in the left chest (90%). Multiple episodes of chest pain (45%) and radiation were common (67%). Associated symptoms were common. Although most patients had prior episodes of chest pain associated with cocaine use (68%), fewer had a prior diagnosis of myocardial infarction (28%) or angina (25%). These baseline demographic and historical features did not differ between study groups (Table 1).

Patients used cocaine a mean of 5 hours, 37 minutes (±5 hours, 49 minutes) prior to ED arrival and determination of cardiac profiles. The most common route of cocaine use was by inhalation/smoking (95%), and patients estimated a mean use of $197 (±$256) worth of cocaine. Most patients were longstanding users of cocaine. The mean frequency was 8.6 (±10.9) times per month, for a mean duration of 8 (±6.5) years. There was no difference between study groups.

Results of the initial ECG are shown in Table 2. All patients were in normal sinus rhythm and most patients had normal or nonspecific ECGs. No patient had ST-segment elevations.

Twenty-five patients (63%) were given an ED diagnosis of possible ischemia, and 37 of 40 patients (93%) were hospitalized in a monitored setting. With respect to final diagnosis, three patients had acute myocardial infarction (7.5%); five had documented unstable angina (13%); and 29 had possible ischemia (79%). Only two patients had clear nonischemic etiologies of their chest pain

TABLE 1. Demographic and Presenting Characteristics of the Study Groups

Characteristic	Diazepam Alone (n = 12)	Diazepam and Nitroglycerin (n = 15)	Nitroglycerin Alone (n = 13)	p-value
Age—mean ± SD (years)	35.6 ± 6.6	35.3 ± 9.3	35.4 ± 6.3	
Gender—male	92%	60%	77%	0.17
Chest pain characteristics				
Occurred at rest	10 (83%)	12 (80%)	12 (92%)	0.84
Multiple episodes	7 (58%)	5 (33%)	6 (46%)	0.32
Pleuritic component	2 (17%)	7 (47%)	5 (39%)	0.18
Character (pressure)	5 (42%)	7 (47%)	7 (54%)	0.49
Radiation	7 (58%)	12 (80%)	7 (54%)	0.48
Associated symptoms				
Diaphoresis	7 (58%)	9 (60%)	6 (46%)	0.74
Nausea	10 (83%)	7 (47%)	8 (62%)	0.15
Vomiting	1 (8%)	3 (20%)	2 (23%)	0.59
Dyspnea	10 (83%)	9 (60%)	11 (85%)	0.24
Palpitations	6 (50%)	11 (73%)	8 (62%)	0.49
Cardiac risk factors				
Hypertension	3 (25%)	4 (27%)	2 (15%)	0.75
Diabetes mellitus	1 (8%)	1 (7%)	1 (8%)	0.99
Family history	2 (17%)	4 (27%)	4 (31%)	0.75
Elevated cholesterol	3 (25%)	2 (13%)	0	0.18
Tobacco use	9 (75%)	15 (100%)	9 (69.2%)	0.07
Past history				
Myocardial infarction	6 (50%)	3 (20%)	2 (15%)	0.11
Angina	3 (25%)	3 (20%)	4 (31%)	0.74
Congestive heart failure	1 (8%)	2 (13%)	0	0.46
Prior cocaine/chest pain	9 (75%)	9 (60%)	9 (69%)	0.70

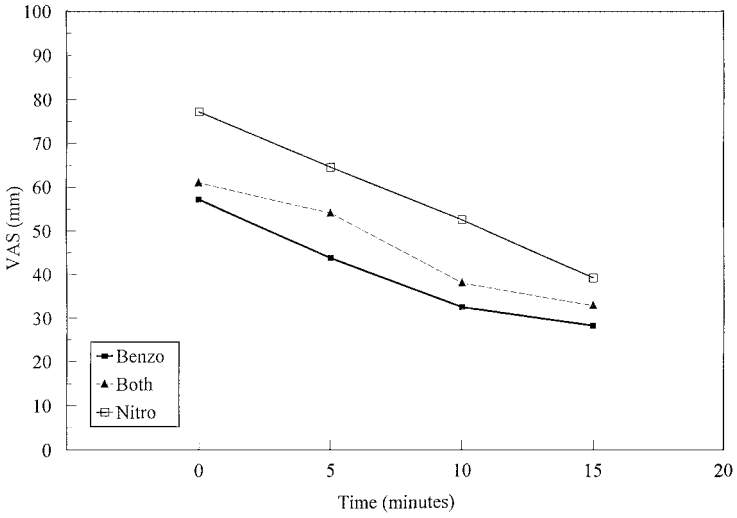

Figure 1. Change in chest pain score for the three treatment groups over the 15-minute treatment period. Scores are adjusted for baseline differences. VAS = visual analog scale; Benzo = benzodiazepine; Nitro = nitroglycerin.

(5%). There was no statistical difference in final diagnosis between treatment groups. No patient had an adverse cardiac event. Patients were hospitalized for a mean of 1.97 (±1.3) days.

The effects of the study medications on hemodynamic and cardiac performance are shown in Figures 1–7. The adjusted mean change over the treatment period for each outcome is summarized in Table 3. For chest pain severity and all hemodynamic and cardiac function outcomes, there was no difference regardless of group assignment. There was a trend toward differences in the interactions between group assignment and time for cardiac output/index and stroke volume/index, but this was not significant after adjustment for multiple comparisons.

DISCUSSION

The clinical approach to treatment of patients with cocaine-associated acute coronary syndromes is based on the premise that the cardiovascular and neuropsychiatric complications are inextricably linked.[1,11] In animal models, successful management of the neuropsychiatric manifestations almost invariably has a salutary impact on resolution of the cardiovascular abnormalities, at least from an emergent or initial care perspective. In these animal models, sedative-hypnotics are uniformly successful for the treatment of cocaine toxicity and the prevention of lethality.[12,13,15] The success of benzodiazepines in these animal models, in other cathecholamine excess clinical states (ethanol withdrawal), and in many anecdotal reports led to their recommendation as a first-line agent for the treatment of cocaine-associated acute coronary syndromes despite a lack of controlled clinical trials.[1]

Treatment of the peripheral manifestations

TABLE 2. Characteristics of the Presenting Electrocardiogram (ECG)

Characteristic	Diazepam Alone (n = 12)	Diazepam and Nitroglycerin (n = 15)	Nitroglycerin Alone (n = 13)	p-value
ECG rhythm (sinus)	12 (100%)	15 (100%)	13 (100%)	1.00
ECG classification				
Normal/nonspecific	9 (75%)	12 (80%)	12 (92%)	
Abnormal, not diagnostic	3 (25%)	—	1 (8%)	
Ischemia—old	—	2 (14%)	—	
Ischemia—new	—	—	—	

TABLE 3. Summary of Adjusted Mean (±SE) Differences between Baseline and End of the 15-minute Treatment Period for Each Outcome

Outcome	Diazepam Alone (n = 12)	Diazepam and Nitroglycerin (n = 15)	Nitroglycerin Alone (n = 13)	Group Term (p-value)	Group × Time Interaction Term (p-value)
Heart rate (beats/min)	4.6 ± 3.1	15.7 ± 2.9	4.8 ± 3.2	0.05	0.06
Mean arterial pressure (mm Hg)	2.1 ± 4.0	−12.1 ± 3.7	−8.4 ± 3.8	0.08	0.04
Cardiac output (L/min)	−0.89 ± 0.49	0.50 ± 0.44	−0.01 ± 0.48	0.90	0.04
Cardiac index (L/min/m^2)	−0.63 ± 0.23	0.29 ± 0.20	−0.02 ± 0.22	0.30	0.20
Stroke volume (mL/beat)	−16.0 ± 6.2	−6.3 ± 5.5	−4.3 ± 5.9	0.70	0.02
Stroke index (mL/beat/m^2)	−8.7 ± 3.3	−3.1 ± 2.8	−1.8 ± 3.1	1.00	0.03
Chest pain score (mm)	−33.3 ± 8.0	−30.7 ± 7.1	−33.0 ± 7.9	0.80	0.60

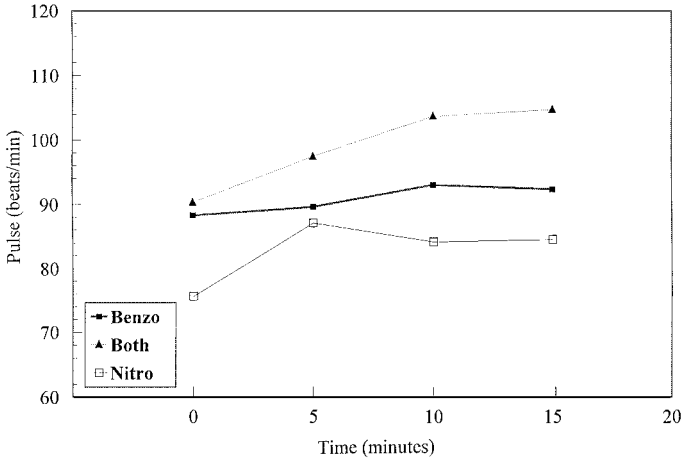

Figure 2. Change in heart rate for the three treatment groups over the 15-minute treatment period. Scores are adjusted for baseline differences. Benzo = benzodiazepine; Nitro = nitroglycerin.

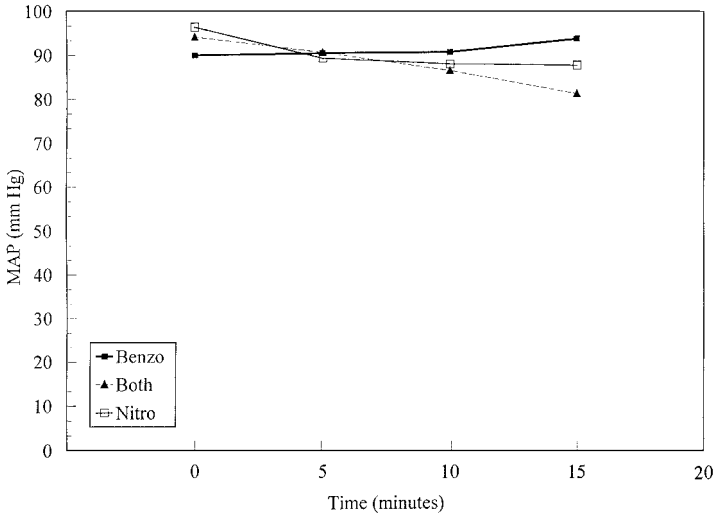

Figure 3. Change in mean arterial pressure (MAP) for the three treatment groups over the 15-minute treatment period. Scores are adjusted for baseline differences. Benzo = benzodiazepine; Nitro = nitroglycerin.

that result from cocaine toxicity may not be effective because of the failure to address the central stimulation. Nitroglycerin decreases the size of acute myocardial infarction and infarct-related complications such as heart block, cardiogenic shock, and in-hospital and one-year mortalities in patients with myocardial ischemia unrelated to cocaine.[17,18] Nitroglycerin is not known to have any centrally mediated effect on coronary arterial responsiveness. Sublingual nitroglycerin, administered in a dose sufficient to reduce mean arterial pressure 10–15%, reverses cocaine-induced coronary artery vasoconstriction.[19] When given via the sublingual route to patients with cocaine-associated chest pain syndromes, one prospective observational study found that nitroglycerin rapidly relieved symptoms in up to 67% of patients.[20] As a result, nitroglycerin has also been recommended as a primary therapy for cocaine-associated acute coronary syndromes despite lack of any randomized controlled clinical trials.[1]

This study compared two therapies that are recommended for the treatment of cocaine-associated acute coronary syndromes. The benzodiazepine is predominantly centrally acting; nitroglycerin exerts its effect peripherally. Both are recommended from experimental data. To the best of our knowledge, neither had been investigated in a rigorous clinical trial.

In our randomized controlled clinical trial of patients with potential cocaine-associated acute coronary syndromes, we were unable to demonstrate any difference between treatments with nitroglycerin, diazepam, or both agents with respect to hemodynamic and cardiac performance. All three treatment groups had similar improvements in severity of chest pain over the 15-minute treatment protocol.

It was our hypothesis that resolution of ischemia would result in measurable improvement in cardiac performance. We chose to use stroke index as our main assessment of cardiac performance because stroke index is not sensitive to either body mass index or heart rate. We expected that nitroglycerin would have positive chronotropic effects increasing cardiac output, thereby confounding assessment of any improvements in cardiac performance that could be attributed to resolution of ischemia.

As we anticipated, assessment of the change in cardiac output (adjusted for baseline differences)

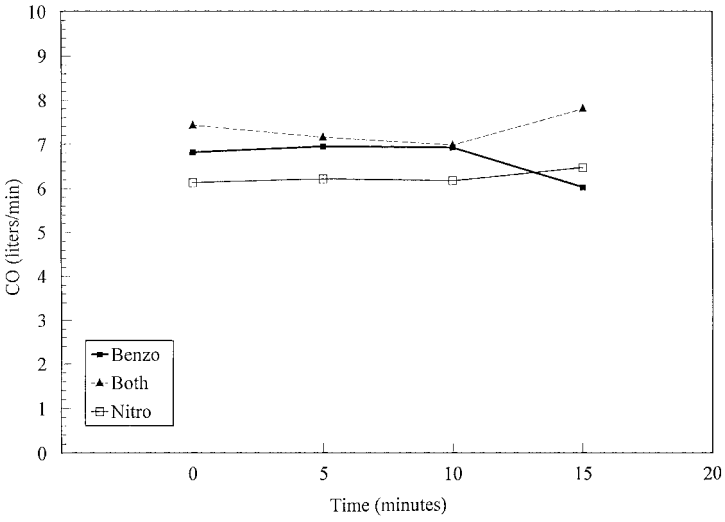

Figure 4. Change in cardiac output (CO) for the three treatment groups over the 15-minute treatment period. Scores are adjusted for baseline differences. Benzo = benzodiazepine; Nitro = nitroglycerin.

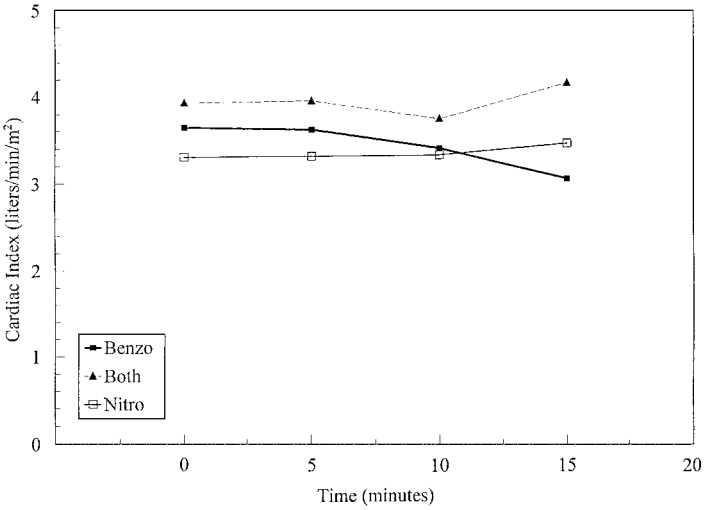

Figure 5. Change in cardiac index for the three treatment groups over the 15-minute treatment period. Scores are adjusted for baseline differences. Benzo = benzodiazepine; Nitro = nitroglycerin.

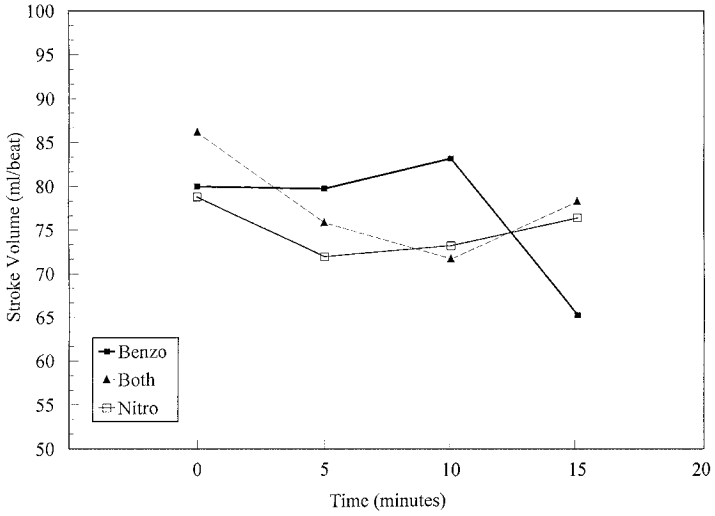

Figure 6. Change in stroke volume for the three treatment groups over the 15-minute treatment period. Scores are adjusted for baseline differences. Benzo = benzodiazepine; Nitro = nitroglycerin.

revealed a 0.5-L/min improvement in cardiac output for the group that received both agents, while the group that received diazepam alone had a decrease in cardiac output of 0.89 L/min. Using stroke index, adjusting for baseline differences between groups, the effects of the different treatments over time, and multiple statistical comparisons, we were unable to demonstrate any difference between treatments with nitroglycerin, diazepam, or both agents. The similar improvements in chest pain severity regardless of treatment group assignment and the lack of difference in cardiac performance between treatment groups suggest that diazepam is as efficacious as nitroglycerin in the treatment of patients with potential cocaine-associated acute coronary syndromes. The combinations of agents did not appear to have any additional benefit.

Limitations and Future Questions

Our study has several limitations. We cannot be certain that all patients had acute coronary syndromes. Previous studies have suggested that many patients with cocaine-associated chest pain do not actually have ischemic chest pain.[16,31] Some patients with cocaine-associated acute coronary syndromes may have coronary artery disease, while others may not. Although we did not determine which patients did or did not have underlying coronary artery disease, our patient population was representative of the "typical" cohort of patients with cocaine-associated chest pain who require treatment. Although our patients did not have evidence of sympathetic excitation with hypertension and tachycardia, they did appear very similar to other large cohorts of patients with potential cocaine-associated acute coronary syndromes.

Some patients did not have clinical evidence of central nervous system excitation. They were not agitated and did not have cognitive functional impairments. It is possible that patients with central nervous system excitation may be more likely to benefit from treatment with sedative-hypnotic agents. Although this was a double-blind study, the effects of repeated doses of diazepam could have been obvious to the clinicians; however, our main outcomes were objective measurements of cardiac performance. Finally, the sample size calculation was based on previous literature that used the

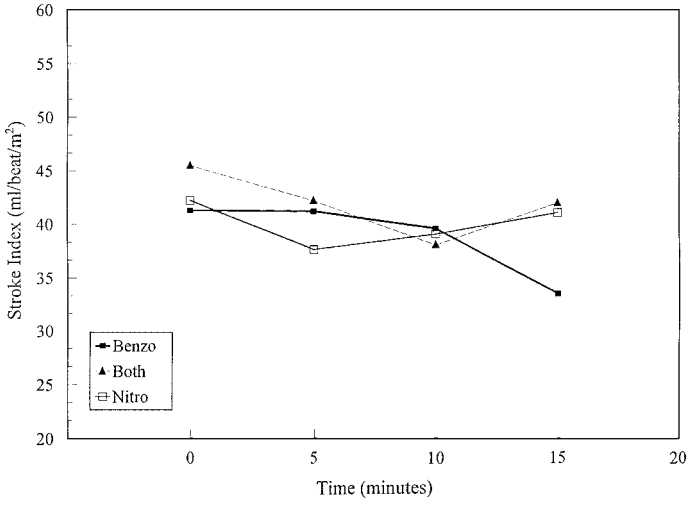

Figure 7. Change in stroke index for the three treatment groups over the 15-minute treatment period. Scores are adjusted for baseline differences. Benzo = benzodiazepine; Nitro = nitroglycerin.

transthoracic cardiac monitor in a more controlled setting. Our observed standard deviation was larger than we anticipated, effectively reducing the power of our study to demonstrate a difference.

Future randomized controlled clinical trials should continue to evaluate the response of patients with cocaine-associated acute coronary syndromes to different individual or combination pharmacotherapies. Future studies should also define patients with known acute coronary syndromes to evaluate the effectiveness of both proposed therapies in this specific patient population.

CONCLUSIONS

Treatment with diazepam and treatment with nitroglycerin had similar effects on chest pain resolution and cardiac function. Combination pharmacotherapy did not offer any additional benefit. Either agent appears adequate for treatment of patients with cocaine-associated acute coronary syndrome. Clinicians may wish to choose treatment based on the presence or absence of concurrent central nervous system symptoms.

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