

In-Hospital and Long-Term Outcomes of Beta-Blocker Treatment in Cocaine Users: A Systematic Review and Meta-analysis

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Abstract

Background: Although β -blocker treatment is generally contraindicated in patients presenting with acute cocaine intoxication due to concern for unopposed α -receptor stimulation, some studies have reported that β -blocker treatment did not increase adverse events in these patients. As this treatment is still controversial, we performed a meta-analysis of observational studies on this topic.

Methods: By searching three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) from their inception to June 11, 2018, we identified eight observational studies with 2,048 patients who presented to hospital with cocaine-associated chest pain or after recent cocaine use. Outcomes of interest were myocardial necrosis or infarction (MI) and death during hospital stay or follow-up. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated by using a random-effects meta-analysis based on the DerSimonian-Laird method.

Results: Among patients presenting with cocaine-associated chest pain or recent cocaine use, there was no significant difference in in-hospital all-cause mortality (RR, 0.59; 95% CI, 0.24 - 1.47) and MI (RR, 1.24; 95% CI, 0.74 - 2.06) between patients who did and did not receive β -blocker treatment during their hospital stay. During long-term follow-up (mean 2.6 years), there was no significant difference in all-cause mortality (RR, 0.79; 95% CI, 0.44 - 1.41) and MI (RR, 0.96; 95% CI, 0.40 - 2.33) between the two groups.

Conclusions: These results suggest that β -blocker treatment in patients presenting with cocaine intoxication may not be as harmful as originally believed. Further clinical studies are needed to investigate this topic.

Keywords: Beta-Blocker; Cocaine; Chest pain

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Introduction

Cocaine is one of the most commonly used illicit drugs in the US. Each year, more than 400,000 of Americans present to the emergency department (ED) with cocaine-associated complications, which account for approximately 40% of all drug-related visits to the ED [1-3]. More than half of these patients had cardiovascular toxicity, and 40% reported chest pain [3, 4]. Incidence of myocardial infarction (MI) among the patients presenting with cocaine-associated chest pain was reported to be 0.7-6% [5, 6]. Cocaine can cause chest pain or acute coronary syndrome (ACS) by increasing myocardial oxygen demand due to its sympathomimetic effect [7] and decreasing oxygen supply via coronary vasoconstriction [8].

Guidelines recommended treating patients presenting with cocaine-associated chest pain or ACS in the same manner as patients with traditional ACS, with few exceptions [3, 9]. Although β -blockers (BB) are a core component of treatment for patients with traditional ACS, they have been contraindicated in patients with signs of acute cocaine intoxication [3, 9, 10]. This is mainly due to concerns regarding coronary vasoconstriction and acute increase in blood pressure due to unopposed α -receptor stimulation after BB treatment in cocaine toxicity [3, 9]. However, there is much debate on this theory because it is largely based on animal studies, case reports, and small retrospective studies [1, 2, 11-13]. In fact, several observational studies have reported that BB treatment in the ED did not increase adverse events and mortality in patients with cocaine-associated chest pain [14-17]. Furthermore, some studies have demonstrated that BB treatment in these patients was associated with better long-term outcomes compared with those who did not receive it [15, 18]. Because of ongoing controversy and inconsistency between studies, we conducted a meta-analysis on the association between BB treatment and clinical outcome in patients presenting with cocaine-associated chest pain.

Materials and Methods

Search strategy and data sources

This study was performed according to the PRISMA statement guidelines (Supplementary Table 1) (www.cardiolo-

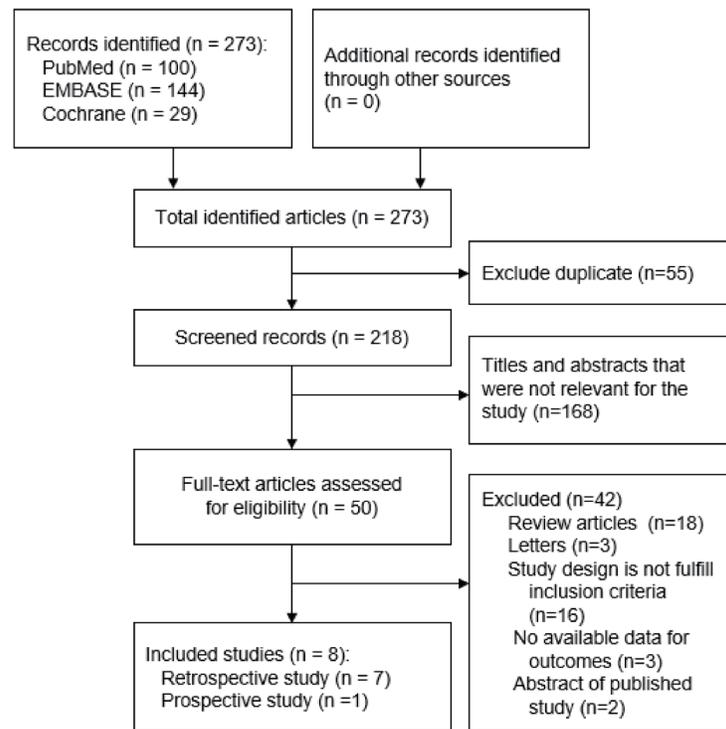


Figure 1. A flow diagram of identification of relevant studies.

gyres.org). Two authors (DS and ESL) independently searched MEDLINE, EMBASE, and the Cochrane Library from their inception until June 11, 2018, using the search terms “Beta-blocker(s)” or “Beta blocker(s)” and “Cocaine” with any restriction on language or publication status. The bibliographies of relevant articles were also reviewed to locate additional publications.

Study selection

We included observational studies that met the following predetermined criteria: 1) Included patients who presented with cocaine-associated chest pain or recent cocaine use; 2) Compared clinical outcomes between patients who received BB treatment during admission or at discharge and those who did not receive it; 3) Reported in-hospital or long-term outcomes including MI (or myocardial necrosis) or death. Both published studies and conference abstracts were considered to be included.

Data extraction and quality assessment

Study eligibility was evaluated by two independent investigators (DS and ESL) based on the predetermined selection criteria. Event numbers of death and MI (or myocardial necrosis) in patients with and without BB therapy were extracted from the studies. Disagreements between the two investigators were resolved by discussion with the other co-authors. The meth-

odological quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS) [19].

Statistical analyses

For outcomes of interest, pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated using the number of events and nonevents extracted from individual studies. Estimates for in-hospital and long-term outcomes were pooled independently. A random-effects meta-analysis based on the DerSimonian-Laird method [20] was used due to functional inequality and difference in true effect sizes among the studies. Heterogeneity of results among the studies was assessed using the Higgins I^2 value [21]. Publication bias was evaluated using Egger’s test [22]. All statistical analyses were performed using Stata, version 12.1 (StataCorp, College Station, Texas, USA).

Results

Identification of relevant studies

Figure 1 displays a flow diagram of identification of relevant studies. A total of 273 articles were identified from the three databases and 218 studies were screened after excluding duplicates. After excluding 168 studies based on titles and abstracts, the full texts of 50 studies were reviewed. Eight cohort studies (seven retrospective [14-17, 23-25] and one prospective [18])

with 2,048 patients met the predetermined selection criteria and were included in the final study. Seven studies were published in journals [14-18, 23, 24] and one was a conference abstract [25].

Characteristics of studies and patients

Table 1 [14-18, 23-25] displays the general characteristics of the included studies. Five studies [14, 16, 17, 23, 24] reported in-hospital outcomes and three studies [15, 18, 25] reported in-hospital and/or long-term outcomes. Median or mean ages of individuals in the study population ranged from 42 to 57 years. Mean NOS score was 7 (Supplementary Table 2) (www.cardiologres.org).

As shown in Table 2 [14-18, 23-25], all studies used urine toxicology results to assess recent cocaine use. MI (or myocardial necrosis) was defined based on elevated serum troponin levels or changes in electrocardiogram. Among studies that specified types of BB, β -selective agents (metoprolol, propranolol, or atenolol) were predominantly used, with the exception of one study in which carvedilol was used in all patients [25]. To investigate in-hospital outcomes, studies included patients who were given BB during their hospital stay or in the ED. For long-term outcomes, studies identified patients who were discharged with BB.

Meta-analysis

Among patients who presented with cocaine-associated chest pain or recent cocaine use, there was no significant difference in in-hospital all-cause mortality (RR, 0.59; 95% CI, 0.24 - 1.47; $I^2 = 0.0\%$) and MI or myocardial necrosis (RR, 1.24; 95% CI, 0.74 - 2.06; $I^2 = 63\%$) between patients who received BB treatment during the hospital stay and those who did not receive it (Fig. 2). During long-term follow-up (mean 2.6 years), there was no significant difference in all-cause mortality (RR, 0.79; 95% CI, 0.44 - 1.41; $I^2 = 26.6\%$) and MI (RR, 0.96; 95% CI, 0.40 - 2.33; $I^2 = 0.0\%$) between the two groups (Fig. 3).

Publication bias

Egger's test did not reveal any evidence of small-study effects on all outcomes, but the number of studies was too small to appropriately assess for publication bias ($P = 0.201$ for in-hospital mortality, 0.580 for in-hospital MI/myocardial necrosis, and 0.737 for long-term mortality). Egger's test could not be performed for long-term MI as there were only two studies.

Discussion

In this meta-analysis, BB treatment in patients presenting with cocaine-associated chest pain or recent cocaine use was not associated with adverse events. More specifically, there was no difference in MI/myocardial necrosis and death during hospital

Table 1. Characteristics of Included Studies

Study	Design	Period	Age, yrs ^{a,b}	Female, % ^b	Follow-up	Number of cases/total patients							
						In-hospital MI or MN		Long-term MI		In-hospital death		Long-term death	
						BB user	Non-user	BB user	Non-user	BB user	Non-user	BB user	Non-user
Mohamad et al [23]	R	2004 - 2005	47 ^c	27 ^c	In-hospital	14/100	13/254	NA	NA	NA	NA	NA	NA
Dattilo et al [14]	R	2000 - 2005	50/44	27/37	In-hospital	2/33	72/277	NA	NA	1/33	13/277	NA	NA
Rangel et al [15]	R	2001 - 2006	51/48	26/29	2.7 yrs	15/151	18/177	NA	NA	2/151	3/177	18/149	27/168
Ibrahim et al [17]	R	1998 - 2011	46/42	23/25	In-hospital	22/162	20/216	NA	NA	NA	NA	NA	NA
Fanari et al [16]	R	2000 - 2007	46/42	32/26	In-hospital	5/164	2/212	NA	NA	3/164	6/212	NA	NA
Schmidt et al [24]	R	2006 - 2009	50/48	12/6	In-hospital	14/26	17/32	NA	NA	0/26	0/32	NA	NA
Finks et al [25]	R	NA	57/54	NA	1 yr	NA	NA	2/47	5/140	NA	NA	6/47	14/140
Cediel et al [18]	P	2001 - 2014	45/43	13/6	4 yrs	NA	NA	6/33	5/24	0/33	2/24	2/33	5/24

BB: β -blocker; MI: myocardial infarction; MN: myocardial necrosis; NA: not available; P: prospective; R: retrospective; Yr: year. ^aMean or median values; ^bBB user/non-user; ^cOnly overall population number is available.

Table 2. Definitions, Types of β -Blocker, and Timing of Administration

Study	Symptoms on presentation	Definition of cocaine use	MI definition	Type of BB	Timing of BB administration
Mohamad et al [23]	Chest pain	Positive UDS	MI (or myocardial necrosis): chest pain and troponin I > 0.02 ng/mL	Not specified	On presentation
Dattilo et al [14]	47% chest pain; 2% heart failure; 3% stroke; 3% seizure; 4% overdose	Positive UDS	Troponin I > 0.10 ng/mL or ECG changes \geq two contiguous leads	66% metoprolol, atenolol, or propranolol; 21% labetalol or carvedilol; 13% both	During admission
Rangel et al [15]	Chest pain	Positive UDS	Troponin > 1.5 ng/mL	74% IV metoprolol; 11% oral metoprolol; 12% IV labetalol; 2% oral labetalol; 1% oral atenolol; 1% oral propranolol	In the ED
Ibrahim et al [17]	Chest pain	Positive UDS and reported cocaine use within the previous 24 h	Troponin I > 0.6 ng/mL and Troponin T > 0.1 ng/mL	53% metoprolol; 27.2% labetalol; 26.6% carvedilol; 2% atenolol	During admission
Fanari et al [16]	Chest pain	Positive UDS and reported cocaine use within the previous 24 h	Troponin T > 0.1 ng/dL or ST-segment elevations in two contiguous leads in ECG	20% metoprolol; 12% labetalol; 11% carvedilol; 1% atenolol	During admission (within the first 24 h)
Schmidt et al [24]	Chest pain	Positive UDS	Positive troponin	50% oral metoprolol; 19% IV metoprolol; 8% IV labetalol; 8% oral carvedilol; 8% oral atenolol; 8% oral propranolol	During admission (while having chest pain) or at discharge
Finks et al [25]	Chest pain	Positive UDS	NA	100% carvedilol	At discharge
Cediel et al [18]	Acute coronary syndrome	Positive UDS within 48 – 72 h of admission	NA	Not specified	During admission or at discharge

BB: β -blocker; ECG: electrocardiogram; ED: emergency department; NA: not available; MI: myocardial infarction; UDS: urine drug screening; IV: intravenous.

stays and long-term follow-up between patients who did and did not receive BB treatment. These results are generally consistent with those reported in the recent meta-analyses [26, 27], but our study is unique in that we included more studies than the prior meta-analyses and differentiated between in-hospital and long-term outcomes for the first time.

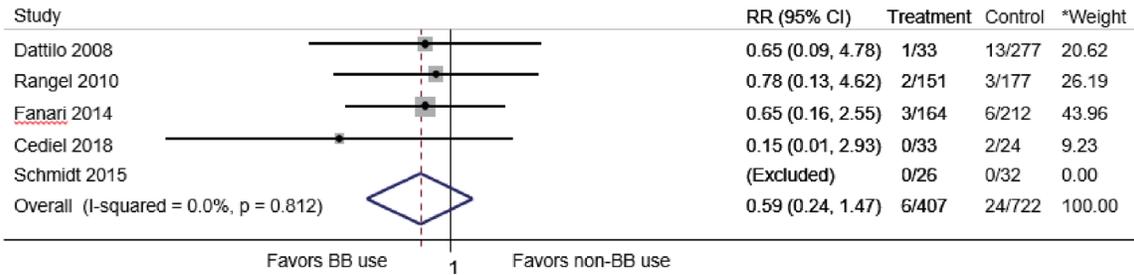
Cocaine induces cardiovascular toxicity through various mechanisms. First, it stimulates the sympathetic nervous system by increasing central sympathetic outflow [28] and blocking reuptake of catecholamines at the presynaptic adrenergic terminal [7, 10]. By doing so, it increases blood pressure, heart rate, and myocardial contractility, and thereby increases myocardial oxygen demand. At the same time, cocaine stimulates coronary vasoconstriction resulting in a decrease in myocardial oxygen supply. Worsening mismatch between myocardial oxygen demand and supply leads to ischemia or infarction. Second, like a class I antiarrhythmic agent, cocaine can cause electrocardiographic changes and induce arrhythmia by blocking sodium and potassium channels [10, 29]. Third, cocaine induces a prothrombotic state by activating platelets and altering the

balance between procoagulant and anticoagulant factors [3].

In cocaine users, blocking β -receptors can leave α -stimulation unopposed, potentiating cocaine-induced systemic and coronary vasoconstriction [10]. This theory is largely based on animal studies and case reports/series [1]. However, some have suggested that the outcomes of these case reports/series may simply be due to the myriad harmful pharmacologic effects of cocaine alone rather than unopposed α -stimulation [2]. There have been two small prospective studies, but only 19 patients received intracoronary/intravenous BB in total [30, 31]. Given the limited evidence, unopposed α -stimulation and its clinical significance are still controversial.

Because of the above-mentioned concerns, current guidelines recommend against use of BB in ACS patients with signs of acute cocaine intoxication, unless patients are receiving a coronary vasodilator (class III recommendation: Harm) [9]. In our study, BB treatment in patients presenting with cocaine-associated chest pain or recent cocaine use did not experience an increase in adverse events during their hospital stays. Since many of the included studies did not precisely specify the tim-

A. In-hospital all-cause death



B. In-hospital myocardial infarction (or necrosis)

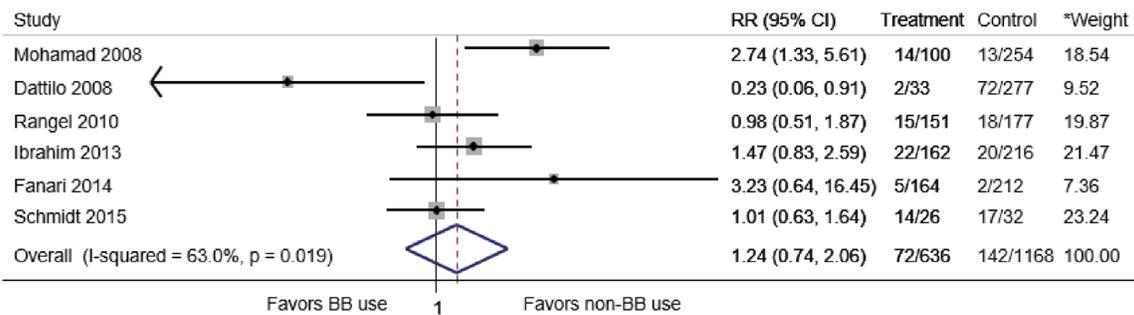
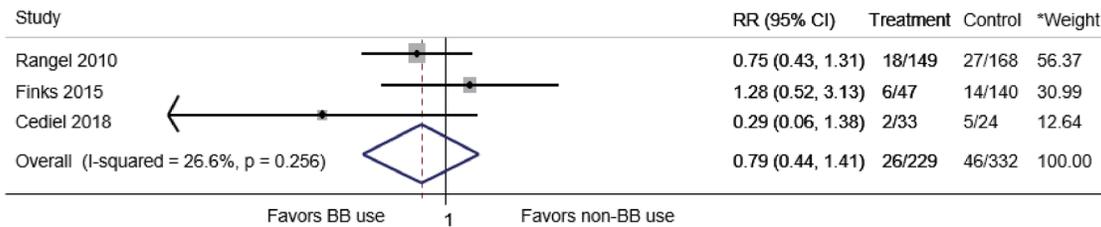


Figure 2. In-hospital all-cause death and myocardial infarction (MI) or myocardial necrosis in patients with cocaine-associated chest pain who did and did not received beta-blocker treatment. BB: beta-blocker; RR: relative risk; CI: confidence interval. *Weights are from random effects analysis.

ing of BB administration, we were unable to further investigate the impact of this timing on clinical outcomes. However, many patients in the included studies may have been given BB in the presence of signs of acute intoxication, because BB is typically used for hypertension and tachycardia, which are manifestations of acute cocaine intoxication. Furthermore, the subgroup

analysis described in the study by Rangel et al identified no significant differences in electrocardiographic changes, troponin levels, ventricular arrhythmia, or death between patients who received BB within 6 h of presentation and those who did not receive BB [15]. Another study reported that administration of BB within the first 24 h of presentation did not increase

A. Long-term all-cause death



B. Long-term myocardial infarction

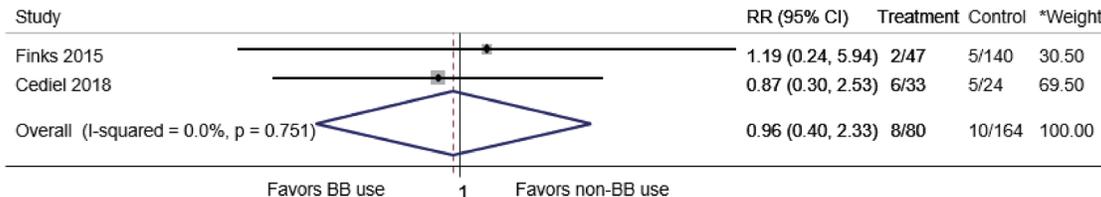


Figure 3. Long-term all-cause death and myocardial infarction (MI) in patients with cocaine-associated chest pain or recent cocaine use who did and did not received beta-blocker treatment. BB: beta-blocker; RR: relative risk; CI: confidence interval. *Weights are from random effects analysis.

death, stroke, MI, and arrhythmia [16]. Based on these results, early use of BB during the acute stages of cocaine intoxication may not be as harmful as previously believed. Therefore, BB may be an effective treatment option, especially for concomitant hypertension and tachycardia secondary to cocaine intoxication, if other options are not working well [2, 13]. As there has been lack of quality evidence, additional studies are needed to investigate risks and benefits of BB treatment in cocaine-associated cardiovascular toxicity.

Long-term use of BB in active cocaine users is also a controversial topic. BB is one of the medicines proven to improve survival in patients after ACS or with heart failure with reduced ejection fraction (HFrEF) [9, 32]. However, due to concerns regarding unopposed α -receptor stimulation, cocaine users were less likely to be prescribed with BB after ACS [33, 34]. In our study, there was no difference in long-term mortality and risk of MI between patients who did and did not receive BB treatment. In individual studies, patients discharged on BB exhibited a significant reduction in cardiovascular death [15] and a higher 90-day survival [18]. Among patients with HFrEF and concurrent cocaine use, BB treatment was associated with a reduced 30-day heart failure-related readmission rate [35] and improvement in functional class and left ventricular ejection fraction at a 12-month follow-up without any major adverse cardiovascular event [36]. These results suggest that more studies are needed to investigate risks and benefits of long-term BB treatment in cocaine users.

Another important question is what type of BB can be used in patients with acute cocaine intoxication. As a major concern is unopposed α -stimulation, which can aggravate vasoconstriction, use of combined α - and β -blocking agents, such as labetalol and carvedilol, or concomitant use of vasodilators with BB may offer theoretical advantages in this patient population [10]. According to a recent review article, no study has reported unopposed α -stimulation with the use of combined α - and β -blocking agents [2]. In the focused update of the 2011 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for unstable angina/non-ST-elevation MI, administration of combined α - and β -blocking agents was classified as a class IIb recommendation, provided that the patient has received a vasodilator within close temporal proximity [37]. However, there was no such recommendation in the 2014 ACC/AHA guideline [9]. Interestingly, metoprolol, a β -1 selective antagonist, was used in most of the studies included in our meta-analysis (Table 2). In the study by Fanari et al, subgroup analysis according to the types of BB revealed that the use of either β -1 selective antagonists or combined α - and β -blocking agents did not increase in-hospital composite end point of death, stroke, MI, and arrhythmia [16]. However, evidence was limited, as the other studies did not differentiate between combined α - and β -blocking agents and β -1 selective agents. It should also be noticed that, in the study by Rangel et al, sublingual or continuous nitroglycerin therapy was more frequently used in patients who received BB treatment than in those who did not [15]. One may argue that concomitant use of nitroglycerine with BB may have mitigated possible unopposed α -stimulation. As most of the other studies did not report such information, we could not further investigate this hypothesis. Therefore, more studies are required to examine

above-mentioned theoretical benefits of using combined α - and β -blocking agents versus β -1 selective agents and concomitant use of vasodilators with BB.

Our study has several limitations. First, we were only able to include observational studies, as there has been no randomized controlled trial on this topic. Second, only a small number of studies were available. Third, small-study effects could not be fully excluded. Fourth, we could not perform subgroup analysis on BB types or the timing of BB administration due to lack of information from individual studies. Finally, definitions of MI were variable among the studies.

In conclusion, our results suggest that BB treatment in patients presenting with cocaine-associated chest pain or recent cocaine use was not associated with in-hospital and long-term death or MI. Additional studies are required to better understand the risks and benefits of BB administration in these patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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