INCIDENCE AND OUTCOMES OF PATIENTS WITH PERI-PROCEDURAL CREATINE KINASE (CK-MB) ELEVATION

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ABSTRACT:

Aims: *Peri-procedural myocardial infarction (MI) is not an uncommon complication of percutaneous coronary intervention (PCI). We investigated the incidence and clinical outcomes of patients with peri-procedural creatine kinase elevation over one year followup.*

Methods: *We prospectively evaluated the consecutive patients undergoing PCI either with acute coronary syndrome (ACS) or chronic stable angina (CSA) as presentation in our unit from July 2014 to December 2015. The term enzymatic infarct (EI) is used to include all patients with peri-procedural CK-MB elevation more than upper limit of normal (ULN). These patients are divided into three categories based on level of enzyme elevation and type of presentation. Type A includes those with CK-MB between 1 to 3 times the ULN, type B includes true peri-procedural MI that means CK-MB >3 times ULN, type C includes patients with baseline CK-MB elevation due to acute MI. We used the PMI definition from the third universal definition of MI: creatine kinase (CK-MB)>3 times upper limit of normal. We followed them up to one year for the major adverse cardiovascular events (MACES) and other complications. We compared the mortality rate between peri-procedural enzymatic infarct group and non peri-procedural enzymatic infarct patients along with incidence of peri-procedural EI in CSA versus ACS subgroups and tested for the significance.*

Results: *Out of total 748 patients who undergone PCI in our unit, the total incidence of peri-procedural EI was 7.7%. Among total 58 peri-procedural EI events, 23(3%) were in patients with ACS presentation (p=0.001) and 34(4.5%) were in patients with CSA presentation (p=0.0001). Patients with peri-procedural EI had significantly higher risk of mortality than those without peri-procedural EI (5.1% versus 0.2%, p= 0.001).In subgroup analysis among patients with peri-procedural EI the mortality is higher in patients with ACS presentation compared to those with CSA as presentation (8.6% versus 2.9%(p=0.01)), and the total mortality is confined to the type B enzymatic infarct group.*

Conclusion: *Among patients undergoing PCI, the occurrence of peri-procedural EI measured by CK-MB mass assay was 7.7% and Peri-procedural EI type B was associated with significant increase in mortality over one year followup.*

Keywords: *Percutaneous coronary intervention, Myocardial infarction, Mortality, Enzymatic infarct*

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INTRODUCTION

Percutaneous coronary intervention (PCI) is an established strategy for the management of obstructive coronary artery disease since past four decades. Now we have to concentrate on factors which are responsible for the outcome of these procedures to give good public health. Percutaneous coronary intervention can be associated with a small but significant incidence of several peri-procedural complications such as myocardial infarction (MI), thrombosis, stroke, major bleeding, or death. Among these events, the long term outcome of peri-procedural MI, which can range from a minor elevation of cardiac enzymes to a large-sized infarct, is not clear from the existing studies [1, 2]. We aimed to study the outcome of peri-procedural MI patients at one year when compared to those patients who did not had in this DES era.

MATERIALS & METHODS

We have retrospectively analyzed the data of 748 patients presenting with obstructive CAD undergoing PCI in our unit of Cardiology, from July 2014 to December 2015. We included both the stable and unstable coronary artery disease patients in our study. We excluded patients with significant renal, hepatic and other systemic dysfunction and patients who are in severe cardiogenic shock. Institutional ethical committee approval was taken. Informed consent was taken from all the patients before inclusion into the study. All patients were evaluated after a detailed history, physical examination, and appropriate investigations. Demographic and clinical characteristics of patients were documented.

PCI was performed according to current standard guidelines. Antiplatelet therapy and peri-procedural anticoagulation were administered according to standard regimens. All patients were pre-treated with oral aspirin and Clopidogrel or Prasugrel or Ticagrelor 2–6 h prior to the procedure and glycoprotein IIb/IIIa inhibitor or Bivalirudin is used in accordance with the discretion of the operator. PCI were done through radial or femoral route as per operator's choice. All patients undergoing PCI were given 70 IU/kg unfractionated heparin before PCI, while drug eluting stents were deployed in all the patients. Dual antiplatelet therapy was recommended post-PCI at least for 1 year.

All the patients were classified according to their angiographic profile as single vessel disease (>70% lesion involving one epicardial coronary artery) or multi vessel disease (>70% stenosis in 2 or more epicardial coronary arteries). Angiographic success was defined as residual coronary artery stenosis < 20% after stent implantation with TIMI grade 3 flow. ECGs were taken immediately after the procedure and after 24 hours to look for any fresh changes.

Routine measurements of CK-MB, as measured by mass assay, were performed in all patients [3,4,5]. CK-MB Mass assay was performed with the immunochemical method as implemented on the ACS-180 analyzer Blood samples were routinely collected for the measurement of CK-MB levels at baseline, every 8 h for the first 24 h after the procedure. For each patient, the CK-MB ratio was calculated as the ratio between the peak CK-MB level and the upper limit of normal. Routine measurements of cardiac troponin after PCI were not performed. All laboratory testing was performed by personnel who were blinded to the patient information and study objectives.

The term enzymatic infarct (EI) is used to include all patients with peri-procedural CK-MB elevation more than upper limit of normal. These patients are divided into three categories based on level of enzyme elevation and type of presentation. Type A includes those with CK-MB between 1 to 3 times the ULN, type B includes true peri-procedural MI that means CK-MB >3 times ULN, type C includes patients with baseline CK-MB elevation due to acute MI.

Peri-procedural EI was defined as an elevation of CK-MB more than upper limit of the normal range in at least two blood samples with a normal range of baseline value within 48 hours of the procedure. If the pre-PCI CK-MB values are elevated more than the upper normal limits, such as patients initially presented with acute MI, CK-MB re-elevation at least 50% greater than the most recent pre-procedure concentration with documentation that the values were stable or falling before PCI was required for the diagnosis of peri-procedural MI in this setting.

FOLLOW UP:

Clinical follow-up was performed via clinic visit or telephone contact at 1, 6 and 12months.At each time of follow-up contact, data pertaining to patients' clinical status and interim occurrence of adverse events were collected.

STATISTICAL ANALYSIS:

Data analysis was performed using Minitab version 16 software. Continuous variables were expressed as mean ± SD. Baseline parameters were compared between groups using the Student t test for continuous variables and the chi-square test for categorical variables. Results with a p value <0.05 is considered to be significant.

RESULTS

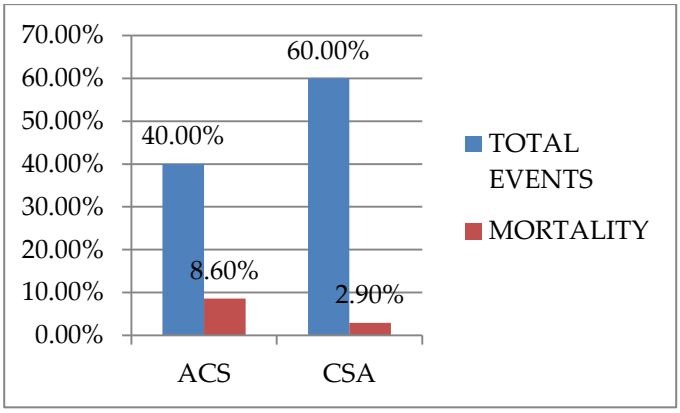
We analyzed data from 748 patients presenting with CAD undergoing PCI from our Cardiology unit of a tertiary care center in southern India (the Nizam's Institute of Medical Sciences, Hyderabad) from July 2014 to December 2015. The baseline characteristics, clinical presentation, angiographic profile and outcomes were given in Table1. Out of total 748 patients who undergone PCI in our unit, the total incidence of peri-procedural EI was 7.7%. Among total 58 peri-procedural EI events, 30 were in type A , 24 in type B and 4 in type C category, and 23(3%) were in patients with ACS as presentation (p=0.001) and 34(4.5%) were in patients with CSA as presentation (p=0.0001). Men are more involved in both groups than women. In the present study the incidence of diabetes is more in non peri-procedural EI group compared to peri-procedural EI group (71.7% vs 53.4%, p=0.007).

Table 1: Baseline characteristics of patients according to peri-procedural enzymatic infarction.

Variables	PEI group (n=58)	Non-PEI group(n=690)	p value
No of patients	58	690	
Female: Male	14: 44	180: 510	
Age (Yrs)	56.9 ±12.2	57.9± 11.1	0.6
HTN	33(56.9%)	459 (66.5%)	0.2
DM	31(53.4%)	495(71.7%)	0.007
SM	12(20.7%)	159 (23.04%)	0.7
Type Of Pres.: ACS	24 (41.3%)	218(18.6%)	0.001
CSA	34(59.7%)	506(81.4)	
LV Dysfunction	37(63.8%)	134(19.4%)	0.0001
Previous PCI	8(13.8%)	33 (19.3%)	0.3
Post CABG	2(0.3%)	0	0.2
Multivessel	17(29.3%)	204 (29.6%)	0.96
Route of PCI: Radial	44(75.9%)	576 (83.5%)	0.2
Complex Lesion (B2 & C)	51(87.9%)	588(85.2%)	0.6
Leuc.Count(cells/cu.mm)	10929±8594	9054±4019	0.02
Hemoglobin(g/dl)	13.2±2.1	12.98±2.1	0.4
Blood urea(mg/dl)	33.1±16.3	28.5±15.3	0.04
Creatinine(g/dl)	1.2±0.4	1.2±0.7	0.9
Pre-Ref.Vess.Dia (mm)	2.5±0.5	2.4±0.6	0.3
Pre-MLD (mm)	1.1±0.4	1.04±0.4	0.2
Pre lesion length (mm)	8.5±3.9	8.4±5.6	0.9
Pre stenosis (%)	60.2±14.7	58.5±13.3	0.4
Post-Ref.Vess.Dia (mm)	2.9±0.9	2.7± 0.5	0.001
Post MLD (mm)	2.3±0.4	2.2±0.4	0.06
Stent size (mm)	2.9 ± 0.4	2.9± 0.3	0.2
Stent length(mm)	22 ± 8.04	21± 8.1	0.4
Peak CPK(U/L)	36503± 269257	276±77.3	0.024
Death at 12months	3(5.1%)	2(0.2%)	0.001

Patients presenting as acute coronary syndromes had higher incidence of peri-procedural EI (41.3% vs 18.6%, p=0.001). LV dysfunction was higher in peri-procedural EI group compared to non peri-procedural EI (63.8% VS 19.3%, P=0.0001).Total leukocyte count and blood urea at presentation were high in peri-procedural EI group(p=0.023, p=0.042). Though the lesion length, stent size and stent length were higher in peri-procedural EI group, they are not statistically significant. Patients with peri-procedural EI had significantly higher risk of mortality than those without peri-procedural EI (5.1% versus 0.2%, p= 0.001) (Fig. 1).

Fig. 1: Mortality in patients with peri-procedural enzyme elevation with ACS vs CSA presentation



Outcomes of the peri-procedural EI were given in Table2. Out of 23 patients in ACS group 1 had congestive cardiac failure and 2 had sub-acute stent thrombosis. Of total 3 deaths in peri procedural EI, 2 were in ACS group and 1 in CSA group.

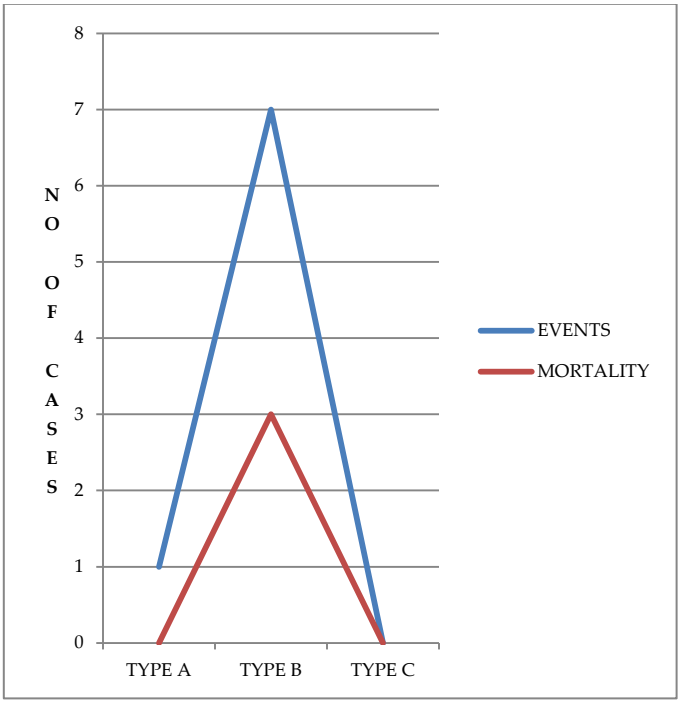
Table 2: Outcomes of patients according to peri-procedural enzymatic infarction

Outcomes	PEI group (n=58)	Non PEI group (n=690)	P value
CCF	1	1	0.24
Chronic stable angina	2	1	0.34
CVA	1	0	0.56
Stent thrombosis	2	2	0.27
Instent restenosis	1	0	0.67
Pseudo aneurysm	4	0	0.45
Death	2	3	0.001

In subgroup analysis among patients with peri-procedural MI the mortality is high in patients with ACS presentation compared to those with CSA as presentation (8.6% versus2.9 %(p=0.01)) (Fig. 1). When the outcomes in three categories of enzymatic infarct group was observed type A had only 1 CSA during 1 year follow up, whereas the total mortality is seen in type B that is true peri-procedural MI with CK-MB

elevation >3 times the ULN. Type C category had no mortality during 1 year follow up (Fig. 2).

Fig. 2: Mortality in peri-procedural enzymatic infarction in all three category patients.



DISCUSSION

Previous several studies reported that the incidence of peri-procedural MI varies from 5 to 30% according to the diagnostic criteria and the local practices. After PCI, a number of factors have been associated with peri-procedural MI, which can broadly be categorized as patient-related factors, lesion-related factors, and procedure-related factors. Patient-related factors, including multivessel disease, evidence of systemic atherosclerosis, reduced left ventricular ejection fraction, diabetes mellitus, older age, and chronic kidney disease, increase the risk of post procedural CK-MB release by 1.3- to 1.8-fold[6, 7, 8]. Systemic inflammation on presentation including elevated
hs–C-reactive protein correlates with post procedural CK-MB elevation, as does an elevated admission white cell count (9.5x106/ L). The clinical syndrome on presentation also affects risk, with enzyme negative patients with acute coronary syndromes (ACS) having up to a 40% incidence of post-PCI enzyme elevations and enzyme-positive ACS patients having even more frequent and larger post procedural MIs. Lesion-related factors [9,10] such as disease burden, calcification, lesion eccentricity, and thrombus predict increased peri procedural enzyme release. Procedure-related variables such as device selection, in particular, atherectomy; aggressive stent expansion resulting in plaque extrusion, side branch occlusion, and side branch stenting; and angiographic complications including distal embolization, coronary dissection, no-reflow, vasospasm, and unsuccessful procedures, are all associated with peri procedural MI.
In totality, these risk factors identify patients with increasing atherosclerotic disease burden, increased thrombotic risk, and with neuro-hormonal activation , that predisposes to either macrovascular complications (side branch occlusion or macro-embolization) or microvascular obstruction (distal embolization of micro-particles), unifying the pathophysiologic basis of myocardial necrosis after PCI. The controversy is whether peri-procedural biomarker elevations are independent predictors of subsequent mortality or merely represent underlying comorbidities and diffuse atherosclerosis. There have been several investigations regarding criteria, risk factors, and impact of peri-procedural MI on outcome. However, the clinical relevance and long-term prognostic value still remain a matter of considerable debate. The purpose of the present study was to determine the frequency, causes, and risk factors of peri-procedural EI and to assess the relationship between peri-procedural EI and mortality.
Park et al. have presented a comprehensive analysis of the incidence, mechanisms, risk factors, and relationship to outcomes of PMI following PCI [11]. It is the largest study, in which CK-MB mass assay was routinely performed in all patients, to systematically evaluate the frequency, causes, predictors, and clinical relevance of peri-procedural MI using patient-level data from several PCI trials. The major findings are (i) the overall incidence of peri-procedural MI was 7%; (ii) side-branch occlusion is the most common cause, and there was no identifiable mechanical cause in one-fifth; (iii) several higher risk clinical, angiographic, and procedural features were identified as independent predictors; (iv) peri-procedural MI was associated with an increased risk of mortality.
In our study, the overall incidence of peri-procedural EI was 7.75%, and true peri-procedural MI (type B) is 3.2 % which was less than the expected range of previous PCI

studies using the same CK-MB criteria. Recent consensus documents support that the preferred biomarker for myocardial necrosis is cardiac troponin (I or T), which has high myocardial tissue specificity as well as high clinical sensitivity [12, 13]. With its increased sensitivity, compared with CK-MB measurement, the use of cardiac troponin might significantly increase the prevalence of peri-procedural MI [14, 15]. Several studies showed that measurement of troponin indeed resulted in a doubling or tripling of the rate of diagnosis of MI. However, until now, there is less experience using this biomarker and it may be overly sensitive for discriminating prognostic impact. In the upcoming years, the specificity for PCI-related coronary events and prognostic relevance of troponin should be confirmed through large clinical trials, and also its increased sensitivity has to be carefully weighed against the reduced specificity for device-specific outcomes. There is limited support in the literature for determining the relative frequency of plausible mechanisms based on large datasets with solid angiographic documentations.

Previous study suggested that the adverse effect of any MI on mortality was confined to patients with evident angiographic complications, not those without angiographic complications [16]. Therefore, it warrants further studies to determine whether additional monitoring or management is indicated for isolated CK-MB elevation without obvious angiographic complications.

There are conflicting data regarding the prognostic relevance of peri-procedural MI [17]. In our study, peri-procedural EI (type B) was associated with an increased risk of morality. However, we cannot address whether peri-procedural MI has direct causality for mortality or it functions as a marker of more severe coronary atherosclerosis and procedural complexity that is responsible for higher mortality after PCI. Meanwhile, in clinical viewpoint, the presence of peri-procedural MI would be used to be an important biomarker descriptor identifying high-risk patients for future clinical events.

In previous study, the incidence of peri-procedural MI was significantly lower in patients with acute coronary syndrome than in those with stable angina (6.3 vs. 8.2%, P,0.001). But in our study the incidence was significantly low in patients with stable angina than those with acute coronary syndrome (6.7 vs 9.9%).Since most cases of NSTEMI or STEMI involve PCI during a period when biomarkers are increasing, a reliable distinction between subsequent MI and index MI event is very difficult in clinical practice. Therefore, to define a second MI for such individuals, clearer guidelines and diagnostic criteria remain to be established. If other mandatory criteria of ischaemic, angiographic, or imaging findings of third definition of MI, which are not currently available in this data sets, are simultaneously applied, the prevalence of MI would be further decreased, but the prognostic influence would be more intensified. Further studies are needed to verify the clinical utility and prognostic value of newer definitions of MI among diverse PCI settings.

We have limitations to this study. 1) It is a study from a single center which is prone to different bias and not a randomized control trial so that we can't draw any conclusions from the study. 2) We didn't study the mechanism of peri-procedural MI.

CONCLUSIONS

Among patients undergoing PCI, the occurrence of peri-procedural EI measured by CK-MB mass assay was 7.7% and true peri-procedural MI (type B EI)was associated with significant increase in mortality over one year follow-up.

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