Self-reported Cocaine Use, Emergency Physician Testing, and Outcomes in Suspected Acute Coronary Syndromes - A Nested, Matched Case-Control Study

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ARTICLE SUMMARY

Article focus:

- Was emergency physicians' propensity for noninvasive cardiac testing in chest pain patients affected by patients' self-reported history of cocaine use prior to studies over the last 10-years which have shown no benefits of noninvasive testing in the cocaine-chest pain population? \

Key messages:

- There was no association between patients' self-report of cocaine use and physicians' testing propensity
- Even prior to recent studies supporting a minimal-testing strategy, emergency physicians were already keeping testing to a minimum in patients with cocaine chest pain, and earlier understanding of that practice pattern may have reduced the amount of resources spent on subsequent studies of noninvasive testing.
- Data analysis of detailed registries can be an important tool in establishing practice patterns from which further comparative effectiveness research can be more selectively conducted

Strengths and limitations:

- Strength – data is obtained from a large multicenter registry of patients with undifferentiated chest pain which means the results are fairly representational of patients and physician practice patterns across the United States.
- Limitation – the database contained a low overall prevalence of self-reported cocaine use which means there was inadequate power to detect any statistically significant differences in morbidity/mortality

ABSTRACT

Objectives: While research over the last 10 years has focused on what noninvasive tests are useful for cocaine users with chest pain, the question of whether cocaine use was even affecting ED physicians' propensity for ordering extensive diagnostic tests had not been answered. Our primary purpose was to compare the odds of ACS-pertinent diagnostic testing between self-reported cocaine users and non-users at the turn of the century. Our secondary purpose was to compare the odds of ACS outcomes between cocaine users and non-users.

Design: We performed a nested, matched case-control study using data from the Internet Tracking Registry of Acute Coronary Syndromes (I*tr*ACS) comparing rates of diagnostic testing and outcomes between self-reported cocaine users and non-users. Matching was based on age, race, sex, and any history of known coronary artery disease (CAD).

Primary and secondary outcome measures: The conditional odds of undergoing invasive angiography and non-invasive testing for coronary artery disease were computed using conditional logistic regression. Occurrences of adverse cardiac outcomes within 30 days are reported.

Results: 249 subjects reporting cocaine use were matched to 249 controls. Cocaine users underwent diagnostic testing at similar rates compared to non-users (invasive plus noninvasive, 9.6% vs. 8.0%; OR 1.24; CI 0.65-2.34). Adverse cardiovascular outcomes occurred in 4 (1.6%) cocaine users and in 7 (2.8%) controls.

Conclusions: There was no increase in propensity for testing associated with self-reported history of cocaine use between 1999 and 2001. This suggests that even 10 years ago cocaine use already had only a limited role in the ED physician's decision-making process. Similar data analyses of detailed registries can offer important contextual information that can better direct resources for future comparative effectiveness research.

Introduction

Cocaine is the most commonly reported illicit drug of abuse among patients presenting to EDs; an estimated 5-10% of the US population has used cocaine, and it is associated with more hospital visits and deaths than any other drug of abuse. [1] Among patients presenting to EDs with chest pain syndrome (CPS), 17% test positive for cocaine on urine drug screen. [2] Owing to the drug's powerful sympathomimetic properties, acute cocaine intoxication has been associated with severe hypertension, coronary vasospasm, myocardial infarction, and cardiac arrest. [3-6] Long-term cocaine abuse has been shown to cause accelerated atherosclerosis, left ventricular hypertrophy, and dilated cardiomyopathy, thus placing patients at higher risk of adverse cardiac events. [3, 7] While cocaine's adverse cardiac effects have been well characterized, recent studies have revealed that low-risk patients who presented to EDs with cocaine-associated CPS can be safely discharged after a 23-hour observation period without further noninvasive testing [8, 9] if serial ECGs and cardiac markers were normal. In fact, over the last decade, multiple studies of various noninvasive cardiac tests have only shown that none of the tests are truly beneficial in the low-risk cocaine-related chest pain population. [10-13] These efforts have given today's ED physicians firm evidence for a streamlined approach to cocaine-associated CPS. However, whether self-reported cocaine-use affected an ED physician's propensity to pursue cardiac testing prior to these more recent findings had not been well described and we questioned whether physicians were actually subjecting cocaine-related CPS patients to extensive cardiac testing. We used data from the Internet Tracking Registry of Acute Coronary Syndrome (I*tr*ACS*) to compare the odds of diagnostic testing for CPS patients who reported recent cocaine use and who did not between 1999 and 2001.

Methods

I*tr*ACS* is a multicenter registry of over 17,000 patients who presented to one of 8 US or 1 Non-US ED between 1999 and 2001 with suspicion of ACS. Prospective data, including presenting signs and symptoms, ECG findings, and the ED physician's initial impression of risk, were systematically collected. Medical record review or daily follow-up was used to obtain cardiac biomarker results, invasive and noninvasive testing, treatments, procedures, and in-hospital outcomes. Medical record review and telephone follow-up were used to obtain thirty-day outcomes. Further details of the registry have been published previously.[14]

For this analysis, we extracted data for patients presenting to one of the 8 institutions in the US; non-US institutions may not have similar practice patterns owing to differences in culture or care standards. The 8 US institutions formed a representative cross-section of providers in the US. There were 6 academic and 2 community hospitals, with census varying between 10,000 and 160,000 visits during the study period. Providers of care to indigent and nonindigent populations were both well represented, with the proportion of patients receiving Medicaid or uninsured ranging from 17% to 67%. Patients with new ST-segment elevation on the presenting ECG or with an initial impression of AMI were not included since management of these patients was likely independent of underlying cardiac risk factors. At the time of the registry data collection, physicians were asked to make a distinction between AMI and unstable angina/non-Q-wave myocardial infarction when making an initial impression before results of any cardiac biomarkers were obtained. From among the remaining patients, cases were selected based on a self-reported history of cocaine use, and each case was then matched with a control based on 5-year age categories, race, sex, and any prior history of coronary artery disease. One to one matching was used because self-reported cocaine use was more common among younger subjects in the registry, and there were insufficient controls for successful age-matching if a higher ratio was used. Matching on additional risk factors was also not performed since the number of younger patients not reporting cocaine use included in the registry was too small.

The primary outcome was the occurrence of noninvasive or invasive assessment of coronary artery disease. Noninvasive testing was defined as exercise-treadmill or rest or stress nuclear scintigraphy or echocardiography. Invasive testing was defined as percutaneous diagnostic coronary angiography. The secondary outcome was a composite outcome of confirmed ACS, coronary revascularization, or all cause mortality within 30 days of the index ED visit. Confirmed ACS was defined as reversible ischemia on provocative testing, coronary artery disease documented to be greater than 70% on coronary angiography, or non-ST-segment-elevation AMI as determined by positive cardiac biomarkers (CK-MB, TnI, or TnT). As different sites participating in the registry used different assays for measuring cardiac biomarkers, results were recorded only as positive or negative.

Data are described using means and standard deviations or frequencies and percentages. Because the design involved matching cases to controls, the observations (or subjects) in the analysis were not independent. To prevent the overestimation of the odds ratio that occurs when matching occurs in the design, conditional logistic

regression was used to determine whether a report of cocaine use impacted the odds of undergoing non-invasive or invasive testing. All analyses were conducted using SPSS v14.0 (SPSS Inc., Chicago, IL).

Results

Data for 17,713 visits are available in the registry. There were 14,185 visits to sites in the US. US visits were excluded for the following reasons: 217 had undocumented age, race or sex, 587 had an initial impression of AMI, and 824 had new ST-segment elevations. Of the remaining 12,631, there were 249 visits (cases) in which the patient self-reported cocaine use (2.0%). Cases were successfully matched 1:1 with visits at which cocaine use was not reported (controls) based on age (5 year bins), race, sex and history of coronary artery disease except for a single case; one male aged less than 25, without a history of coronary artery disease was matched with a male aged 26 years without a history of coronary artery disease.

Characteristics of cases and controls are described in Table 1. The proportion of tobacco users was greater among the cases than controls (73.1% vs. 43.4%), and more cases prompted an initial physician impression of high risk chest pain (34.9% vs. 20.1%). More controls had an initial physician impression of a non-cardiac etiology than the cases (32.9% vs. 16.5%). Statistical testing of differences was not performed due to the matched nature of the data.

Table 2 shows the rates of testing conducted among cocaine users and controls, and the conditional odds ratios. Overall, the rates of non-invasive testing and angiography were similar between the self-reported cocaine users and the controls. Table 3 shows the incidence and odds ratios of various methods of noninvasive myocardial perfusion evaluation. No patient had a myocardial perfusion evaluation within 30 days following hospital discharge. The primary outcomes of combined angiography or non-invasive testing occurred in only 9.6% and 8.0% of self-reported cocaine users and controls respectively. The numbers of non-invasive and invasive procedures cannot be summed as an individual patient could have had both types of testing performed. Also, adverse events were rare in both cases and controls (1.6% and 2.8% respectively) with only 1 death overall (a control) within 30 days.

Discussion

We found that patients presenting to the ED with CPS and a self-reported history of recent cocaine use, without ECG changes suggestive of new ACS, received similar rates of objective testing for coronary artery disease

when compared to case matched control patients without a self-reported history of cocaine use. Our study is the first to specifically report ED physicians' testing propensity for underlying coronary artery disease in low-risk patients with self-reported cocaine associated chest pain during a time period when outcome data was only just emerging. Early work had suggested that patients presenting with cocaine-related CPS are at high risk for short term adverse outcomes. [3, 5] However, more recent studies have revealed that the short-term rate of adverse events for patients with cocaine-related CPS is actually lower than those with non-cocaine-related CPS. [8, 9] The entry criteria of self-reported cocaine usage is clinically important as patient history is the primary means by which emergency physicians determine what level of evaluation is necessary in patients presenting with chest pain syndrome.

Our finding of a lack of difference in testing propensity may initially seem surprising owing to the amount of literature in the 1990s suggesting that cocaine usage was associated with increased risk of short term adverse outcomes [6, 15, 16]. However, while cocaine was reported to induce coronary vasospasm [4, 17, 18] and cocaine users were being reported as having a higher risk of acute myocardial infarction immediately after their last use, [6] Amin and Hollander had reported that the majority of at-risk patients were presenting with initial ECG changes suggestive of ACS. [15, 19, 20] Our study group was fairly young, and the majority did not have multiple traditional cardiac risk factors in their histories (Table 1) or any ischemic ECG changes. More recent work by Hermann et al in 2009 has shown that in young, low-risk chest pain patients without a history of cocaine use, positive noninvasive cardiac tests are primarily false positives, and that there is no role for noninvasive testing in such a population. [21] Our primary outcome shows that even a decade ago, ED physicians had already in practice extended Hermann's findings to their approach to cocaine users as well; that in a low-risk population, even with the possibility of additional risk conferred by cocaine use, noninvasive cardiac testing was unnecessary and suspicion of underlying coronary artery disease was low.

While self-reported cocaine users received an evaluation similar to putatively lower risk patients without cocaine use, our secondary outcome suggests the ED physicians' clinical decision-making process was appropriate. Despite the lack of aggressive testing, the occurrence of 30-day ACS outcomes was low (2-3%, Table 2) and is consistent with rates reported in more recent studies of low risk chest pain patients where cocaine users were specifically excluded. [22, 23]

Over the last 10 years, several groups have looked at various noninvasive methods of detecting coronary artery disease in cocaine users including dobutamine stress testing, myocardial perfusion imaging, or more recently computerized tomography angiography. [10-13] None of the studies has convincingly demonstrated a benefit to more testing in self-reported cocaine users. In fact, results of cardiac testing in low-risk cocaine-users have been similar to those found in non-cocaine-users: mandatory exercise stress testing results in a low rate of positive findings; [9] myocardial perfusion testing does not detect any reversible ischemia in patients without ECG changes; [11] and there is limited angiographic evidence of coronary disease in patients without an abnormal ECG or elevated troponins. [24] Diercks et al found a rate of positive non-invasive test results of 17% and 14% for stimulant and cocaine users admitted to a chest pain observation unit, respectively. However, whether other factors influenced either the decision for testing or the high rate of positive results was unclear, and the high positive rate may suggest this was a high-risk population at baseline. [25]

Our data from this registry show that as far back as 10 years ago, in an otherwise low risk population without ischemic ECG changes, self-reported cocaine use alone did not increase ED physicians' propensity for further cardiac testing. This practice pattern has been more recently validated by studies by Weber and Cunningham. Weber found that the 30-day events rates were similar in patients with cocaine associated chest pain whether they received an inpatient evaluation for coronary artery disease or not. Weber's reported 1.6% rate of non-fatal MIs at 30 days is similar to our combined adverse events rate of 1.6%. [9] Cunningham found that in 219 cocaine-users with low-intermediate risk of CAD presenting to an ED with CPS, discharge after an uneventful stay in a 23-hour observation unit resulted in no missed MIs at 1 year follow up. [8]

Our study has several limitations. Foremost is that we were not able to differentiate between those patients who presented immediately after cocaine use and those who merely reported a prior history of cocaine use. As the highest risk period is shortly after cocaine use, a sample of patients that presented later may have resulted in a lower complication rate than expected. Second, the 2% prevalence of cocaine use by self report is much lower than the 17% prevalence of cocaine use confirmed by laboratory results cited by other studies. The potential lack of detection of cocaine in some percentage of the non-cocaine group may have made the two groups more similar than different. However, the rates of noninvasive testing and adverse events in both group were already so low that any more rigorous distinction of users from nonusers would probably not have been able to reduced the control group's

rates to any statistically or clinically significant degree. Third, while matching was based on demographics and any known CAD, we did not match for the presences of other cardiac risk factors. Since physicians use cardiac risk factors to help determine the extent of cardiac testing, a more rigorous case-matching may have eliminated several possible confounders. However, too-rigorous matching could also result in overestimation of effects, and despite the large sample size of the registry, we found that we were already not able to completely match the two groups. The only two notable differences between our cases and controls, more tobacco use and more initial impressions of high risk chest pain in the cocaine-users, would have been expected to bias our results toward a greater difference in testing propensity between the two groups. The lack of a difference in testing propensity despite the differences suggests that further matching may not be necessary and that the cases and controls were somewhat homogeneous. Fourth, it is possible that practice patterns were hospital dependent, so we conducted a sensitivity analysis that adjusted the model for the primary outcome for site. The conditional OR for the primary outcome in that analysis was 0.80 (95%CI 0.39-1.66), p=0.556, which does not change our conclusion. We note that the magnitude of the difference between cases and controls was only 1.6% and in our data the proportion of discordant pairs was 0.15. The observed power was therefore about 9%. With a sample size of 249 pairs, the difference in proportions would need to be 6.8% or greater to have achieved statistical significance. Lastly, by specifically excluding patients with ST elevations on ECG or those with initial impressions of AMI from our study, we selected lower risk cocaine users without obvious acute pathophysiology. This was consistent with our intention to determine the impact of a self-reported history of cocaine use on emergency physicians' management strategy. While exclusion of those with obvious acute presentations may have underestimated the incidence of diagnostic testing in all cocaine users, the presence of concerning ECG changes or elevated biomarkers would have led to further cardiac testing in any patient regardless of history.

Our study is a descriptive evaluation of ED physicians' practice patterns in managing self-reported cocaine users presenting with a single episode of acute chest pain 10 years ago. Our patients were relatively young and had few risk factors for adverse cardiac events. Our analysis was not powered to detect a difference in the rate of adverse cardiac events. Our low rates at 30-day follow up should not be interpreted as an accurate reflection of life-long cardiac disease burden in cocaine users, and certainly does not reflect long term consequences of cocaine use. Especially since others have found that even in cocaine addicts with a mean age of 32 years, 36% had greater than 75% atherosclerotic stenosis in at least one epicardial coronary artery. [3] Also, the 1.6% recurrent MIs in Weber's

study were found exclusively in those who continued to use cocaine. [9] Chronic or older cocaine users probably require closer routine monitoring, and may benefit from outpatient noninvasive testing, long-term follow up and drug dependence interventions. In fact, while a history of cocaine use may not have a significant role in an ED physician's decision making process regarding diagnostic testing, it should be noted that current ACS treatment recommendations do vary based upon recent use of cocaine, [26] and therefore it is still important to solicit this information in the ED. Future studies may be needed to further define the morbidity or mortality benefits of earlier initiation of outpatient cardiac testing in cocaine users.

Our findings are consistent with currently published guidelines on the management of cocaine chest pain and should not alter them. However, our findings do highlight the utility of registry data. During the last decade, multiple studies have been conducted on extensive testing strategies, despite the fact that a minimalist practice pattern was already in place and was yielding a very low rate of adverse outcomes. In fact, no study on noninvasive cardiac testing protocols in a similar population has demonstrated any improvement in overall mortality beyond what has been shown with a 23-hour observation period. The I*tr*ACS* registry was compiled in an era when electronic medical records (EMRs) were still under development, and data entry was done by hand. While raw data was collected between 1999 and 2001, the registry was not completed and published until 2006. The availability of computerized means of data collection and extraction would mean earlier availability of descriptive and outcome reports. If, over a decade ago, we had EMRs efficiently providing quality data to help us describe and evaluate the treatment patterns for cocaine-related chest pain patients, we may have potentially spared all the more recent resources that were used to disprove the utility of noninvasive cardiac testing. As EMRs become more advanced and ubiquitous, we have the opportunity to build detailed registries across the entire spectrum of disease processes encountered in the ED. The increased focus on comparative effectiveness research means that descriptive outcomes studies will only become more vital in establishing the contextual background against which different therapies may be compared. Without an understanding of established practice patterns and outcomes, we cannot know what, much less how, to improve upon them.

Conclusion

We found that between 1999 and 2001, in patients presenting to the ED with CPS but without ECG changes or an initial impression of AMI, there was no association between physician practice-patterns and a self-

reported history of cocaine use. Furthermore, the risk of ACS events within 30 days of presentation was low. Our findings show that almost 10 years prior to recent prospective studies validating the safety of a 23-hours observation protocol and disproving the utility of extensive noninvasive cardiac testing, ED physicians were already electing for a minimally involved workup. Furthermore, the low rate of adverse events associated with their practice pattern has yet to be significantly reduced by any more recent published studies involving more extensive cardiac testing protocols. Our study illustrates the importance of registries in patient centered outcomes research. In the era of EMRs, the ability to efficiently build registries and generate outcomes data will be essential as focus shifts towards comparative effectiveness research and more efficient utilization of resources.

Competing interests: None of the authors have any competing interests to declare.

Contributors: Yang Wang, Christopher J. Lindsell, and W. Frank Peacock were involved in the conception and design, acquisition of data, and analysis and interpretation of data; Yang Wang and W. Frank Peacock were involved in drafting the article; all authors were involved in critical revisions for important intellectual content and have given final approval of the version to be published.

Data-sharing statement: There is no additional data available for this study.

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Table 1

Characteristics of cases and controls. Data are given as means and standard deviations or frequencies and percentages.

	Controls		Cases	
Demographics				
Age in years	39.9	(9.1)	39.9	(9.1)
Female	70	(28.1)	70	(28.1)
Male	179	(71.9)	179	(71.9)
White	40	(16.1)	40	(16.1)
African-American	178	(71.5)	178	(71.5)
Other	31	(12.4)	31	(12.4)
History				
Family history of heart disease	77	(30.9)	81	(32.5)
Current smoker	108	(43.4)	182	(73.1)
Diabetes	33	(13.3)	26	(10.4)
Hypertension	83	(33.3)	79	(31.7)
Hyperlipidemia	20	(8.0)	15	(6.0)
Angina	16	(6.4)	18	(7.2)
Coronary artery disease	23	(9.2)	23	(9.2)

Congestive heart failure	13	(5.2)	10	(4.0)
Initial Impression				
Unstable angina/Non-Q-Wave MI	13	(5.2)	6	(2.4)
High risk chest pain	50	(20.1)	87	(34.9)
Low risk chest pain	104	(41.8)	115	(46.2)
Noncardiac chest pain	82	(32.9)	41	(16.5)

Table 2

Outcomes experienced among cases and controls. The conditional odds of outcomes are shown.

	Controls	Cases	Conditional OR	95%CI(OR)	P-value
Non-invasive testing	13 (5.2)	19 (7.6)	1.55	(0.72 – 3.30)	0.261
Angiography	10 (4.0)	10 (4.0)	1.00	(0.42 – 2.40)	1.000
Primary outcome	**20 (8.0)**	**24 (9.6)**	**1.24**	**(0.65 – 2.34)**	**0.517**
Recurrent MI	5 (2.0)	2 (0.8)			
Percutaneous coronary intervention	1 (0.4)	1 (0.4)			
Coronary artery bypass graft	1 (0.4)	0 (0.0)	Not done – too few outcomes		
Death	0 (0.0)	1 (0.4)			
Revascularation, recurrent MI or death	**7 (2.8)**	**4 (1.6)**			

Table 3

Rate of each type of noninvasive testing performed during hospital stay for controls and cases.

	Controls		Cases	
	N	**%**	**N**	**%**
Any testing	13	5.2	19	7.6
Exercise treadmill	6	2.4	4	1.6
Stress nuclear medicine or echocardiogram study	3	1.2	9	3.6
Rest nuclear medicine or echocardiogram study	5	2.0	9	3.6

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	5-6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	6
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7-8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Self-reported Cocaine Use, Emergency Physician Testing, and Outcomes in Suspected Acute Coronary Syndromes - A Nested, Matched Case-Control Study

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Self-reported Cocaine Use, Emergency Physician Testing, and Outcomes in Suspected Acute Coronary Syndromes - A Nested, Matched Case-Control Study

ARTICLE SUMMARY

Article focus:

- Was emergency physicians' tendency for noninvasive cardiac testing in chest pain patients affected by patients' self-reported history of cocaine use prior to studies over the last 10-years which have shown no benefits of noninvasive testing in the cocaine-chest pain population?

Key messages:

- There was no association between patients' self-report of cocaine use and physicians' testing tendency
- Even prior to recent studies supporting a minimal-testing strategy, emergency physicians were already keeping testing to a minimum in patients with cocaine chest pain, and earlier understanding of that practice pattern may have reduced the amount of resources spent on subsequent studies of noninvasive testing.
- Data analysis of detailed registries can be an important tool in establishing practice patterns from which further comparative effectiveness research can be more selectively conducted

Strengths and limitations:

- Strength – data is obtained from a large multicenter registry of patients with undifferentiated chest pain which means the results are fairly representational of patients and physician practice patterns across the United States.
- Limitation – the database contained a low overall prevalence of self-reported cocaine use which means there was inadequate power to detect any statistically significant differences in morbidity/mortality

ABSTRACT

Objectives: Our primary purpose was to compare the odds of ACS-pertinent diagnostic testing between self-reported cocaine users and non-users at the turn of the century. Our secondary purpose was to compare the odds of ACS outcomes between cocaine users and non-users.

Design: Nested, matched case-control study using data from the Internet Tracking Registry of Acute Coronary Syndromes (I*tr*ACS*).

Setting: Extracted data of patients from 8 US institutions composed of 6 academic and 2 community hospitals, with census varying between 10,000 and 160,000 visits per year.

Participants: 249 cases of self-reported cocaine users and 249 matched controls. Matching was based on age, race, sex, and any history of known coronary artery disease (CAD). Exclusion criteria were new ST-elevations on initial ECG and initial physician impression of acute myocardial infarction (AMI).

Primary and secondary outcome measures: Primary outcome was the conditional odds of undergoing noninvasive and invasive testing for coronary artery disease. Secondary outcome was the occurrences of adverse cardiac outcomes within 30 days.

Results: Cocaine users underwent diagnostic testing at similar rates compared to non-users (9.6% vs. 8.0%; OR 1.24; CI 0.65-2.34). Adverse cardiovascular outcomes occurred in 4 (1.6%) cocaine users and in 7 (2.8%) controls.

Conclusions: There was no increase in tendency for testing associated with self-reported history of cocaine use between 1999 and 2001. This suggests that even 10 years ago cocaine use already had only a limited role in the ED physician's decision-making process. Similar data analyses of detailed registries can offer important contextual information that can better direct resources for future comparative effectiveness research.

Introduction

Cocaine is the most commonly reported illicit drug of abuse among patients presenting to EDs; an estimated 5-10% of the US population has used cocaine, and it is associated with more hospital visits and deaths than any other drug of abuse. [1] Among patients presenting to EDs with chest pain syndrome (CPS), 17% test positive for cocaine on urine drug screen. [2] Owing to the drug's powerful sympathomimetic properties, acute cocaine intoxication has been associated with severe hypertension, coronary vasospasm, myocardial infarction, and cardiac arrest. [3-6] Long-term cocaine abuse has been shown to cause accelerated atherosclerosis, left ventricular hypertrophy, and dilated cardiomyopathy, thus placing patients at higher risk of adverse cardiac events. [3, 7] While cocaine's adverse cardiac effects have been well characterized, recent studies have revealed that low-risk patients who presented to EDs with cocaine-associated CPS can be safely discharged after a 23-hour observation period without further noninvasive testing [8, 9] if serial ECGs and cardiac markers were normal. In fact, over the last decade, multiple studies of various noninvasive cardiac tests have only shown that none of the tests are truly beneficial in the low-risk cocaine-related chest pain population. [10-13] These efforts have given today's ED physicians firm evidence for a streamlined approach to cocaine-associated CPS. However, whether self-reported cocaine-use affected an ED physician's tendency to pursue cardiac testing prior to these more recent findings had not been well described and we questioned whether physicians were actually subjecting cocaine-related CPS patients to extensive cardiac testing. We used data from the Internet Tracking Registry of Acute Coronary Syndrome (I*tr*ACS*) to compare the odds of diagnostic testing for CPS patients who reported recent cocaine use and who did not between 1999 and 2001.

Methods

I*tr*ACS* is a multicenter registry of over 17,000 patients who presented to one of 8 US or 1 Non-US ED between 1999 and 2001 with suspicion of ACS. Prospective data, including presenting signs and symptoms, ECG findings, and the ED physician's initial impression of risk, were systematically collected. Medical record review or daily follow-up was used to obtain cardiac biomarker results, invasive and noninvasive testing, treatments, procedures, and in-hospital outcomes. Medical record review and telephone follow-up were used to obtain thirty-day outcomes. Further details of the registry have been published previously.[14]

For this analysis, we extracted data for patients presenting to one of the 8 institutions in the US; non-US institutions may not have similar practice patterns owing to differences in culture or care standards. The 8 US institutions formed a representative cross-section of providers in the US. There were 6 academic and 2 community hospitals, with census varying between 10,000 and 160,000 visits during the study period. Providers of care to indigent and nonindigent populations were both well represented, with the proportion of patients receiving Medicaid or uninsured ranging from 17% to 67%. Patients with new ST-segment elevation on the presenting ECG or with an initial impression of AMI were not included since management of these patients was likely independent of underlying cardiac risk factors. At the time of the registry data collection, physicians were asked to make a distinction between AMI and unstable angina/non-Q-wave myocardial infarction when making an initial impression before results of any cardiac biomarkers were obtained. From among the remaining patients, cases were selected based on a self-reported history of cocaine use, and each case was then matched with a control based on 5-year age categories, race, sex, and any prior history of coronary artery disease. One to one matching was used because self-reported cocaine use was more common among younger subjects in the registry, and there were insufficient controls for successful age-matching if a higher ratio was used. Matching on additional risk factors was also not performed since the number of younger patients not reporting cocaine use included in the registry was too small.

The primary outcome was the occurrence of noninvasive or invasive assessment of coronary artery disease. Noninvasive testing was defined as exercise-treadmill or rest or stress nuclear scintigraphy or echocardiography. Invasive testing was defined as percutaneous diagnostic coronary angiography. The secondary outcome was a composite outcome of confirmed ACS, coronary revascularization, or all cause mortality within 30 days of the index ED visit. Confirmed ACS was defined as reversible ischemia on provocative testing, coronary artery disease documented to be greater than 70% on coronary angiography, or non-ST-segment-elevation AMI as determined by positive cardiac biomarkers (CK-MB, TnI, or TnT). As different sites participating in the registry used different assays for measuring cardiac biomarkers, results were recorded only as positive or negative.

Data are described using means and standard deviations or frequencies and percentages. Because the design involved matching cases to controls, the observations (or subjects) in the analysis were not independent. To prevent the overestimation of the odds ratio that occurs when matching occurs in the design, conditional logistic

regression was used to determine whether a report of cocaine use impacted the odds of undergoing non-invasive or invasive testing. All analyses were conducted using SPSS v14.0 (SPSS Inc., Chicago, IL).

Results

Data for 17,713 visits are available in the registry. There were 14,185 visits to sites in the US. Of those visits, 647 (4.6%) were entirely lost to follow up. US visits were excluded for the following reasons: 217 had undocumented age, race or sex, 587 had an initial impression of AMI, and 824 had new ST-segment elevations. Of the remaining 12,631, there were 249 visits (cases) in which the patient self-reported cocaine use (2.0%). Cases were successfully matched 1:1 with visits at which cocaine use was not reported (controls) based on age (5 year bins), race, sex and history of coronary artery disease except for a single case; one male aged less than 25, without a history of coronary artery disease was matched with a male aged 26 years without a history of coronary artery disease. Of the 249 cases of self-reported cocaine-users, 20 (8.0%) were entirely lost to follow up. Of the 249 matched controls, 20 (8.0%) were also lost to follow up.

Characteristics of cases and controls are described in Table 1. The proportion of tobacco users was greater among the cases than controls (73.1% vs. 43.4%), and more cases prompted an initial physician impression of high risk chest pain (34.9% vs. 20.1%). More controls had an initial physician impression of a non-cardiac etiology than the cases (32.9% vs. 16.5%). Statistical testing of differences was not performed due to the matched nature of the data.

Table 2 shows the rates of testing conducted among cocaine users and controls, and the conditional odds ratios (ORs) and 95% confidence intervals (CIs). The OR (CI) for non-invasive testing and angiography are 1.55 (0.72-3.30) and 1.00 (0.42-2.40) respectively. Overall, the rates of non-invasive testing and angiography were similar between the self-reported cocaine users and the controls, with a combined OR (CI) of 1.24 (0.65-2.34). Table 3 shows the incidence and odds ratios of various methods of noninvasive myocardial perfusion evaluation. No patient had a myocardial perfusion evaluation within 30 days following hospital discharge. The primary outcomes of combined angiography or non-invasive testing occurred in only 9.6% and 8.0% of self-reported cocaine users and controls respectively. The numbers of non-invasive and invasive procedures cannot be summed as an

individual patient could have had both types of testing performed. Also, adverse events were rare in both cases and controls (1.6% and 2.8% respectively) with only 1 death overall (a control) within 30 days.

Discussion

We found that patients presenting to the ED with CPS and a self-reported history of recent cocaine use, without new ST-segment elevation on the presenting ECG or an initial impression of AMI, received similar rates of objective testing for coronary artery disease when compared to case matched control patients without a self-reported history of cocaine use. Our study is the first to specifically report ED physicians' testing tendency for underlying coronary artery disease in low-risk patients with self reported cocaine use during a time period when outcome data was only just emerging. Early work had suggested that patients presenting with cocaine-related CPS are at high risk for short term adverse outcomes. [3, 5] However, more recent studies have revealed that the short-term rate of adverse events for patients with cocaine-related CPS is actually lower than those with non-cocaine-related CPS. [8, 9] The entry criteria of self-reported cocaine usage is clinically important as patient history is the primary means by which emergency physicians determine what level of evaluation is necessary in patients presenting with chest pain syndrome.

Our finding of a lack of difference in testing tendency may initially seem surprising owing to the amount of literature in the 1990s suggesting that cocaine usage was associated with increased risk of short term adverse outcomes [6, 15, 16]. However, while cocaine was reported to induce coronary vasospasm [4, 17, 18] and cocaine users were being reported as having a higher risk of acute myocardial infarction immediately after their last use, [6] Amin and Hollander had reported that the majority of at-risk patients were presenting with initial ECG changes suggestive of ACS. [15, 19, 20] Our study group was fairly young, and the majority did not have multiple traditional cardiac risk factors in their histories (Table 1) or any ischemic ECG changes. More recent work by Hermann et al in 2009 has shown that in young, low-risk chest pain patients without a history of cocaine use, positive noninvasive cardiac tests are primarily false positives, and that there is no role for noninvasive testing in such a population. [21] Our primary outcome shows that even a decade ago, ED physicians had already in practice extended Hermann's findings to their approach to cocaine users as well; that in a low-risk population, even with the possibility of additional risk conferred by cocaine use, noninvasive cardiac testing was unnecessary and suspicion of underlying coronary artery disease was low.

While self-reported cocaine users received an evaluation similar to putatively lower risk patients without cocaine use, our secondary outcome suggests the ED physicians' clinical decision-making process was appropriate. Despite the lack of aggressive testing, the occurrence of 30-day ACS outcomes was low (2-3%, Table 2) and is consistent with rates reported in more recent studies of low risk chest pain patients where cocaine users were specifically excluded. [22, 23]

Over the last 10 years, several groups have looked at various noninvasive methods of detecting coronary artery disease in cocaine users including dobutamine stress testing, myocardial perfusion imaging, or more recently computerized tomography angiography. [10-13] None of the studies has convincingly demonstrated a benefit to more testing in self-reported cocaine users. In fact, results of cardiac testing in low-risk cocaine-users have been similar to those found in non-cocaine-users: mandatory exercise stress testing results in a low rate of positive findings; [9] myocardial perfusion testing does not detect any reversible ischemia in patients without ECG changes; [11] and there is limited angiographic evidence of coronary disease in patients without an abnormal ECG or elevated troponins. [24] Diercks et al found a rate of positive non-invasive test results of 17% and 14% for stimulant and cocaine users admitted to a chest pain observation unit, respectively. However, whether other factors influenced either the decision for testing or the high rate of positive results was unclear, and the high positive rate may suggest this was a high-risk population at baseline. [25]

Our data from this registry show that as far back as 10 years ago, in an otherwise low risk population without ischemic ECG changes, self-reported cocaine use alone did not increase ED physicians' tendency for further cardiac testing. This practice pattern has been more recently validated by studies by Weber and Cunningham. Weber found that the 30-day events rates were similar in patients with cocaine associated chest pain whether they received an inpatient evaluation for coronary artery disease or not. Weber's reported 1.6% rate of non-fatal MIs at 30 days is similar to our combined adverse events rate of 1.6%. [9] Cunningham found that in 219 cocaine-users with low-intermediate risk of CAD presenting to an ED with CPS, discharge after an uneventful stay in a 23-hour observation unit resulted in no missed MIs at 1 year follow up. [8]

Our study has several limitations. Foremost is that we were not able to differentiate between those patients who presented immediately after cocaine use and those who merely reported a prior history of cocaine use. As the highest risk period is shortly after cocaine use, a sample of patients that presented later may have resulted in a lower

complication rate than expected. Second, the 2% prevalence of cocaine use by self report is much lower than the 17% prevalence of cocaine use confirmed by laboratory results cited by other studies. The potential lack of detection of cocaine in some percentage of the non-cocaine group may have made the two groups more similar than different. However, the rates of noninvasive testing and adverse events in both group were already so low that any more rigorous distinction of users from nonusers would probably not have been able to reduced the control group's rates to any statistically or clinically significant degree. Third, while matching was based on demographics and any known CAD, we did not match for the presences of other cardiac risk factors. Since physicians use cardiac risk factors to help determine the extent of cardiac testing, a more rigorous case-matching may have eliminated several possible confounders. However, too-rigorous matching could also result in overestimation of effects, and despite the large sample size of the registry, we found that we were already not able to completely match the two groups. The only two notable differences between our cases and controls, more tobacco use and more initial impressions of high risk chest pain in the cocaine-users, would have been expected to bias our results toward a greater difference in testing tendency between the two groups. The lack of a difference in testing tendency despite the differences suggests that further matching may not be necessary and that the cases and controls were somewhat homogeneous. Fourth, it is possible that practice patterns were hospital dependent, so we conducted a sensitivity analysis that adjusted the model for the primary outcome for site. The conditional OR for the primary outcome in that analysis was 0.80 (95%CI 0.39-1.66), p=0.556, which does not change our conclusion. We note that the magnitude of the difference between cases and controls was only 1.6% and in our data the proportion of discordant pairs was 0.15. The observed power was therefore about 9%. With a sample size of 249 pairs, the difference in proportions would need to be 6.8% or greater to have achieved statistical significance. Lastly, by specifically excluding patients with ST elevations on ECG or those with initial impressions of AMI from our study, we selected lower risk cocaine users without obvious acute pathophysiology. This was consistent with our intention to determine the impact of a self-reported history of cocaine use on emergency physicians' management strategy. While exclusion of those with obvious acute presentations may have underestimated the incidence of diagnostic testing in all cocaine users, the presence of concerning ECG changes or elevated biomarkers would have led to further cardiac testing in any patient regardless of history.

Our study is a descriptive evaluation of ED physicians' practice patterns in managing self-reported cocaine users presenting with a single episode of acute chest pain 10 years ago. Our patients were relatively young and had

few risk factors for adverse cardiac events. Our analysis was not powered to detect a difference in the rate of adverse cardiac events. Our low rates at 30-day follow up should not be interpreted as an accurate reflection of life-long cardiac disease burden in cocaine users, and certainly does not reflect long term consequences of cocaine use. Especially since others have found that even in cocaine addicts with a mean age of 32 years, 36% had greater than 75% atherosclerotic stenosis in at least one epicardial coronary artery. [3] Also, the 1.6% recurrent MIs in Weber's study were found exclusively in those who continued to use cocaine. [9] Chronic or older cocaine users probably require closer routine monitoring, and may benefit from outpatient noninvasive testing, long-term follow up and drug dependence interventions. In fact, while a history of cocaine use may not have a significant role in an ED physician's decision making process regarding diagnostic testing, it should be noted that current ACS treatment recommendations do vary based upon recent use of cocaine, [26] and therefore it is still important to solicit this information in the ED. Future studies may be needed to further define the morbidity or mortality benefits of earlier initiation of outpatient cardiac testing in cocaine users.

Our findings are consistent with currently published guidelines on the management of cocaine chest pain and should not alter them. However, our findings do highlight the utility of registry data. During the last decade, multiple studies have been conducted on extensive testing strategies, despite the fact that a minimalist practice pattern was already in place and was yielding a very low rate of adverse outcomes. In fact, no study on noninvasive cardiac testing protocols in a similar population has demonstrated any improvement in overall mortality beyond what has been shown with a 23-hour observation period. The I*tr*ACS* registry was compiled in an era when electronic medical records (EMRs) were still under development, and data entry was done by hand. While raw data was collected between 1999 and 2001, the registry was not completed and published until 2006. The availability of computerized means of data collection and extraction would mean earlier availability of descriptive and outcome reports. If, over a decade ago, we had EMRs efficiently providing quality data to help us describe and evaluate the treatment patterns for cocaine-related chest pain patients, we may have potentially spared all the more recent resources that were used to disprove the utility of noninvasive cardiac testing. As EMRs become more advanced and ubiquitous, we have the opportunity to build detailed registries across the entire spectrum of disease processes encountered in the ED. The increased focus on comparative effectiveness research means that descriptive outcomes studies will only become more vital in establishing the contextual background against which different therapies may

be compared. Without an understanding of established practice patterns and outcomes, we cannot know what, much less how, to improve upon them.

Conclusion

We found that between 1999 and 2001, in patients presenting to the ED with CPS but without ECG changes or an initial impression of AMI, there was no association between physician practice-patterns and a self-reported history of cocaine use. Furthermore, the risk of ACS events within 30 days of presentation was low. Our findings show that almost 10 years prior to recent prospective studies validating the safety of a 23-hours observation protocol and disproving the utility of extensive noninvasive cardiac testing, ED physicians were already electing for a minimally involved workup. Furthermore, the low rate of adverse events associated with their practice pattern has yet to be significantly reduced by any more recent published studies involving more extensive cardiac testing protocols. Our study illustrates the importance of registries in patient centered outcomes research. In the era of EMRs, the ability to efficiently build registries and generate outcomes data will be essential as focus shifts towards comparative effectiveness research and more efficient utilization of resources.

Competing interests: None of the authors have any competing interests to declare.

Contributors: Yang Wang, Christopher J. Lindsell, and W. Frank Peacock were involved in the conception and design, acquisition of data, and analysis and interpretation of data; Yang Wang and W. Frank Peacock were involved in drafting the article; all authors were involved in critical revisions for important intellectual content and have given final approval of the version to be published.

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Table 1

Characteristics of cases and controls. Data are given as means and standard deviations or frequencies and percentages.

	Controls		Cases	
Demographics				
Age in years	39.9	(9.1)	39.9	(9.1)
Female	70	(28.1)	70	(28.1)
Male	179	(71.9)	179	(71.9)
White	40	(16.1)	40	(16.1)
African-American	178	(71.5)	178	(71.5)
Other	31	(12.4)	31	(12.4)
History				
Family history of heart disease	77	(30.9)	81	(32.5)
Current smoker	108	(43.4)	182	(73.1)
Diabetes	33	(13.3)	26	(10.4)
Hypertension	83	(33.3)	79	(31.7)
Hyperlipidemia	20	(8.0)	15	(6.0)
Angina	16	(6.4)	18	(7.2)
Coronary artery disease	23	(9.2)	23	(9.2)

Congestive heart failure	13	(5.2)	10	(4.0)
Initial Impression				
Unstable angina/Non-Q-Wave MI	13	(5.2)	6	(2.4)
High risk chest pain	50	(20.1)	87	(34.9)
Low risk chest pain	104	(41.8)	115	(46.2)
Noncardiac chest pain	82	(32.9)	41	(16.5)

Table 2

Outcomes experienced among cases and controls. The conditional odds of outcomes are shown.

	Controls	Cases	Conditional OR	95%CI(OR)	P-value
Non-invasive testing	13 (5.2)	19 (7.6)	1.55	(0.72 – 3.30)	0.261
Angiography	10 (4.0)	10 (4.0)	1.00	(0.42 – 2.40)	1.000
Primary outcome	**20 (8.0)**	**24 (9.6)**	**1.24**	**(0.65 – 2.34)**	**0.517**
Recurrent MI	5 (2.0)	2 (0.8)			
Percutaneous coronary intervention	1 (0.4)	1 (0.4)			
Coronary artery bypass graft	1 (0.4)	0 (0.0)	Not done – too few outcomes		
Death	0 (0.0)	1 (0.4)			
Revascularation, recurrent MI or death	**7 (2.8)**	**4 (1.6)**			

Table 3

Rate of each type of noninvasive testing performed during hospital stay for controls and cases.

	Controls		Cases	
	N	**%**	**N**	**%**
Exercise treadmill	6	2.4	4	1.6
Stress nuclear medicine or echocardiogram study	3	1.2	9	3.6
Rest nuclear medicine or echocardiogram study	5	2.0	9	3.6

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