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ORIGINAL ARTICLE

Effect of chronic pretreatment with beta-blockers on no-reflow phenomenon in diabetic patients with acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

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KEYWORDS

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Abstract *Background:* No-reflow is an important factor as it predicts a poor outcome in patients undergoing primary angioplasty. In comparison with patients attaining TIMI 3 flow, patients with no-reflow have an increased incidence of ventricular arrhythmias, early congestive cardiac failure, cardiac rupture and cardiac death. As such, it is of paramount importance to consider strategies to prevent the occurrence of no-reflow phenomenon. Previous evidence suggests that Beta (β) blockers have multiple favorable effects on the vascular system not directly related to their effect on blood pressure. However, there are insufficient data regarding the effects of prior Beta blocker use on coronary blood flow after primary PCI in patients with AMI.

Aim: The aim of this study was to test the hypothesis that Beta blocker treatment before admission would have beneficial effects on the development of the no-reflow phenomenon after acute myocardial infarction.

Methods and results: The study included 107 diabetic patients who had presented with acute STEMI within 12 h from the onset of chest pain. All of them have undergone primary angioplasty at Ain Shams University hospitals or National Heart institute. The incidence of no-reflow phenomenon was 21%. No-reflow phenomenon was significantly lower in patients on chronic B-blocker therapy (12% vs. 28%; $P = 0.04$). The heart rate was significantly lower in the normal reflow group than in the no-reflow group ($P = 0.03$). The study also showed that B-blocker pretreatment is an independent protective predictor for the no-reflow phenomenon (P = 0.045).

Abbreviations: TIMI, thrombolysis in myocardial infarction; ECG, electrocardiogram; CABG, coronary artery bypass grat; AMI, acute myocardial infarction; B-Blocker, beta-blocker; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation; IRA, infarct related artery; LVEF, left ventricular ejection fraction; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery

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Conclusion: Chronic pre-treatment with B-blocker in diabetic patients presenting with STEMI, is associated with lower rate of occurrence of no-reflow phenomenon after primary PCI.

1. Introduction

Primary percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI) has been used as an important therapeutic method since the last decade of the twentieth century and has gradually become the method of choice in many medical centers. Various studies have shown that primary PCI is associated with lower rates of mortality, reinfarction and cerebral hemorrhage in comparison with thrombolytic treatments.[1] Recently, attention has been shifted from epicardial artery patency to the status of the microvasculature.[2]

Previous studies have shown that 5–30% of patients treated with primary PCI fail to achieve thrombolysis in myocardial infarction (TIMI) flow grade 3 after successful re-opening of the artery without angiographic evidence of mechanical obstruction. This phenomenon is deemed as no-reflow, which determines the prognosis in patients after AMI.[3] Several mechanisms responsible for no-reflow have been identified in experimental models, including extravascular compression, microvascular vasoconstriction, and platelet/leukocyte capillary plugging.[4]

Clinically, no-reflow is important as it predicts a poorer outcome and is associated with ongoing symptoms and persistent ECG changes. In comparison with patients attaining TIMI 3 flow, patients with no-reflow have an increased incidence of ventricular arrhythmias, early congestive cardiac failure, cardiac rupture and cardiac death. As such, it is of paramount importance to consider strategies to prevent the occurrence of no-reflow phenomenon.[5,6] However, to the best of our knowledge, there are insufficient data regarding the effects of prior Beta blocker use on coronary blood flow after primary PCI in patients with AMI.

Previous evidence suggests that Beta blockers have multiple favorable effects on the vascular system not directly related to their effect on blood pressure.[7]

1.1. Aim of the study

The aim of this study was to test the hypothesis that Beta blocker treatment before admission would have beneficial effects on the development of the no-reflow phenomenon after acute myocardial infarction.

2. Patients and methods

A total of 107 diabetic patients who were presented to Ain Shams University hospital and the National Heart Institute (Cairo, Egypt) in the period from February 2015 to September 2015 with a diagnosis of STEMI, were enrolled into the study. STEMI was diagnosed with the presence of chest pain lasting for 20 min with electrocardiographic changes (new ST elevation at the J point in at least 2 contiguous leads of $\geq$2 mm [0.2 mV] in males, or $\geq$1.5 mm [0.15 mV] in females in leads V2-V3, or $\geq$1 mm [0.1 mV] in other leads or new left bundle branch block).[9]

The patients were then divided into two groups based on prior treatment with oral β blockers for at least 3 months (Group 1, who were on β blocker therapy for at least 3 months, and group 2 who did not receive any β blocker therapy). Patients with history of previous MI, angioplasty or CABG were excluded. Patients presenting with severe chronic heart failure, severe valvular heart disease, cardiogenic shock or thrombolytic therapy before angioplasty, pain to balloon time over 12 h, acute or chronic renal impairment (serum creatinine > 2 mg/dl), known major comorbidity, such as malignancy and patient refusal were the other exclusion criteria.

All patients were subjected to history taking and physical examination with special emphasis on chest pain and its duration, past history of coronary artery disease, as well as an inquiry about Beta blocker use and the indication for it. Electrocardiography to diagnose STEMI, and routine laboratory tests were done for all the patients.

This study was approved by the local ethics committee, conforming to the ethical guidelines of the 1975 Declaration of Helsinki, and written informed consents were obtained from all the participants.

On admission, the patients received 150–300 mg aspirin orally, and a loading dose of 600 mg of clopidogrel. Primary PCI was carried out immediately. All the interventions were performed through the femoral approach. Technical choices, as percutaneous transluminal coronary angioplasty (PTCA), PTCA and stenting or direct stenting, and adjunctive pharmacologic treatment, such as glycoprotein IIb/IIIa inhibitors were placed at the discretion of the attending operator consistent with the lesion characteristics.

Angiographic success was determined as residual stenosis of the treated lesion < 50% on visual estimation and in case of stenting, desired position of the stent with TIMI grade III flow. No-reflow was defined as a TIMI flow of less than three in the absence of evident vessel dissection, obstruction or distal vessel embolic cutoff.[10] Routine trans-thoracic echocardiography was done for all the patients with emphasis on ejection fraction by 2-dimensional eye-balling and any mechanical complications, within 48–72 h post-angioplasty.

2.1. Statistical analysis

Data were expressed as mean value ± SD for continuous variables, and as percentages for categoric variables. In this study, statistical significance was set at $p < 0.05$. Comparisons between continuous variables were performed using the paired t-test, unpaired t-test or Mann–Whitney U-test. For comparisons of categoric variables, frequency tables and Chi-square analyses were used. All analyses of the present study were done using the IBM® SPSS® Statistics version 21 software (see Tables 1 and 2).

Table 1 Showing the demographics and risk factors of the two groups.

Data	β-blocker (n = 50)	No β-blocker (n = 57)	P-value
Age (years ± SD)	54 ± 9.5	56 ± 8.9	0.13
Sex (male/female)	34/16	32/25	0.21
HR (bpm)	78 ± 7	88 ± 10	<0.001
SBP (mmHg)	147 ± 11	144 ± 11	0.14
DBP (mmHg)	88 ± 6	90 ± 6	0.13
Height (cm)	168 ± 6	167 ± 5	0.32
Weight (kg)	95 ± 8	92 ± 7	0.06
BMI (kg/m^2)	34 ± 3	33 ± 3	0.42
Killip Class I	33	41	0.51
Killip Class II	17	16	
Killip Class III	0	0	
Hypertension, n (%)	50(100)	25(44)	<0.001
Dyslipidemia, n (%)	10(20)	11(19)	0.93
Smoking, current and past, n (%)	22(44)	19(33)	0.26
Family history of CAD, n (%)	7(14)	8(16)	0.78
Diabetic control (diet/oral anti-diabetics/insulin)	3/36/11	3/45/9	0.69
Admission blood glucose, mg/dl	185 ± 31	195 ± 29	0.09

Table 2 Angiographic data in each group.

Angiographic data		β-blocker (n = 50)	No β-blocker (n = 57)	P-value
Pain-to-balloon inflation (hours ± SD)		5.1 ± 2	4.9 ± 1.8	0.7
No-reflow, n (%)		6(12)	16(28)	0.04
IRA	LAD	43(53)	10(53)	0.97
	LCX	12(15)	1(5)	0.26
	RCA	26(32)	8(42)	0.41

Table 3 Angiographic and Post-PCI echocardiographic characteristics of the patients stratified according to final reflow.

Angiographic and echocardiographic features	Normal reflow (n = 85)	No-reflow (n = 22)	P-value
Stent diameter (mm ± SD)	3.1 ± 0.3	3 ± 0.2	0.31
Stent length (mm ± SD)	22.1 ± 5	24.3 ± 7	0.10
LVEF (% ± SD)	49 ± 8	35 ± 5	<0.001

3. Results

Forty-five (70%) patients in the β-blocker group were using bisoprolol, while eleven (22%) were receiving atenolol, and four (8%) were taking nebivolol.

Angiographic no-reflow phenomenon occurred in 22 patients, while 85 patients had normal reflow. The incidence of the no-reflow phenomenon was significantly lower in patients on chronic β-blocker therapy (12% vs. 28%; P = 0.04). However, pain-to-balloon inflation interval was similar in both groups.

Table 3 emphasizes that the Infarct-Related Artery (IRA), the stent diameter and stent length did not affect the incidence of the no-reflow phenomenon ($P > 0.05$). However, LVEF measured Post-PCI by echocardiography was lower in patients who had no-reflow than those who had normal reflow. The difference was statistically highly significant ($P < 0.001$).

Multivariate logistic regression analyses of the association between angiographic no-reflow phenomenon and multiple parameters are listed in Table 4. Increased heart rate was significantly associated with increased incidence of no-reflow phenomenon (P = 0.009).

β-blocker pretreatment was an independent protective predictor for the occurrence of no-reflow phenomenon (P = 0.045). Other parameters, such as age, hypertension, hyperlipidemia, smoking, Killip class, pain-to-balloon inflation and IRA were statistically not significant.

4. Discussion

No-reflow phenomenon remains a serious complication of PCI in patients with acute myocardial infarction.[11,12] It is associated with short-term and long-term clinical outcomes.[13–15] Currently, there is still lack of targeted therapy to reverse the no-reflow phenomenon. Therefore, prediction and prevention, rather than treatment of no-reflow, are likely to have an important impact on the outcome of primary PCI. No-reflow is associated with an adverse outcome and higher mortality

Table 4 Independent predictive factors for no-reflow phenomenon.

Parameters	Odds ratio	95% CI	P-value
Age	1.39	0.22–8.85	0.729
Heart rate	1.10	1.02–1.19	0.009
Hypertension	0.59	0.16–2.2	0.428
Hyperlipidemia	2.19	0.46–10.30	0.323
Smoking	0.39	0.10–1.446	0.161
Killip class I/II/III	2.26	0.46–10.97	0.313
Pain-to-balloon inflation	1.26	0.37–4.30	0.708
IRA	2.35	0.62–8.87	0.209
β-blocker pretreatment	0.10	0.01–0.94	0.045

in patients with ST-segment elevation acute myocardial infarction whose PCI is considered a dynamic process characterized by multiple patho-genetic components.[16]

The main mechanisms of the beneficial effects of β-blockers in patients with STEMI are decreasing blood pressure, decreasing cardiac work and oxygen demand, and attenuation of the deleterious effects of the dysregulated Renin Angiotensin Aldosterone System (RAAS).[14,17–19] Our study showed that no-reflow phenomenon was significantly lower in patients on chronic β-blocker therapy (12% vs. 28%; $P = 0.04$), and this difference was still present after multivariate regression analysis, showing that β-blocker pretreatment is an independent protective predictor against no-reflow phenomenon (P = 0.045). Wang and colleagues [20] evaluated the impact of prior long term β-blocker use before STEMI on the no-reflow phenomenon in 1615 patients after primary PCI. They found that the occurrence of no-reflow was significantly lower in the β-blocker group than in the non-β blocker group [13.6% (35/257) vs. 21.2% (289/1358), P = 0.017]. They also found that β-blocker use was a protective predictor of no-reflow (OR = 0.594, 95% CI: 0.394–0.893, P = 0.012). In concordance with the results of the Wang et al. study,[20] we found that the incidence of no-reflow phenomenon was significantly lower in the β-blocker group, 12% (6/50), than in those not receiving β blocker group 28% (16/57), P = 0.04. Similarly, our results revealed that pre-PCI β-blocker usage is a protective predictor of the no-reflow phenomenon (OR = 0.35, 95% CI: 0.12–0.98, P = 0.045).

The incidence of no-reflow phenomenon in the Wang et al.'s study[20] was 20%. Similarly, incidence of no-reflow phenomenon in our study was 21%. The reason behind the high occurrence of no-reflow in our patients might be the fact that all of our patients were diabetics, possibly with preexisting microvascular dysfunction, exacerbating the degree of microvascular obstruction that develops after infarct-related PCI, explaining the association of diabetes mellitus with dyslipidemia and no-reflow.[21] Wang et al. found that aging and Killip class are significant risk factors for the development of the no-reflow phenomenon post-PCI,[20] while our study, similar to other studies,[22,23] showed that age and Killip class were not significant factors in the development of no-reflow post PCI.

However, Wang et al.'s study[20] was a retrospective study while ours was prospective. Another point of difference was that they took non-diabetic patients, while we took only diabetics. To the best of our knowledge no any other published study had the same scope of our study.[20] However, other studies were trying to find the impact of chronic pretreatment with other drugs on the occurrence of no-reflow phenomenon post-PCI, like angiotensin-converting enzyme inhibitor and angiotensin receptor blockers.[23,24]

Zhao and colleagues [24] in a prospective study, evaluated the effect of chronic pretreatment with ACE inhibitors on no-reflow phenomenon, although the subgroup of patients who were on β-blocker pretreatment had less no-reflow in the study, the difference was statistically non-significant. They also found that heart rate on admission was not significantly associated with no-reflow phenomenon ($P = 0.24$). Similarly, Hu et al. [23] in a prospective study, evaluated the impact of chronic pretreatment of angiotensin receptor blocker on the occurrence of no-reflow. Again patients on β-blocker treatment had less no-reflow in the study, but the difference was not significant. These results were discordant to our study findings. The reason may be due to sampling differences, but also may simply signify the better effect of β-blocker pretreatment in diabetic patients.

The current study showed that the heart rate was significantly lower in the normal reflow group than in the no-reflow group ($P = 0.03$) and multivariate regression analysis showed that increasing heart rate is a highly significant predictor of no-reflow phenomenon. These are in agreement with the findings of a study undertaken by Iwakura and colleagues [25] which showed that the heart rate was significantly lower in the normal reflow group than in the no-reflow group ($P = 0.01$).

5. Conclusion

From the current study it can be concluded that chronic pretreatment with β-blocker in diabetic patients presenting with STEMI, is associated with lower rate of occurrence of no-reflow phenomenon after primary PCI. Thus, whenever there is an indication for β-blocker use, Diabetes Mellitus should not constitute a contraindication per se, as these patients may gain short- and long-term benefits. Secondly large-scale randomized controlled trials are needed to evaluate the role of chronic β-blocker pre-treatment on no-reflow phenomenon in diabetic patients, with follow-up for longer periods. Further studies are needed to find whether heart rate independently affects no-reflow phenomenon.

The authors do not have any potential conflicts of interest pertaining to this study. This study was approved by the local ethics committee; conforming to the ethical guidelines of the 1975 Declaration of Helsinki, and written informed consents were obtained from all the participants.

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