ORIGINAL ARTICLE

Cardiac Troponin-I And CK-MB for Risk Stratification in Acute Myocardial Infarction (First Attack): A Comparative Study

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ABSTRACT

Myocardial infarction is associated with release of two important enzymes. The enzymatic diagnosis is mainly based on the measurement of CK-MB and troponin-I. Cardiac troponin-I(cTnI) is known to have higher specificity and analytic sensitivity than CK-MB for detection of myocardial injury & risk stratification. These are used both as diagnostic and prognostic marker. This prospective observational study included 60 patients of 40-65 years age range, diagnosed as acute myocardial infarction. The mean ages were 50 ± 8 years and 53 ± 8 years respectively. Male and female patients included were 86.7% and 13.3%; BMI was 25.3 ± 1.5. The two important cardiac markers troponin-I and CK-MB were studied in 60 patients, admitted in the hospital with acute MI. Blood samples to estimate these markers were collected from the patients after admission at 6-9 hours, 9-24 hours and after 24 hours and their mean values with ± SD were calculated, evaluated and compared between the two groups of patients with low and high risk MI. The patients with low risk MI were those who recovered early and the high risk patients improved later in comparison to low risk group. Out of 60 patients, 37 had troponin-I level > 1.5 ng /ml. Among them 29 developed high risk MI and 8 recovered earlier than high risk group. 23 patients had troponin-I < 1.5 ng /ml, out of whom 10 were high and 13 were low risk. The difference of troponin-I levels between high and low risk groups of patients was statistically significant ($p < 0.01$). On the other hand CK-MB level was > 7 ng /ml in 33 patients. Out of them 22 patients developed high and 11 patients were low risk but 18 patients out of 27 who had CK-MB < 7 ng /ml became high and 9 patients were low risk. The difference of outcome in respect to higher and lower values of CK-MB between the two groups was not statistically significant ($p > 0.05$). Both troponin-I and CK-MB were estimated in all 60 patients on three occasions. The mean troponin-I levels were statistically significant between the high and the low risk groups on all occasions .On the contrary, the values of CK-MB were not statistically significant on two occasions but was significant ($p < 0.01$) on one occasion when it was estimated at 9 - 24 hour. Serum cTnI is better and more characteristic biomarker than CK-MB for risk prediction and prognosis evaluation in AMI patients.

Key Words: Cardiac Troponin-I, CK-MB, Acute Myocardial Infarction, Risk Stratification

Introduction

Ischemic heart disease (IHD) is a major global health problem and the most common cause of premature morbidity and mortality among men in the developed world[1]. Mortality rates attributed to IHD vary among countries. The WHO MONICA study monitoring IHD and risk factors in 38 population from 21 countries in four continents showed fatal and non-fatal rates ranged from 30/100,000 in Spain to 915

/100,000 in Finland[2]. During recent years, more than 6 million people worldwide died of Ischaemic heart disease, which was predicted to be the leading cause deaths all over the world[3]. There is a progressive rise of the incidence of IHD in Bangladesh. A study done at National Institute of Cardio Vascular Disease from 1981-89 reported that 14 persons per thousand populations suffered for IHD and mortality from AMI in untreated patients were 40% to 50% within the first two hours of the onset[4].Another study done in 1987 showed that AMI is the leading cause of death in Bangladesh in the 4th decade of life. So, in our population myocardial infarction emerged as a major killer and in the long run a major cause of morbidity[5]. The World Health Organization (WHO) lists three criteria for the diagnosis of AMI; Chest pain, electrocardiographic changes and increases in Biochemical Markers[6]. Facilitation of earliest possible diagnosis is very important for the treatment and risk stratification of patients with suspected coronary artery disease[7].

Lack of diagnostic sensitivity and specificity of clinical and conventional markers prevent or delay the treatment, leading to undue sufferings to the patients[8]. ECG and measurement of serum creatinine kinase (CK) isoenzyme are necessary for diagnosis[9]. The ECG remains the cornerstone for the early diagnosis of acute ischaemia[10]. Moreover, the traditional enzyme markers for the detection of myocardial injury are also of questionable sensitivity and specificity[11]. National Academy of Clinical Biochemistry (NACB) and the International Federation of Clinical Chemistry (IFCC) recommend myoglobin/CK-MB isoform for early detection of AMI and cTnI / CK-MB mass for definitive diagnosis of AMI[12]. AMI patients are, therefore more, confidently predicted on an increased cardiac troponin concentration in blood and regarded as the most cardiac specific of currently available biochemical markers for the diagnosis of myocardial injury[6]. Increased levels of cardiac Troponin-I gets correlated with the mortality; absolute risk of mortality was 1.7% for a Troponin-I level from 0.4 ng/ml to 1 ng /ml and 7.5% for a Troponin-I level greater than 9.0 ng /ml.This relationship was independent of CK-MB, Age, Electrocardiographic changes, and other co-factors[13].

Therefore, MI patients need to be evaluated for prediction of future risk to reduce the morbidity and mortality and for this prediction serum cardiac markers assay (cTnI and CK-MB) may be used.

This type of study is yet be done in our population although incidence of AMI gradually increasing. So the present study was designed for the assessment of risk stratification of AMI.

Materials and Methods

This was a prospective observational case study of two years duration from January 2002 to December 2003, conducted in the Department of Biochemistry, BSMMU in collaboration with Z.H. Sikder Women's Medical College, Dhaka, Bangladesh.60 patients aged 40-65 years, who suffered from AMI and got themselves admitted into CCU of Zainul Haque Sikder Cardiac Care and Research Center, Dhaka, were in the study. After taking ethical approval from the authority of the concerned hospital and informed consent from all participants, three consecutive blood samples were collected from each of the study subjects. First sample was collected within 9 hour of attack, second sample between 9-24 hour and third one after 24 hour. All patients were followed up to 30 days after attack by taking history, clinical examination, biochemical investigation and imaging technique. During follow up, depending on the clinical and laboratory, findings patients were categorized into low risk and high risk groups. Patients with atypical symptoms, normal or non specific ECG finding and normal cardiac enzyme levels are at low risk. Patients with history of accelerating symptoms, prolonged (> 20 minutes) rest pain, evidence of congestive heart failure, advanced age, ST-segment changes or elevated cardiac biomarkers (CK-MB and Troponin-I) are at high risk.

Estimation of serum cardiac troponin-I (cTnI), serum creatinine kinase MB isoenzyme (CKMB) and echocardiography were done. Data was

expressed as mean ± SD. Statistical difference between different groups was calculated by student's t-test and ANOVA. Statistical analysis was performed with the software SPSS version 11.0 for windows.

Results

The mean values of troponin-I between low and high risk groups were statistically significant when estimated on three occasions. On the other hand, the mean values of CK-MB were not significant on two occasions but was significant ($p < 0.01$) on one occasion when it was estimated at 9-24 hour.

Table I: Comparison of Troponin-I and CK-MB between low risk and high risk groups at different times of attack

Characteristics	Low risk	High risk	t-value	p-value
CK-MB (mean ± SEM) 6-9 hr	8.10 ± 2.80	9.20 ± 6. 10	0.527	> 0.05
9-24 hr	9.90 ± 3.10	17.60 ± 12. 70	3.67	< 0.01
> 24 hr	14.10 ± 5.40	20.70 ± 7.80	1.60	> 0.05
Troponin-I (mean ± SEM) 6-9 hr	1.60 ± 0.80	2.70 ± 1.40	2.12	< 0.05
9-24 hr	2.90 ± 1.20	4.90 ± 3.20	3.46	< 0.01
> 24 hr	4.40 ± 3.70	9.20 ± 4.30	2.1	< 0.05

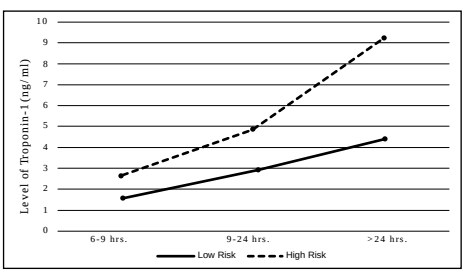

Figure 1: Comparison of Troponin-I between low and high risk groups at different times of attack

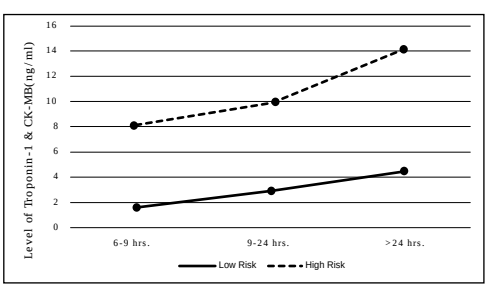

Figure 2: Comparison of CK-MB between low and high risk groups at different times of attack

Table II: Comparison to trend of Troponin-I and CK-MB level in low risk groups at different times of attack

Markers	6-9 hrs. vs 9 24 hrs.			9-24 hrs. vs > 24 hrs.		
	m ± SD	t-value	p-value	m ± SD	t-value	p-value
CK-MB (mean ± SEM)	8.10 ± 2.80 vs 9.90 ± 3.10	1.217	> 0.05	9.90 ± 3.10 vs 14.10 ± 5.40	3.868	< 0.05
Troponin-I (mean ± SEM)	1.60 ± 0.80 vs 2.90 ± 1.20	4.677	< 0.01	2.90 ± 1.20 vs 4.40 ± 3.70	1.465	> 0.05

The mean value of CK-MB in low risk group after 24 hour was more than that of 9-24hour which was statistically significant ($p < 0.05$).But the mean values CK-MB detected on two occasions (at 6-9 hr and 9-24 hr) were statistically insignificant ($p > 0.05$).On the contrary, the mean values of troponin-I estimated at 6-9 hr and at 9-24 hr were statistically significant ($p < 0.01$) but when detected after 24 hr it was insignificant ($p > 0.05$).

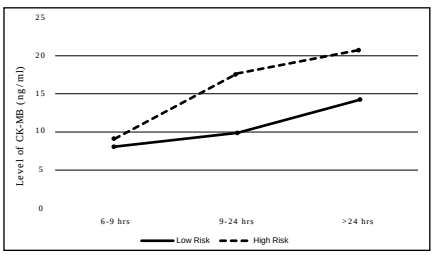

Figure 3: Comparison to trend of Troponin-I and CK-MB level in low risk groups at different times of attack

Table III: Comparison to trend of Troponin-I and CK-MB level in high risk groups at different times of attack

Markers	6-9 hrs. vs-9 24 hrs.			9-24 hrs. vs > 24 hrs.		
	m ± SD	t-value	p-value	m ± SD	t-value	p-value
CK-MB (mean ± SEM)	9.20 ± 6.10 vs 17.60 ± 12.70	5.259	< 0.001	17.60 ± 12.70 vs 20.70 ± 7.80	1.684	> 0.05
Troponin-I (mean ± SEM)	2.70 ± 1.40 vs 4.90 ± 3.20	5.000	< 0.001	4.90 ± 3.20 vs 9.20 ± 4.30	7.149	< 0.001

Levels of troponin-I in high risk group detected on three occasions were higher than normal and the mean values were statistically significant ($p < 0.001$).But CK-MB levels though higher than normal on three occasions, the level after 24 hr was not statistically significant ($p > 0.05$)

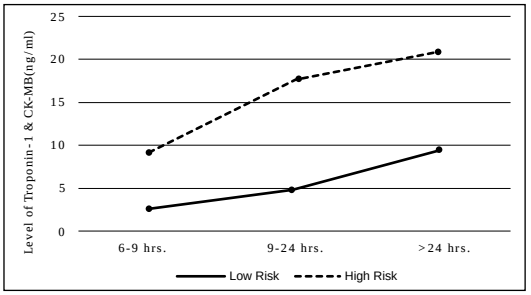

Figure 4: Comparison to trend of Troponin-I and CK-MB level in high risk groups at different times of attack

Table IV: Evaluation of Troponin-I & CK-MB with respect to the clinico-pathological (within 30 days) outcome of study subjects

Biomarker level		Follow-up		Total	2	p value
		Low risk	High risk			
Troponin-I	> 1.5 ng/ml	8	29	37	7.544	< 0.01
	≥ 1.5 ng/ml	13	10	23		
CK-MB	> 7 ng/ml	11	22	33	0.000	> 0.05
	≥ 7 ng/ml	9	18	27		

The evaluation of differences of clinicopathological outcome among 60 patients revealed that higher values of troponin-I are associated with increased high risk in an increased number of study subjects (29 out of 37). But comparatively a small number of patients developed high risk with higher values of CK-MB (22 out of 33).

Discussion

In this prospective observational study we have evaluated the serum cardiac troponin-I and CK-MB for risk stratification in post myocardial infarction of patients first ever attacked by MI. Total 60 patients with a recent history of chest pain diagnosed as Q-wave AMI (30) and non Q-wave AMI by conventional ECG and cardiac markers within 24 hours of attack and admitted in CCU were selected for study.

Although Q-wave AMI is claimed to have more myocardial damage than non Q-wave AMI; our findings of serum CK-MB and cTn-I failed to support this since the concentration of these cardiac markers were not different between two groups. This was further supplemented by our findings of no difference between the two groups with respect to their adverse cardiac outcome. This might be due to the fact that the myocardial damage in Q-wave AMI were just enough to make Q-wave in ECG but yet to cause hectic release of cardiac markers. CK-MB and cTnI were further evaluated between stable and unstable groups both longitudinally (within group) and horizontally (between group) with respect to the time of attack. Troponin-I of unstable group maintained its higher concentration compared to stable group throughout the follow-up period. On the other hand CK-MB found to be statistically similar between stable unstable group at 6-9 hours and > 24 hours of attack. But only at 9-24 hours CK-MB was significantly higher in unstable group compared to stable group.

This finding is apparently convincing to believe that it is the cTnI rather than CK-MB which is a more consistent and reliable marker of cardiac damage to indicate the worst outcome following AMI. This credential own by the cTnI might be due to its higher specificity and diagnostic sensitivity to ischaemic myocardial damage in comparison to CK-MB. A study done by Lee et al. showed that traditional markers such CK-MB suffer from low cardiac specificity and sensitivity. Whereas troponin-I assay appears to be a more sensitive indicator of myocardial cell injury than CK-MB[14]. Test systems for cardiac troponin-I (cTnI) provide the highest specificity and analytical sensitivity for detection of myocardial injury and serum cTnI helps to assess the true complication of the patients[15]. Several other studies also have documented the prognostic superiority of the serum cTn-I for early and safe risk stratification of patients with acute chest pain[16].

The study conducted by Bodi stated that troponin-I is better diagnostic marker than CK-MB. They found CK-MB to be increased in patients with acute and chronic skeletal muscle disease with normal serum cTn-I[17]. Braunwald recommended that troponin-I as the the best cardiac markers for diagnostic and prognostic purpose.The uses of cardiac troponin will undoubtly increases the number of event

recorded in particular trial because of increase sensitivity for detecting MI[18]. In our study we have also evaluated the serum CK-MB and cTnI with respect to a definite cut-off value and the clinico-pathological outcome. At cTnI > 1.5 the tendency of unstability was found to be significantly more than that at cTnI ≤1.5 where as no such predictable association of stability and unstability of patients was found in relation to the CK-MB above and below 7 ng/ml. So the difference of clinico-pathological outcome with respect to higher and lower value of troponin-I was found significant and characteristic but the same was not found true for CK-MB. Milenko et al in their study with serum cTnI cut-off value 0.4 ng/ml showed that patients with cTnI levels of 0.4 ng/ml or greater had a significantly increased risk of death compared with patients with cTnI less than 0.4 ng/ml. The risk of death they found to increase further with increasing troponin-I levels[19].

Steinberg et al used serum cTn-I concentration for risk stratification in 885 patients with acute MI and they found the elevated troponin-I levels greater than 1 ng/ml to be positively correlated with death within 30 days and correlation between elevated troponin-I and death was independent of CK-MB levels[20]. Antman et al showed that mortality rate was consistently higher among patient with cardiac troponin-I more than 0.4 ng/ml than those with cTnI less than 0.4 ng/ml inspite of normal CK-MB in these patients[14].

Therefore, our findings are in line with many other previous studies suggest that serum cTnI is better and more characteristic biomarker than a CK-MB for risk prediction in AMI patients. AMI patients with raised serum cTn-I and its progressively increasing pattern are more prone to develop adverse cardiac outcome in subsequent couple of weeks.

In conclusion, serum cardiac troponin-I rather then CK-MB can be entertained as a good early marker of short term risk stratification in AMI because cTn-I maintain longitudinal rising trend but CK-MB showed early rising trend but subsequently fail off within 24 hours. Cardiac troponin-I is the most specific and sensitive marker of myocardial cell injury and therefore have replaced CK-MB. Cardiac troponin-I has high specificity for cardiac injury because it is not found in skeletal muscle during neonatal development and adulthood .Cardiac troponin-I is released into blood within hours of the onset of symptoms of myocardial infarction and that it remains elevated for several days of post-infarction. Measurement of cardiac troponin-I levels provides sensitive and specific determination of myocardial injury over a wide diagnostic time window. We suggest identical study with greater sample size involving different hospital nationwide. Moreover the study might include troponin isoform to make out much greater objective view for cardiac marker in risk stratification of AMI.

References

1. Wrights RA, Fox KA. Prognosis in ischaemic heart diseases. Medicine International 1993; 6:384-388.
2. Shaper GA. Epidemoology of ischaemic heart disease,Medicine International, 6th ed. John Bernard Henry. WB Saunders Company, Philadelphia 1997; 6: 38-43.
3. Lopez AD, Murray CC. The global burden of ischaemic heart disease 1990-2020. Nat Med 1998; 4:1241-1249.
4. Amanullah M, Zaher A. Trends of ischaemic heart disease and relationship with known risk factors in Bangladesh, National congress of cardiology 1994; 28:13-16
5. Khondokar RK, Hossain D, Hossain M. Retrospective analysis of acute myocardial infarction. Bang Heart J 1987; 1:14.
6. Jaffe AS, Lant Y, Parvin CA. Comparative sensitivity of cardiac troponin I and lactyate dehydrogenase isoenzymes for diagnosing actue MI. Clinical Chemistry 2000; 42:1770-1776.
7. McCarthy BD, Wong JB Seiker HP. Detecting acute cardiac ischaemia in the emergency Department. J Gen Intern Med 1990; 5:365-373.
8. Chalif PO. Troponin T ro troponin I or CK-MB, Eur Heart J, 1992; 1:16-24.
9. Adam JE III, Bordar GS, Davila-Roman VG. Cardiac troponin-I: A. marker with high specificity for cardiac injury. Circulation 1993; 88:101-106.

10. Rouan GW, Lee TH Cook EF. Clinical characteristics and outcome of acute myocardial infraction in patients with initially normal or nonspecific electrocardiograms, Am J Cardiol 1989; 64:1087-1092.

11. Panteghini M. Biochemical assessment of myocardial damage with new diagnostic tools. Cardiologia 1999; 44: 419-425.

12. WuAHB, Apple FS, Gibter WB. National Academy of clinical biochemistry standards of laboratory practice. Clin Chemistry 1999; 45:1104-1121.

13. Antman EM, Tanasijevic MJ, Thompson B. Cardiac-specific troponin-I levels to predict the risk mortality in patients with ACS. New Engl J Med 1996; 335:1342-1349.

14. Christian Hamm W.2002,Cardiac troponin elevations in patients without acute coronary syndrome, Circulation 106: 2871-2872.

15. Katus HA,Remppis A, Scheffold T, Diederich KW. Intracellular compartmentization of cardiac troponin T and its release kinetics in patients MI. Am J Cardiol 1991; 67:1360-1367.

16. Sato GS, Poole WR, Muller JE. Electrocardiographic and clinical criteria for recognition of acute MI. Am J Cardiol 2001; 52: 936-942.

17. Bodi VV. Is tropnin I useful for predicting in hospital risk for unstable angina patients in a community hospital? Rev Esp Cardiol 2002; 55:100-106.

18. Braunwald M, Goldman L. Serum enzyme essays in the diagnosis of acute myocardial infarction. Recommendations based on a quantitative analysis, Ann Intern Med 2000; 105:221-233.

19. Milenko JR, Kannel WB, Feinleich M. Clinical feature of unrecognized myocardial infarction, Am J Cardial 1999; 32: 1-7.

20. Steinberg WJ, Balfe DI, Kustner HG. Decline in the ischaemic heart diseases mortality rates of South Africans, South African Med J 1998; 74: 547-550.