**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

<table>
<thead>
<tr>
<th>Eric Lavonas, MD</th>
<th>Date Submitted for review:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>January 30, 2010</td>
</tr>
</tbody>
</table>

**Clinical question.**

**ALS-SC-073-06B**

**Primary question:**

In adult cardiac arrest (prehospital or in-hospital) due to cocaine toxicity (P), does use of any specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (e.g. ROSC, survival)?

**Secondary question:**

In adults with severe cardiovascular toxicity (prehospital or in-hospital) due to cocaine toxicity (P), does use of any specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (e.g. ROSC, survival)?

The management of cocaine-associated chest pain and myocardial infarction (in the absence of life-threatening acute cardiovascular toxicity) is beyond the scope of this worksheet.

Is this question addressing an intervention/therapy, prognosis or diagnosis? Therapy

State if this is a proposed new topic or revision of existing worksheet: New

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

MEDLINE (via Ovid) (1950 to 2009 week 46), EMBASE (via Ovid), and the AHA EndNote master database were searched for the keyword Cocaine. Reports were imported into EndNote. An EndNote keyword search for “human” was applied. Duplicates were removed. The resulting search yielded 3,829 apparently unique citations.

The final search was applied on November 27, 2009.

The above strategy was supplemented in two ways:

1. The bibliographies of major review articles and textbook chapters were reviewed for relevant studies that may have been missed.
2. Because of the risk that an important article was overlooked during manual review of the 3,829 articles, a more focused MEDLINE search was conducted. The MeSH terms “cocaine” [or] “cocaine-related disorders” were cross-referenced with the MeSH term “heart arrest” [or] the keyword “cardiac arrest.” This search was conducted on December 29, 2009, using the Ovid search engine and the MEDLINE database (1950 to 2009 Present with Daily Update). This search retrieved 46 citations; no new studies meeting inclusion criteria were identified.

**State inclusion and exclusion criteria**

**Inclusion criteria:**

Any published human study (clinical trial or consecutive patient case series case series) related to cocaine-associated cardiac arrest.

Prospective human studies of the treatment of cocaine toxicity (other than cardiac arrest or peri-arrest states) were included, but considered LOE 5 because they involve a different population than that of this manuscript.

**Exclusion criteria**

- Non-human studies
- In vitro studies
- Case reports of a single patient or convenience case series
- Studies focusing on the treatment of dependence or withdrawal

**Number of articles/sources meeting criteria for further review:**

3,829 unique articles were retrieved by the literature search and hand-searched for relevance.
### Summary of evidence

#### Evidence Supporting Primary Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Evidence Supporting Primary Clinical Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>Shih, 1995, 702 (B) (lidocaine for V-Tach)</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
</tr>
</tbody>
</table>

#### Evidence Supporting Secondary Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Evidence Supporting Secondary Clinical Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Lange, 1989, 1557 (E) (phenolamine)</td>
</tr>
<tr>
<td></td>
<td>Baumann, 2000, 878 (E) (NTG, diazepam)</td>
</tr>
<tr>
<td></td>
<td>Honderick, 2003, 39 (E) (NTG, lorazepam)</td>
</tr>
<tr>
<td></td>
<td>Negus, 1994, 501 (E) (verapamil)</td>
</tr>
<tr>
<td></td>
<td>Saland, 2002, 810 (E) (morphine)</td>
</tr>
<tr>
<td></td>
<td>Brogan, 1991, 581 (E) (NTG)</td>
</tr>
<tr>
<td>Fair</td>
<td>Vongpatanasin, 1999, 497 (E) (propranolol)</td>
</tr>
<tr>
<td></td>
<td>Dattilo, 2008, 117 (C,E) (beta blockers)</td>
</tr>
<tr>
<td></td>
<td>Sofuoglu, 2000, 69 (E) (carvedilol)</td>
</tr>
<tr>
<td></td>
<td>Sofuoglu, 2000, 255 (E) (labetolol)</td>
</tr>
<tr>
<td></td>
<td>Hollander, 1994, 243 (E) (NTG, diazepam)</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
</tr>
</tbody>
</table>

**Level of evidence**

- A = Return of spontaneous circulation
- B = Survival of event
- C = Survival to hospital discharge
- D = Intact neurological survival
- E = Other endpoint
- Italics = Animal studies
### Evidence Neutral to the Primary Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hsue, 2007, 822 (A,B,C,D) (Standard therapy)</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

### Evidence Neutral to the Secondary Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Boehrer, 1993, 608 (E) (labetolol)</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Level of evidence**
- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
- **Italics** = Animal studies
### Evidence Opposing the Primary Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Evidence Opposing the Secondary Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Italicics = Animal studies*

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint

**Lange, 1990, 897 (E)**  
(propranolol)  
**Sand, 1991, 161 (E)**  
(esmolol)
REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Cocaine is a common and important cardiovascular toxin. Cocaine is a direct myocardial depressant, an indirect cardiac stimulant (via central mechanisms leading to catecholamine release), and an inhibitor of cardiac sodium and potassium channels. (Crumb, 1992, 910) With a relatively long dissociation constant (8.5 seconds), cocaine’s electrophysiologic characteristics are similar to those of Vaughn-Williams class IC anti-dysrhythmics. (Wood, 2009, 14) In addition, cocaine can cause myocardial infarction by inducing plaque rupture, coronary artery vasospasm, or coronary artery dissection. Cocaine intoxication increases myocardial oxygen demand through indirect stimulation of beta-andrenergic receptors while simultaneously increasing afterload.

This review is limited to the treatment of cardiac arrest and peri-arrest states due to cocaine abuse. Though beyond the scope of this review, the diagnosis and treatment of cocaine-associated chest pain and myocardial infarction is the topic of a recent American Heart Association Scientific Statement. (McCord, 2008, 1897)

Cardiac arrest:

No clinical trials were found that addressed the treatment of cardiac arrest due to cocaine intoxication.

Only one case series of cocaine-associated cardiac arrest was identified. (Hsue, 2007, 822) In this series of 22 patients with arrest/ROSC after cocaine use, neither the presenting rhythm nor QT interval differentiated cocaine users from sequential controls. However, overall survival and neurologically intact survival (12/22, 55%) were both significantly better in cocaine users than in the comparison populations. This study did not examine treatments employed.

Strong animal evidence supports a role for sodium bicarbonate and/or lidocaine for wide complex dysrhythmias due to cocaine intoxication (Wood, 2009, 14). However, the human evidence is sparse. No human studies of sodium bicarbonate for WCT were found. A single LOE 4 study supports the use of lidocaine in cocaine-associated ventricular tachycardia (Shih, 1995, 702). In this retrospective case series, 8/8 patients with cocaine-associated ventricular tachycardia (2 sustained, 6 non-sustained) survived the event. No data were provided on concomitant therapies, nor on patients who did not receive lidocaine, and it is unclear how many of these 8 patients were in cardiac arrest.

Severe/life-threatening acute cardiovascular toxicity (the peri-arrest setting):

No human studies of treatment of cocaine intoxication in the peri-arrest setting were found. In the absence of these data, treatment recommendations will need to be made by inference from studies in different patient populations. Although often of high quality, these studies are all LOE 5 because they did not directly study human subjects with acute, life-threatening cardiovascular effects due to cocaine intoxication.

The greatest volume and quality of data come from a series of similar studies performed at a single institution. All are of high methodologic quality. Cocaine-naïve patients undergoing diagnostic cardiac catheterization were given a relatively low dose of intranasal cocaine (2 mg/kg), followed by candidate therapies. Vital signs and coronary artery diameter were measured before cocaine, after cocaine, and after treatment with active drug or placebo. Cocaine reliably produces modest coronary artery vasoconstriction in this model. This vasoconstriction was reversed by morphine (Saland, 2002, 810), nitroglycerine (Brogan, 1991, 581), phentolamine (Lange, 1989, 1557), and verapamil (Negus, 1994, 501), not changed by labetolol (Boehrer, 1993, 608), and exacerbated by propranolol (Lange, 1990, 897). In a similar model, propranolol blunted the sympathomimetic effects of cocaine (Vongpatanasin, 1999, 497; coronary arteries not studied).

Studies of patients who present to the emergency department show symptomatic improvement and blunting of tachycardia and hypotension following administration of benzodiazepines (Baumann, 2000, 878), nitroglycerine (Baumann, 2000, 878; Honderick, 2003, 39; Hollander, 1994, 243), and the combination of benzodiazepines plus nitroglycerine (Baumann, 2000, 878; Honderick, 2003, 39). Esmolol infusion appears to be harmful in this population (Sand, 1991, 161). However, in a large retrospective study, administration of beta blockers was associated with reduced mortality in patients hospitalized with cocaine-associated ACS. (Dattilo, 2008, 117)

Finally, pretreatment with the mixed alpha- and beta-blocking drugs carvedilol and labetolol blunt the sympathomimetic effects of cocaine in crack cocaine addicts. (Sofuoglu, 2000, 69; Sofuoglu, 2000, 255)

Acknowledgements:
Citation List


LOE 5, good quality, supporting. This was a well-conducted prospective trial of three competing treatment strategy for patients presenting to the emergency department with cocaine-associated chest pain. This study was LOE 5 because it dealt with a different patient population than the clinical questions (cardiac arrest and severe/life-threatening cardiovascular toxicity).


LOE 5, good quality, neutral. This was one of several methodologically excellent clinical trials conducted over a period of several year at Parkland Memorial Hospital, Dallas, TXs. Study subjects were cocaine-naïve patients undergoing diagnostic cardiac catheterization for medical reasons, generally unstable angina pectoris. Subjects received a moderate dose of intranasal cocaine (2 mg/kg) (or placebo), chosen because this dose produces increased cardiac workload and coronary artery vasoconstriction without causing chest pain, myocardial infarction, or life-threatening dysrhythmia. Subjects then received antidote (or placebo). Physiologic measurements and coronary artery diameter were measured at baseline, after cocaine (or placebo), and after antidote (or placebo). All of the Parkland studies are LOE 5 because they dealt with a different patient population than the clinical questions (cardiac arrest and severe/life-threatening cardiovascular toxicity). This study showed improvement in cocaine-induced hypertension and neither improvement nor worsening in coronary artery vasoconstriction following labetalol therapy.


LOE 5, good quality, supporting. Another Parkland study (see discussion of Boehrer 1993 reference).


LOE 5, fair quality, supporting. This is a large retrospective case series from a single institution. Study subjects were all patients admitted to the hospital for suspected ACS in the setting of cocaine use. It is unclear how many of these patients had cardiac arrest or severe, life-threatening cardiovascular toxicity, but the relatively low death rate suggests that this is not the same population as our target question. The rate of MI was higher in patients who received beta-blockade than in those who did not. Because this study was unable to tease out confounders (for example, whether the patients who received beta blockers were more severely ill on presentation), it must be considered hypothesis-generating only. However, these findings call into question whether the use of beta blockers for cocaine-associated ACS actually causes harm.


LOE 5, fair quality, supporting. This was a prospective observational study. This study was LOE 5 because it dealt with a different patient population than the clinical questions (cardiac arrest and severe/life-threatening
cardiovascular toxicity). It is unclear why only 34% of the candidate population received nitroglycerine, or how this group differed from the group who did not receive NTG.


LOE 4, fair quality, neutral. This interesting retrospective case series involved patients who had cocaine-associated cardiac arrest, achieved ROSC, and survived to hospital admission. The survival rate in this select group of patients was high (55%). How this population compares with those who did not survive to hospital admission is unclear.


LOE 5, good quality, supporting. This study was LOE 5 because it dealt with a different patient population than the clinical questions (cardiac arrest and severe/life-threatening cardiovascular toxicity).


LOE 5, good quality, supporting. Another Parkland study (see discussion of Boeher 1993 reference).


LOE 5, good quality, supporting. Another Parkland study (see discussion of Boeher 1993 reference).


LOE 5, good quality, supporting. Another Parkland study (see discussion of Boeher 1993 reference). In this study, administration of verapamil, 10 mg IV, was associated with resolution of hypertension and coronary artery vasoconstriction produced by intranasal cocaine.


LOE 5, good quality, supporting. Another Parkland study (see discussion of Boeher 1993 reference). In this study, administration of morphine sulfate, 0.25 mg/kg IV (maximum: 25 mg), was associated with resolution of coronary artery vasoconstriction produced by intranasal cocaine. No significant effect on hemodynamics was seen in this study.

LOE 5, fair quality, opposing. This study was LOE 5 because it dealt with a different patient population than the clinical questions (cardiac arrest and severe/life-threatening cardiovascular toxicity). Although this was a retrospective cohort study of patients who received esmolol, it is unclear how this population compares with the larger population of patients presenting to the emergency department with cocaine-associated chest pain or ACS.


LOE 4, fair quality, supporting. This was a retrospective cohort study of patients who received lidocaine for cocaine-associated MI. Each participating institution enrolled an average of 1 patient; how patients treated with lidocaine differed from those who did not receive lidocaine cannot be determined. 8 patients in this series had ventricular tachycardia (2 sustained, 6 non-sustained); all survived the event. Information about concomitant therapies received is sparse.


LOE 5, fair quality, supporting. This study and its sister (Sofuoglu, 2000, 255, below) involved pretreatment with oral beta-blocking agents that have partial alpha-1 receptor antagonism, followed by cocaine use. Although it is difficult to extrapolate from these studies to therapy administered after the onset of cocaine-associated cardiac arrest or severe cardiovascular toxicity, the lack of harm from administration of mixed beta- and alpha-blocking medications is noteworthy.


LOE 5, fair quality, supporting. See Sofuoglu, 2000, 69, above.


LOE 5, fair quality, supporting. This study employed a dose of cocaine (2 mg/kg intranasal) shown in the Parkland studies to induce a mild sympathetic response and coronary artery vasoconstriction, but not chest pain, MI, or dysrhythmia. In this study, propranolol 0.2 mg/kg IV blocked the sympathetic response and did not cause symptoms or apparent harm. Coronary artery diameter was not measured. This study was LOE 5 because it dealt with a different patient population than the clinical questions (cardiac arrest and severe/life-threatening cardiovascular toxicity).