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β-Blocker treatment and prognosis in acute coronary syndrome associated with cocaine consumption: The RUTI-Cocaine Study☆

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ABSTRACT

Background: The use of β-blocker therapy in the setting of acute coronary syndrome (ACS) associated with cocaine consumption (ACS-ACC) is discouraged due to the risk of coronary vasoconstriction. We examined the prognostic value of β-blocker therapy in a contemporary ACS cohort.

Methods and results: Prospective, single-center study conducted between January 2001 and December 2014 that examined cocaine use among young (≤50-year-old) consecutive patients admitted with an ACS. During the study period, 1002 patients were admitted; of these, 57 (5.7%) had a positive cocaine urine test We collected data on clinical characteristics and major adverse cardiovascular events (MACE) during follow-up. Among ACS-ACC patients, 33 (57.9%) received β-blocker therapy during hospital admission and after discharge. During a median follow-up of 4.0 (IQR: 2.4–6.5) years after the index event, 2 (6.1%) patients treated with β-blocker therapy died and 6 (18.2%) experienced hospital re-admission for myocardial infarction (MI); in contrast, there were 5 (20.8%) deaths and 5 (20.8%) readmissions due to MI in patients without β-blocker therapy. Lower rates of MACE were observed in patients treated with β-blocker therapy (30.3%) than those without β-blocker therapy (41.7%). The 90-day survival was higher in patients treated with β-blocker therapy (87.5% vs. 100%; Log rank test $p = 0.035$).

Conclusions: In patients with ACS-ACC, β-blocker treatment was associated with a significantly better clinical outcome, with lower rates of death and MI. Our findings support the evidence for long-term β-blocker administration in high-risk patients and highlight the need for large prospective multicenter studies of β-blocker treatment in ACS-ACC.

1. Introduction

Cocaine use has increased in recent years, being the second most frequently consumed drug in Europe after cannabis. Its growing consumption has generated an increase in the number of admissions in emergency departments due to clinical conditions resulting from its toxicity [1]. The vast majority of these patients are admitted for chest pain, and the incidence of cocaine-induced myocardial infarction is reported to be around 6% [2]. Current recommendations for management of these patients are largely based on expert consensus [3].

The use of β-blocker therapy in the setting of acute coronary syndrome (ACS) associated with cocaine consumption (ACS-ACC) is discouraged due to the risk of coronary vasoconstriction secondary to unopposed α-receptor stimulation [4,5]. However, the management of ACS has evolved substantially over the past two decades, and the value of β-blockade in this setting has not been re-evaluated. Accordingly, we examined the prognostic value of β-blocker therapy in a contemporary ACS cohort.

2. Methods

The RUTI-Cocaine Study was a prospective study conducted between January 2001 and December 2014 that examined cocaine use among young (≤50-year-old) consecutive patients admitted to a single center with an ACS. The center is located in the metropolitan area of Barcelona and served a population of 817,000 inhabitants. The admission protocol for ACS patients under the age of 50 included a questionnaire about cocaine use and frequency of use as well as a urine test for cocaine within 48–72 h of admission. A urine test for cocaine was performed qualitatively using immunoenzyme analysis (Dimension Flex Reagent Cartridge; Siemens Healthcare Diagnostics Ltd., Frimley, Camberley, UK).

Demographic and clinical data were collected. The study complies with the Helsinki Declaration, was approved by the local ethics committee, and all patients provided informed consent prior to participation.

The main clinical outcome of this study was the composite of major adverse cardiovascular events (MACE), which were identified as all-cause mortality, cardiovascular mortality, readmission due to myocardial infarction and revascularization. In-hospital

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mortality was also analyzed. The follow-up events were obtained from patients' electronic clinical records and from death registers.

2.1. Statistical analysis

Data are presented as medians and IQRs for continuous variables and as counts with percentages for categorical variables. The baseline characteristics of patients were compared using the Wilcoxon rank-sum test for continuous variables and Pearson's c2 test for categorical variables or Fisher's exact test when needed. Kaplan–Meier survival curves and the Log rank test were used to assess differences in 90-days survival. Differences were considered statistically significant at $p < 0.05$. STATA V.13.0 (College Station, Texas, USA) was used for all analyses (Tables 1 and 2).

3. Results

During the study period, 1002 patients were admitted; of these, 864 (86.2%) underwent cocaine urine testing. The study included the 57 (5.7%) patients with a positive cocaine urine test. Of these, 33 (57.9%) received β-blocker therapy during hospital admission and after discharge during follow-up. The median age was 44 (38–47) years, and 52 (91.2%) were male. Baseline age, smoking status, and comorbidities including diabetes, dyslipidemia or history of MI were similar between patients who were and were not treated with β-blocker therapy, except for a higher prevalence of arterial hypertension in those treated with β-blocker (30.3% vs. 8.3%, $p = 0.045$).

There were no significant differences in terms of STEMI presentation (90.9% vs. 75%; $p = 0.146$), disease severity (Killip-Kimball class III or IV: 9.1% vs. 8.3%, $p = 1.00$), frequency of anterior wall myocardial infarction (45.5% vs. 37.5%, $p = 0.55$), left ventricle ejection fraction (52 [39–60] vs. 55 [45–61], $p = 0.57$) or coronary revascularization (72.7% vs. 66.6%, $p = 0.66$). Extensive coronary artery disease (3-vessel disease) was similar in both groups (10.0% vs. 10.0%, $p = 1.00$).

3.1. Clinical outcomes

During the median follow-up of 4.0 (IQR: 2.4–6.5) years after the index event, 2 (6.1%) patients treated with β-blocker therapy died (1 cardiovascular death), 6 (18.2%) experienced hospital re-admission for MI and 3 (9.1%) required revascularization; in contrast, there were 5 (20.8%) deaths (3 cardiovascular deaths), 5 (20.8%) readmissions due to MI and 3 (12.5%) revascularization procedures in patients without β-blocker therapy. When these events were considered mutually exclusive, the clinical composite end-point occurred in 10 (30.3%) patients treated with β-blocker therapy and in 10 (41.7%) patients without β-blocker therapy. The 90-day survival was higher in patients treated with β-blocker therapy (87.5% vs. 100%; Log rank test $p = 0.035$) (Fig. 1).

Table 2
In-hospital mortality and clinical outcomes during follow-up.

	Without β-blocker treatment (n = 24)	With β-blocker treatment (n = 33)
In-hospital mortality	2 (8.3)	0
All-cause mortality	5 (20.8)	2 (6.1)
Cardiovascular mortality	3 (12.5)	1 (3.0)
Myocardial infarction	5 (20.8)	6 (18.2)
Revascularization	3 (12.5)	3 (9.1)
MACE	10 (41.7)	10 (30.3)

Data represent the number (%) of patients in each group; MACE was defined as the composite of mortality, re-admission for acute myocardial infarction or revascularization.

4. Discussion

This study reveals that in patients with ACS-ACC, β-blocker treatment was associated with a significantly better clinical outcome, with lower rates of death, revascularization and myocardial infarction. These findings suggest that β-blocker therapy is safe and effective in the management of patients with ACS-ACC.

The link between cocaine use and myocardial ischemia is well known and may involve catecholamine accumulation [6], thrombosis [7–9], premature atherosclerosis [10], and coronary spasm [11,12]. Physicians became alarmed about β-blocker use in patients with ACS-

Table 1
Baseline characteristics of the patients with and without β-blocker treatment.

	Overall (n = 57)	Without β-blocker treatment (n = 24)	With β-blocker treatment (n = 33)	p value
Demographics				
Age, years	44 (38–47)	43 (37–47)	45 (42–48)	0.296
Male sex	52 (91.2)	21 (87.5)	31 (93.9)	0.640
Clinical history				
Prior MI	6 (10.5)	2 (8.3)	4 (12.1)	1.000
Previous PCI	5 (8.8)	1 (4.2)	4 (10.1)	0.385
Dyslipidemia	22 (38.6)	7 (29.2)	15 (45.5)	0.212
Diabetes mellitus	6 (10.5)	2 (8.3)	4 (12.1)	1.000
Arterial hypertension	12 (21.1)	2 (8.3)	10 (30.3)	0.045
Peripheral arterial disease	2 (3.5)	1 (4.2)	1 (3.0)	1.000
Current or previous smoker	55 (96.5)	23 (95.8)	32 (96.9)	1.000
Familiar history of ischemic cardiomyopathy	13 (22.8)	4 (16.7)	9 (27.3)	0.346
Physical examination				
Killip I	44 (77.2)	18 (75.0)	26 (78.8)	0.736
Killip II	4 (7.0)	1 (4.2)	3 (9.1)	0.631
Killip III–IV	5 (8.8)	2 (8.3)	3 (9.1)	1.000
Characteristics of ACS				
STEMI	48 (84.2)	18 (75.0)	30 (90.9)	0.146
Anterior location	24 (42.1)	9 (37.5)	15 (45.5)	0.548
Troponin I, peak, ng/L	30.7 (10.3–68.3)	12.4 (4.3–45.7)	37.3 (15.9–72.0)	0.055
LVEF at discharge, %	53 (45–60)	55 (45–61)	52 (39–60)	0.571
Coronary angiography (n = 50)				
Main epicardial coronary arteries >70% stenosis				
0	6 (12.0)	6 (30.0)	0	0.002
1	31 (62.0)	10 (50.0)	21 (70.0)	0.153
2	8 (16.0)	2 (10.0)	6 (20.0)	0.450
3	5 (10.0)	2 (10.0)	3 (10.0)	1.000
Coronary revascularization	40 (70.2)	16 (66.6)	24 (72.7)	0.655

Data are presented as no. (%) or median (IQR).
MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; LEVF, left ventricular ejection fraction.

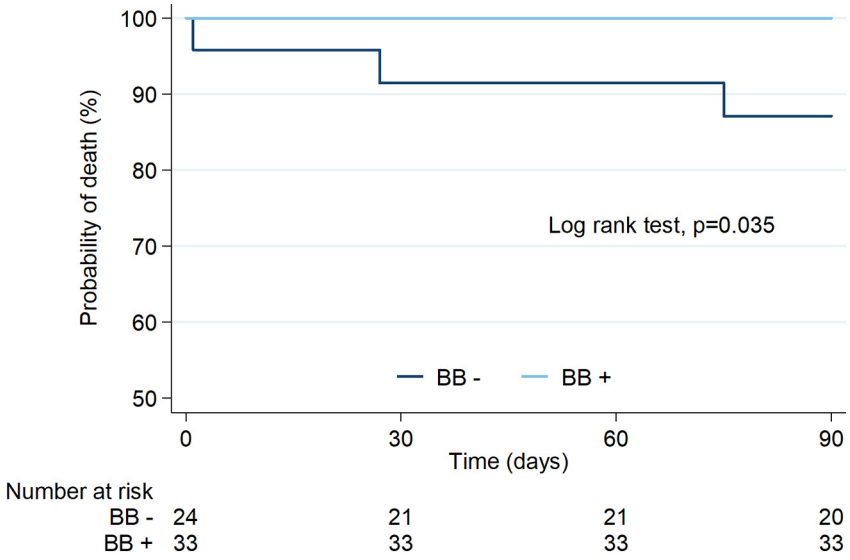

Fig. 1. Kaplan–Meier curves showing overall survival during 90 days of follow-up.

ACC in the 1980s after case reports showed that β-blockers elicited adverse events in the setting of cocaine toxicity. Since then and for over 30 years, the paradigm of "unopposed α-stimulation" endures in medical literature. In fact, clinical practice guidelines do not recommend β-blocker therapy in this population [4–13]. However, the use of β-blockers in ACS-ACC remains controversial due to a lack of prospective contemporary clinical studies evaluating its safety and/or efficacy in this clinical setting. Endorsing the controversy, a recent study has shown that in a considerable percentage of patients with ACS-ACC, β-blocker treatment is used in the in-hospital setting [14] and our study reveals that in a high percentage of patients with ACS-ACC, β-blocker use was introduced upon discretion by the physician in charge. These findings suggest that many clinicians appear to be disregarding the paradigm.

Regarding the use of β-blocker therapy in different clinical settings related to cocaine consumption, a recent systematic review found that β-blockers more reliably mitigated cocaine-induced concomitant tachycardia and hypertension than other classes of medication [15]. Several retrospective analyses examining the safety and efficacy of β-blocker use in patients with cocaine chest pain did not find any harm. Dattilo et al. [16] reported that β-blocker therapy was associated with a reduction in the incidence of MI after cocaine use. Rangel et al. [17] found that the mortality rate in chest pain patients with cocaine-positive urine tests was significantly reduced during follow-up when they were discharged with β-blocker therapy. Fanari et al. [18], found that no differences in outcomes were observed between patients treated or not treated with β-blocker therapy in the setting of cocaine-related chest pain and Espana Schmidt et al. [19] did not found any in-hospital cardiovascular complication in patients with cocaine associated chest pain who had an early dose of β-blocker.

Our data are consistent with the studies mentioned above suggesting not only that β-blocker therapy is a safe treatment option, but also, that is associated with a significantly better clinical outcome. These findings seem to have a pathobiological basis: first, the enormous adrenergic overload from acute cocaine use can desensitize cellular adrenoreceptors via uncoupling or actual receptor loss; thus, the hyperadrenergic state produced by cocaine probably decreases α-adrenergic responses [20], and second, the use of β-blockers as an essential therapy in the setting of myocardial infarction, is due to their ability to decrease myocardial work, oxygen consumption, and provide protection for myocardial muscle in times of decreased flow and increased demand [21]. Consequently, the myocardial protective benefits of β-blockers may offset cocaine-derived concerns and may provide important long-term prognostic benefits as we observe in our study. This new evidence supports routine β-blocker use in young patients with ACS-ACC, which is growing alarmingly in Western countries [22].

Our study has several limitations. This is a single center study with a limited number of patients. Due to the small sample size, it was not possible to perform a complete analysis on the impact of β-blockers on in-hospital outcomes. Different types of β-blockers were used. We were not able to distinguish precise timing of cocaine consumption. The test for the presence of cocaine metabolites in the urine is a qualitative analysis not being possible to estimate the amount of cocaine ingested by the patients.

In conclusion, the RUTI-Cocaine Study generates new evidence about the use of β-blocker therapy in patients with ACS-ACC, which is associated with a better clinical outcome. This study underscores the evidence for long-term β-blocker administration in high-risk patients with ACS-ACC, and highlights the need for large prospective multicenter studies assessing the relative benefits and risks of β-blocker treatment in this population.

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Conflict of interest

None of the authors have any disclosures relevant to the content of the manuscript.

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