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Original Article

Correlation between Post-Percutaneous Coronary Intervention CKMB Elevation and One-Year Major Adverse Cardiac and Cerebrovascular Events

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ABSTRACT

Background: CKMB elevation after percutaneous coronary intervention (PCI) correlates with major adverse cardiac and cerebrovascular events (MACCE). There is, however, some controversy over this issue, with some studies having reported different conclusions. We assessed the correlation between the CKMB level after PCI and one-year MACCE incidence in these patients.

Methods: We measured the CKMB level before and after PCI in 221 patients with normal baseline CKMB who underwent PCI at Ekbatan University Hospital, Hamedan, Iran, between April 2013 and October 2013, and divided them into 4 groups based on the post-PCI CKMB level. Then, we evaluated one-year MACCE incidence.

Results: CKMB elevation was detected in 81 (37.6%) patients and MACCE occurred in 11 (5%) patients. CKMB elevation after PCI was correlated to MACCE. The predictors of CKMB elevation were hyperlipidemia, number of deployed stents, stent diameter ≥4 mm, and complicated PCI.

Conclusions: CKMB elevation after PCI was detected in 37.6% of the study population and was common in the setting of hyperlipidemia, more than 1 stent deployment, stent diameter ≥4 mm, and complicated PCI. MACCE at 1 year occurred in 5% of the patients and was correlated with the post-PCI CKMB level ≥3 times of normal, history of diabetes mellitus, history of hypertension, and inappropriate use of clopidogrel. ***(Iranian Heart Journal 2015; 16(4): 41-46)***

Keywords ■Percutaneous coronary intervention ■ CKMB ■ Major adverse cardiac and cerebrovascular events

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Periprocedural myocardial infarction (MI) is a common complication of percutaneous coronary intervention (PCI) and is defined as CKMB elevation after PCI.[1] Previously, 2 definitions were given for periprocedural MI. The WHO has defined postprocedural MI as a CK level >2 times the normal value with CKMB isoform elevation after PCI. The FDA has defined postprocedural MI as the CKMB level >3 times the normal value after PCI.

Depending on local practices and criteria used, 5-30% of patients who undergo PCI have evidence of periprocedural MI. However, the clinical significance of these events and their management remain a matter of considerable controversy and uncertainty.[2,3] Consequently, numerous publications have demonstrated that CK and CKMB elevations have prognostic implications, even in the absence of pathological Q waves. The cutoff values of CK and/or CKMB used to define periprocedural MI in these studies varied widely. Numerous investigators have used the cutoff value of 3 times the upper limit of normal (ULN) of CK or CKMB (3×ULN) as the defining threshold of periprocedural MI, although it has been traditional to report > 1×ULN, >5×ULN, and occasionally >8× ULN values as well.[3]

The current PCI guidelines give a class I recommendation for the measurement of cardiac biomarkers (the MB fraction of creatine kinase [CK-MB], cardiac troponin, or both) in patients who have signs or symptoms suggestive of MI during or after PCI, and for those who have undergone complicated procedures.[2,4] In addition, a class IIa recommendation is given for the routine measurement of cardiac biomarkers, 8 to 12 hours after the procedure. In either case, a new CKMB or troponin I or T rise >5 times ULN would constitute a clinically significant periprocedural MI.[1,2,3,4]

Mechanisms corresponding to cardiac events and poor prognoses in these patients are microreentry leading to ventricular arrhythmia, decreased collateral flow, and microvascular dysfunction.[2,3,5] Major adverse cardiac and cerebrovascular events (MACCE) include cardiac mortality, non-fatal MI, target vessel revascularization (TVR), and cerebrovascular accident. The mechanisms of cardiac enzyme elevation after PCI are plaque debris embolization to the distal parts of the vascular field, side branch occlusion, stent thrombosis, vasoactive peptide release, and platelet activation.[3]

METHODS

This longitudinal, prospective study was done at Ekbatan University Hospital, Hamedan, Iran. All patients who underwent PCI between April 2013 and October 2013 were considered. Patients with abnormal baseline CKMB levels (checked a day before the procedure) were excluded from the study. The total number of the patients entered in this study was 221. These patients underwent PCI and had a normal preprocedural CKMB level. The patients were followed up over a 12-month period after the procedure for MACCE occurrence with routine visits. The patients who had problems or hospital admissions during this period were visited again. The primary data collected from the patients included age; gender; history of hypertension; history of diabetes mellitus; history of hyperlipidemia; current smoking; preprocedural left ventricular ejection fraction; size, number, and type of deployed stents; target vessel; number of diseased vessels; postprocedural CKMB level; and PCI complications (i.e., side branch occlusion, slow flow, no reflow, coronary dissection, and plaque shift).

After the procedure, blood samples were drawn and electrocardiograms (ECGs) were recorded twice: once on the same day and

thereafter on the next day. If there were no complications or symptoms and no significant CKMB elevation or ECG changes, the patients were discharged a day after the procedure. The patients were divided into 4 groups based on the maximum level of postprocedural CKMB: normal level, 1-3×ULN, 3-5×ULN, and >5×ULN. The types of the stents deployed were the drug-eluting stent (DES) and the bare-metal stent (BMS) based on the operator's decision and the current guidelines. The length and diameter of the deployed stents were classified as stent length more or less than 20 mm, stent diameter <3 mm, 3-4 mm, and >4 mm. The patients were divided into 2 groups based on their left ventricular ejection fraction: more or less than 40%. All the patients were given ASA (325 mg), clopidogrel (600 mg), and atorvastatin (40 mg) before the procedure, and these medications were prescribed after the procedure as routine.

Statistical Analysis

The Pearson chi-square test and the Fisher exact test were carried out to compare the nominal variables between the subgroups. Statistical significance was defined at the level of 0.05 or less. The Kaplan–Meier methods were applied to estimate survival curve. All the analyses were performed using SPSS, version number 20.

RESULTS

From the 221 patients, 68.3% were male and 31.7% were female, and the mean age was 59.6 years. The prevalence of diabetes mellitus, hypertension, hyperlipidemia, and cigarette smoking was 20.4%, 43%, 29.4%, and 30.3%, respectively. From these 221 patients, 36.7% had elevated CKMB levels after PCI (Table 1). In addition, 76.9% of the study population had single-vessel disease (SVD), 17.6% 2-vessel disease (2VD), and 5.4% 3-vessel disease (3VD). Target vessels were the left anterior descending (LAD) in 58.8%, right coronary artery (RCA) in 25.8%, left circumflex (LCX) in 16.7%, obtuse marginal (OM) in 9.5%, and diagonal in 3.2%. The incidence of complicated PCI was 7.2%, and the CKMB level in this group was higher than that in the non-complicated group.

Table 1. Classification of the postprocedural CKMB level

CKMB Level	Frequency	Percentage	Cumulative Percentage
Normal	63.5	63.3	140
1-3 times of normal	96.4	33.0	73
3-5 times of normal	99.5	3.2	7
>5 times of normal	100	0.5	1
Total		100	221

MACCE occurred in 11 (5%) patients during the 12-month follow-up. Cardiac death occurred in 1.3%, non-fatal MI in 2.3%, TVR in 0.9%, and cerebrovascular accident in 0.9%. During this follow-up period, 95% of the patients used aspirin, 89% clopidogrel, and 93% atorvastatin correctly. There was no in-hospital mortality. Our data analysis showed a correlation between 1-year MACCE and post-PCI CKMB >3×ULN (P=0.01). Also, MACCE was correlated with the incorrect use of clopidogrel (P=0.001), hypertension (P=0.008), and diabetes mellitus (P=0.03) (Table 2). There was no correlation between MACCE and the other factors such as age, gender, target vessel, type of stents, number of stents, length of stents, diameter of stents, number of diseased vessels, incorrect use of aspirin or atorvastatin, and preprocedural ejection fraction. Also, there was no correlation between MACCE and complicated PCI directly, but CKMB elevation was more common in the complicated PCI group.

Estimated MACCE-free survival rate of 12 months, using the Kaplan–Meier method, was 95%.

Based on our data collected from this study, elevated post-PCI CKMB levels had correlations with complicated PCI (P<0.0001), stent diameter ≥4 mm (P=0.002),

and hyperlipidemia (P=0.04), whereas there were no correlations with the other factors such as age, gender, target vessel, type of stents, number of stents, length of stents, number of diseased vessels, and preprocedural ejection fraction.

Table 2. Baseline characteristics and their correlations with 1-year major adverse cardiac and cerebrovascular events (MACCE)

Characteristics		Total Number	MACCE (%)	P Value
Gender	Male	151	7 (4.6%)	0.7
	Female	70	4 (5.7%)	
Diabetes mellitus	yes	45	5 (11.1%)	0.03
	no	176	6 (3.4%)	
Hypertension	yes	95	9 (9.5%)	0.008
	no	126	2 (1.6%)	
Smoking	yes	67	5 (7.5%)	0.2
	no	154	6 (3.9%)	
Hyperlipidemia	yes	65	4 (6.2%)	0.6
	no	156	7 (4.5%)	
CKMB level	<3 normal	213	9 (4.2%)	0.01
	≥3 normal	8	2 (25%)	
Clopidogrel correct usage	yes	197	6 (3%)	0.001
	no	24	5 (20%)	
Atorvastatin correct usage	yes	207	9 (4.3%)	0.09
	no	14	2 (14.3%)	
ASA correct usage	yes	210	11 (5.2%)	0.4
	no	11	0 (0%)	
In-lab complications	yes	16	1 (6.2%)	0.8
	no	205	10 (4.9%)	
Ejection fraction	≥40%	155	9 (5.8%)	0.2
	<40%	19	0 (0%)	
Stent type	Drug	125	6 (4.8%)	0.8
	Bare	106	5 (5.7%)	
Number of vessel disease	1VD	170	6 (3.5%)	0.1
	2VD	39	4 (10.3%)	
	3VD	12	1 (8.3%)	
Number of stents	1	168	8 (4.8%)	0.8
	2	42	2 (4.8%)	
	≥3	11	1 (9.1%)	
Stent length	>20 mm	139	9 (6.5%)	0.1
	≤20	82	2 (2.4%)	
Stent diameter	≤4 mm	24	1 (4.2%)	0.8
	3-3.5 mm	137	8 (5.8%)	0.4

DISCUSSION

In patients with ischemic heart disease, a slight elevation in cardiac biomarkers is frequently detected after percutaneous coronary revascularization, but their clinical significance is still uncertain.[2,3,6] CKMB isoenzyme can be released from myocardial necrosis or severe ischemia. Patients with acute coronary syndromes are more likely to develop periprocedural MI. However, studies examining the incidence of periprocedural MI in this patient population have been limited by certain methodological difficulties. First, it is difficult and more controversial to define periprocedural MI when patients present with elevated markers prior to PCI. Therefore, most of the studies on this topic have excluded these patients from their analysis.[6]

Periprocedural MI is a common complication of PCI and is defined as CKMB elevation. Depending on local practices and criteria used, periprocedural MI was seen in 5-30% of the patients who underwent PCI.[1]

Although there is much controversy surrounding the definition and prevalence of periprocedural MI with everyday PCI, there is no dispute that significant periprocedural MI is associated with an increased mortality risk. There remains controversy about the pathophysiological mechanisms underlying

this association as well as the definition and the size of periprocedural MI that would confer such increased risk. However, there is convincing evidence that any periprocedural MI is associated with some degree of increased risk of death, particularly with longer follow-up.[3]

The risk of periprocedural MI is significantly increased in patients with evidence of more severe atherosclerotic disease. Multivessel and/or more diffuse coronary artery disease is associated with an approximately 50% increase in the relative risk of developing periprocedural MI.[3]

The predictors of periprocedural MI can be broadly categorized as patient-, lesion-, and procedure-related risk factors. The major risk factors, in terms of both frequency and potency, are complex lesions (e.g., the presence of thrombus, stenosis of a saphenous vein graft, or lesion type), complex procedures (e.g., treatment of multiple lesions or use of rotational atherectomy), and associated complications (e.g., abrupt vessel closure, side branch occlusion, distal embolization, or no reflow). Findings suggest that factors other than the burden of plaque microembolization influence the likelihood of periprocedural MI such as the release of vasoactive factors from the atherosclerotic plaque, platelet activation, and preexisting vulnerability of the myocardium.[2] The present prospective study showed that in the patients with a normal baseline serum CKMB level, minor elevation (<3 times) occurred in 33% of the patients after PCI, but this minor elevation was not associated with MACCE during a 12-month follow-up. On the other hand, 3.7% of the patients had CKMB elevation >3 times, which was correlated with a higher rate of MACCE and reduced event-free survival at 12 months. Numerous investigators have used the cutoff value =3× ULN of CK or CKMB as the defining threshold of periprocedural MI, although it has been traditional to report >1× ULN, >5× ULN, and occasionally >8×ULN values as well.[3] Kavallini et al.[7] showed a linear association between the 2-year mortality rate and the CKMB level, but Kjellvikenes et al.[8] showed that CKMB mass value ≥3 times after elective angioplasty was able to predict reduced long-term event-free survival. However, in another study, Azarnik et al.[9] showed that the mid-term survival of patients with CKMB and/or troponin elevation after PCI was similar to that in individuals with normal enzymes and that stable patients with low-to-medium CKMB and troponin elevation were routinely discharged 2 days after intervention without apparent short-term adverse events.

A contemporary analysis on the prognostic significance of periprocedural MI in patients from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial suggested that periprocedural MI was a marker of baseline risk, atherosclerosis burden, and procedural complexity but in most cases, it did not appear to have an independent prognostic significance.[10] In our study, the most powerful predicting factors for MACCE occurrence after PCI were hypertension, incorrect use of clopidogrel, CKMB elevation >3 times, and history of diabetes mellitus. This suggests that the modification of coronary risk factors and correct use of medications such as clopidogrel can reduce MACCE after PCI.

Large periprocedural MIs are usually due to angiographically visible complications; however, this is generally not the case in the vast majority of patients with elevated biomarker levels after PCI. In this study, we also showed the risk factors of post-PCI CKMB elevation. The most powerful risk factors were the occurrence of in-lab complications, number of stents, stent diameter ≥4 mm, and history of hyperlipidemia, respectively. In some studies, risk factors which correlate to CKMB elevation were the occurrence of in-lab complications, multi-vessel intervention, low baseline ejection fraction, peripheral vascular disease, and use of glycoprotein IIb/IIIa inhibitors during intervention.[2,11,12,13]

CONCLUSIONS

CKMB elevation after PCI, which is the definition of periprocedural MI, was detected in 37.6% of the patients and was common in the patients with hyperlipidemia, deployment of more than 1 stent, stent diameter ≥4 mm, and complicated PCI. MACCE at 1 year occurred in 5% of the patients and correlated with the post-PCI CKMB level ≥3×UNL, history of diabetes mellitus or hypertension, and incorrect use of clopidogrel in the 12-month follow-up duration.

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