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Impact of Postoperative Elevation of Creatine Kinase-MB on in-Hospital and Long-term Outcome in Patients Undergoing Drug-Eluting Stent Implantation

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Abstract

Background: The assessment of potential benefits and harms of a medical procedure is essential for both physicians and patients to make an informed choice among treatment options. There is a paucity of studies on the role of creatine kinase-MB (CKMB) in the prediction of patient outcome after elective percutaneous intervention

Objectives: The current study aimed to assess the association of CKMB level with demographic characteristics and major adverse cardiac events (MACES) after percutaneous coronary intervention (PCI) with drug-eluting stent implantation.

Methods: The study was conducted based on the data concerning the consecutive patients hospitalized for PCI and followed for 12 months. We examined the association between CKMB levels at 12 h post-PCI in patients with drug-eluting stent implantation and demographic characteristics. MACEs were defined as death, myocardial infarction, the need for re-revascularization in the first 48 h after the procedure and during a 1-year follow-up in 2898 patients who underwent PCI in Tehran Heart Center within 2015-2016.

Results: In multivariate logistic regression, after adjustment for differences, no relationship was observed between CKMB level at 12 h post-PCI and 12-month MACEs; nonetheless, in-hospital MACEs were higher in patients who had CKMB> 3 times the upper limit of normal. Furthermore, thrombus, angulated segment, and coronary perforation during the procedure were more prevalent in patients with higher CKMB levels.

Conclusion: The obtained results demonstrated that in patients with elective drug-eluting stent implantation, the moderate elevation of post-procedural CKMB>3 times was associated with in-hospital MACEs. Moreover, no association was found between 1-year adverse events and >3 times the elevation of CKMB.

Keywords: CKMB, Drug-eluting stent, MACE, Percutaneous coronary intervention

1. Background

Percutaneous coronary intervention (PCI) has been extensively used for the treatment of coronary lesions. In comparison with medical therapy, PCI reduces mortality rate and recurrent ischemia and brings incremental benefits to the quality of life among patients with coronary artery disease (CAD). Nonetheless, the assessment of potential benefits and harms is essential for physicians and patients to make an informed choice among treatment options (1). There are numerous reports on clinical and angiographic parameters to assess the risk of major adverse cardiovascular events (MACEs) in various investigations about PCI (2).

Cardiothoracic surgeons are of the belief that creatine kinase-MB (CKMB) can be used for the diagnosis of permanent myocardial injury after cardiac surgery (3), and CKMB>20 UNL is a strong predictor of postoperative mortality (4). Although resisted by some cardiology interventionists, it became evident that even small degrees of CKMB elevation after PCI is associated with a higher risk of death. This association is even stronger if the CKMB is elevated one to threefold upper the limit of normal.

In light of emerging evidence on the modification of this risk by treatment (particularly if it is confirmed), monitoring the CK-MB level should be considered mandatory (5). The risk of death after CK-MB elevation appears to depend on at least four factors: the amount of CKMB elevation, left ventricular function, completeness of revascularization, and the use of statin.

2. Objectives

There is a paucity of studies on the role of CKMB in the prediction of patient outcome after the elective percutaneous intervention. Nowadays, with improvement in PCI techniques and a new generation of the drug-eluting stent, there is uncertainty about the role of increased CKMB. With this background in mind, the present study aimed to reevaluate the power of CKMB in the prediction of in-hospital and 1-year adverse events in patients undergoing elective percutaneous intervention.

3. Methods

3.1. Study population

This cross-sectional study was conducted on 3059

male and female patients aged 18-80 years old undergoing elective PCI with drug-eluting stent implantation within 21st January 2016-20th January 2017. The data were retrieved from the patients' files. The investigation was approved by the Institutional Review Board of our university. All the patients admitted to Shahid Rajaee hospital (Tehran) for elective PCI were included in the study. The exclusion criteria were as follows: 1) the history of the recent acute coronary syndrome (including myocardial infarction or unstable angina in past 3 weeks), 2) left ventricular ejection fraction (LVEF) <35%, 3) creatinine level>1.5mg/dl, and 4) any muscle dystrophy or Parkinson disease. On admission, CKMB was measured for all patients and only patients with a normal range of CKMB were included. After PCI, patients were transferred to the ward, and 2 cc blood sample was taken for CKMB analysis after 12 h. Definitions of the CKMB level of patients were checked via the International Federation of Clinical Chemistry (IFCC) method, Pars Azmoon Kits.

The exclusion criteria entailed: myocardial infarction during one week before the procedure, all the primary PCI cases, the patients with CKMB levels higher than normal before the procedure, and losing 12-month follow-up, and lack of recorded data of CKMB count in the Laboratory Registry. A number of 161 (5.3%) patients were excluded since they did not complete a 12-month follow-up. All patients were premedicated with 325 mg aspirin, followed with the same dose for 1 month tapering to 80 mg daily for lifelong. Moreover, 600 mg clopidogrel was administered prior to the procedure and followed for at least 6-12 months based on patients' characteristics. Intravenous heparin bolus (10,000 U) was also administered after sheath insertion.

The patients were contacted 1, 6, and 12 months after their procedure and yearly thereafter. Follow-up information was obtained by direct clinical review of patients, telephone interviews, hospital medical records, and the referring system. Patients were not subjected to further coronary angiography unless clinically indicated. MACES were defined as the presence of cardiac death, non-fatal myocardial infarction (MI), or target vessel revascularization (TVR), and the need for Coronary artery bypass grafting (CABG) during the follow-up period. Hypertension was defined as systolic blood pressure>140 and/or diastolic blood pressure>90 at the office or taking anti-hypertension drugs (6). hyperlipidemia was characterized as an LDL level higher than 160 mg/dl or taking proper medication (7). In addition, coronary artery lesion complexity was identified according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (8).

3.2. Statistical analysis

All the statistical analysis was carried out in Statistical Package for Social Sciences (version 15) (SPSS Inc., Chicago, Illinois, USA). Frequencies were expressed as number or percentages, and continuous variables were represented as mean±standard deviation (SD). The 2 by 2 contingency table in the chi-square (x2) test was used to analyze the frequencies. A p-value less than 0.05 was considered statistically significant. Moreover, different levels of CKMB were compared using the CKMB values between normal and higher than normal.

4. Results

This cross-sectional study was conducted on 3059 patients who underwent PCI with drug-eluting stent implantation. A number of 2898 (94.7%) patients completed a 12-month follow-up and were included in the final analysis. The study population included 2174 (71%) males. After the procedure, 11.1% of the patients had elevated CKMB. Baes on the results, CKMB was normal in 2577 (88.9%) patients, it was within 1-3 times the upper limit of normal in 302(10.4%) patients, and it was higher than 3 folds upper normal range in 19 patients (0.7%).

Although CKMB levels were higher in older ages (normal or 1-3 folds higher than normal in patients aged 51-60 years and higher than 3 folds in cases within the age range of 61-70 years), this correlation was not statistically significant. In addition, no association was observed between gender and CKMB level (P=0.686). According to smoking status, 651 (21.4%) patients were current smokers, 1741 (56.9%) subjects had never smoked, and 648 (21.2%) cases were former smokers. Moreover, it is worth noting that 701 (23%) patients had diabetes mellitus, 1254 (41.2%) cases had hypertension, 1640 (53.9%) subjects had hyperlipidemia, and 784 (26%) patients had a positive family history of coronary artery disease.

The current study evaluated the association of CKMB level with age, gender, and CAD risk factors (e.g., diabetes mellitus, hypertension, hyperlipidemia, smoking, and familial history of CAD). In this regard, the obtained results showed no association between the aforementioned factors and elevated CKMB after the procedure (All p-values>0.05; Table 1). Table 2 displays the association between the complexity of lesion and CKMB levels. It also shows the relationship between coronary artery lesion type during PCI and CKMB levels.

The obtained results demonstrated a significant association between in-hospital MACE and post-PCI CKMB. Patients with CKMB 1-3 times the upper limit of normal had 10 times more in-hospital MACEs, compared to those with normal CKMB (P=0.002). Moreover, when CKMB increased to more than 3 times the upper limit of normal, in-hospital MACE increased to 10% (P=0.001; Table 3). Furthermore, PCI of severely angulated segments, thrombus

Table1. Association between Creatine kinase-MB and coronary artery disease risk factors

Variable	N=2898	Normal CKMB N=2577	CKMB 1-3 times higher N=302	CKMB >3 times higher N=19	P-value
Age (years) n%	≤40 41-50 51-60 61-70 >70 P-value	178 (6.9) 598 (23.2) 853 (33.1) 685 (26.6) 263 (10.2)	12 (4.0) 73 (23.5) 96 (31.8) 85 (28.1) 36 (11.6)	1 (0.5) 4 (21.1) 5 (26.3) 6 (31.6) 3 (16)	0.725
Gender (male) n%		1935 (89.0)	224 (10.33)	15 (0.66)	0.686
CAD risk factors					
Smoking n%	Current N=651 No N=1741 Quitted N=648	584 (89.8) 1550 (89) 569 (87.8)	61 (9.4) 179 (10.3) 76 (11.7)	6 (0.8) 12 (0.7) 3 (0.5)	0.681
Diabetes mellitus n%					
Yes	701	624 (89)	71 (10.2)	6 (0.8)	0.919
No	2345	2085 (88.9)	264 (10.5)	14 (0.6)	
Hypertension n%					
Yes	1254	1122 (89.5)	124 (9.9)	8 (0.6)	0.728
No	1791	1587(88.6)	191(10.7)	13(0.7)	
Hyperlipidemia n%					
Yes	1640	1465(89.3)	162 (9.9)	13 (0.8)	0.447
No	1405	1243(88.5)	154(11)	8(0.5)	
Family history n%					
Yes	784	693 (88.4)	85 (10.9)	6 (0.7)	0.913
No	2261	2012(89)	233(10.3)	16(0.7)	

Table 2. Lesion type according to the American College of Cardiology/American Heart Association Guideline and Creatine kinase-MB level

American College of Cardiology/American Heart Association typing	Normal CKMB	High CKMB	P-value
Non-complex lesion (A+B1) n%	648 (25)	67(21)	0.092
Complex lesion (B2+C) n%	1911(75)	252(79)	

Table3. Association of Creatine kinase-MB level with in-hospital major adverse cardiac events and 1-year adverse events

Value	1-3 folds higher n% N=321	Normal CKMB n% N=2577	Relative risk	95% CI	P-value
In-hospital MACE	5(1)	3(0.1)	5.6425	3.2666 to 9.7466	< 0.0001
One year MACE*	19(5.9)	145(5.6)	1.0488	0.6782 to 1.6220	0.8303
Cardiac death	2(0.7)	15(0.6)	1.0625	0.2878 to 3.9220	0.9275
Non-fatal MI	7(2)	49(1.9)	1.1314	0.5614 to 2.2801	0.7299
TVR	7(2.5)	62(2.6)	0.914	0.4494 to 1.8590	0.8040
CABG	3(1.1)	19(0.8)	1.2333	0.4287 to 3.5480	0.6973

*1-year MACE consisted of cardiac death, non-fatal myocardial infarction, target vessel revascularization, and coronary artery bypass grafting.

formation during the procedure, and coronary artery perforation were significantly associated with CKMB elevation (Table 4).

5. Discussion

As evidenced by the results of the present study, after successful stent implantation in native coronary arteries, the majority of patients (88.9%) had normal CKMB levels 24 h after the intervention. It was found that while the severe elevation of CKMB (>1-3 times the upper limit of normal) predicts unfavorable in-hospital outcome, it could not predict long term mortality and outcome. According to previous studies, the minor elevation of CKMB concentration is reported in 11.5–26% of patients undergoing successful coronary intervention. Some discrepancy surrounds the effect of CKMB elevation on patient long term outcome (9).

Kong et al. followed up 253 patients with total CK and CKMB fraction elevation after PTCA and 120 control patients. They found that late cardiac mortality was increased with CKMB elevation (P=0.02) (10). Ioannidis et al. performed a meta-analysis including 23,230 subjects to clarify the clinical significance of small CKMB elevation after PCI. They reported that any increase in CKMB after PCI was associated with an increased risk of death during follow-up (11).

In the same direction, Kini et al. studied 2873 patients with elective PCI. Consistent with the results of the current study, the mentioned study showed

Table 4. Lesion type and post-procedural Creatine kinase-MB levels

Lesion characteristics	Normal CKMB	High CKMB	P-value
Ostial	86(3.3)	10(3.1)	0.720
Proximal	1388(53.9)	184(57.6)	0.779
Tubular	1238(48)	150(47)	0.960
Diffuse	1071(41.5)	146(45.7)	0.328
Calcified	99(3.8)	13(4)	0.679
Bifurcation	84(3.2)	17(5.2)	0.172
Eccentric	665(26)	105(33)	0.130
Severe tortuosity	182(7)	20(6)	0.464
Severe angulation	51(2)	32(10)	0.046
Thrombus	61(2.4)	16(5)	0.009
Totally occulted lesion	216(8.4)	25(7.8)	0.848
Abrupt closure	2(0.08)	0 (0.0)	0.883
Side branch	85(3.2)	11(3.4)	0.247
Dissection	12(0.5)	2(0.5)	0.909
Coronary perforation	1(0.04)	1(0.3)	0.001
Ulceration	84(3.2)	11(3.4)	0.810
Aneurysmal	100(3.8)	12(3.7)	0.494

that CKMB>3 times normal had a significant association with in-hospital mortality. CKMB>5 times normal could predict 1-year mortality. CKMB>5 times the upper limit of the normal subgroup was not assessed in the present study. Nonetheless, similar to this study, our results demonstrated that CKMB>3 times the upper limit of normal was not associated with 1-year adverse events (12).

In a similar vein, Ellis et al. studied 8409 non-acute myocardial infarction patients who underwent PCI. 38+/-25 months follow-up indicated that only CKMB 5-times upper limit of normal was correlated with death, and the risk of death was higher in the first 3-4 months (13). Stone et. who studied 7148 patients undergoing elective coronary angiography showed that CKMB level >8 times the upper limit of normal had a significant association with post-procedural 2-year mortality. The observed 2-year mortality rate in this study was reported as 16.3% (hazard ratio, 2.2; P<0.0001) (14).

Contrary to our findings, Abdelmeguid et al. suggested that even minor elevation in post-PCI CKMB had a significant correlation with 3-year mortality. The mentioned study included 4484 patients with successful PCI (15). In agreement with the results of the present study, Kugelmass et al. who studied 565 patients showed that minor CKMB elevation after PCI was detected in 11.5% of patients and did not have any association with long term adverse outcome. Only 2.3% of patients showed a significant increase in CKMB; nonetheless, even this increase was not significantly correlated with long term adverse events (P=0.08) (16).

Furthermore, the results of the present study found a significant correlation between CKMB>3 times normal and in-hospital mortality. Contrary to our study, Ellis et al. showed that in patients with CKMB 1-5 times the upper limit of normal, the risk of death in the first week after the intervention was very low increasing during the next 4 months with increasing CKMB level (13).

6. Conclusion

The results of the present study indicated that in patients with elective drug-eluting stent implantation, the moderate elevation of post-procedural CKMB>3 times was associated with in-hospital MACE. Moreover, no association was found between 1-year adverse events and >3 times elevation of CKMB.

Footnotes

Authors' Contribution: Study concept and design: Ebrahim Nematipour, Behzad Rahimi; analysis and interpretation of data: Reza Hajizadeh; critical revision of the manuscript for important intellectual content: Hamidreza Poorhossein; administrative, technical, and material support: Behzad Rahimi and Reza Hajizadeh.

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Informed Consent: Questionnaires and data were collected after obtaining written consent from patients and in accordance with the provisions of the Helsinki Declaration.

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