Original Article

Admission creatine kinase as a prognostic marker in acute myocardial infarction

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Abstract

Objectives: To investigate the prognostic significance of creatine kinase (CK) in Pakistani patients suffering from acute myocardial infarction (AMI) and to find out if CK combined with troponin T (TnT) could be a better predictor for long-term adverse cardiac event.

Methods: One hundred and eighty six consecutive patients with AMI who were eligible for streptokinase (SK) treatment were included in this prospective cohort study. The relationship between their serum/plasma CK and TnT levels at the time of admission and clinical outcome was investigated over a mean follow up of 24.12 ± 3.75 months.

Results: Admission CK was found to be associated with subsequent cardiac event and mortality (P< 0.01 and P< 0.04 respectively). Admission CK was also mildly associated with time interval between onset of symptoms to SK treatment (correlation coefficient 'r' = 0.23). Odds of encountering a cardiac event in AMI patients with above-normal CK levels (adjusted for gender) were 3.46 times higher than the odds in patients with normal CK levels. Similarly, odds of mortality in patients with positive TnT were 4.6 times the odds in patients with negative TnT. The two biochemical markers, CK and TnT, together did not provide any further information about prognosis of the disease.

Conclusion: Admission CK is a better prognostic marker for a subsequent cardiac event, while TnT is a better predictor of mortality over a mean follow up of nearly 2 years. Together, they do not improve predictability of an adverse cardiac event (JPMA 59:819; 2009).

Introduction

Creatine kinase (CK) is an enzyme that is abundantly present in myocardial tissue. After the onset of symptoms of acute myocardial infarction (AMI), circulating levels of CK begin to increase within a few hours (3-12 hours) and after reaching a peak fall to normal ranges within 24-36 hours.[1] Therefore, it is a sensitive marker of myocardial infarction (MI) but has relatively low specificity because of presence of CK in skeletal muscles.

If CK in an AMI patient is at a low level in serum at the time of admission, it indicates minimal amount of myocardial damage, and the possibility of successful treatment exists as a result of which mortality and morbidity could be decreased.[2]

Although now more new sensitive and more specific markers are available, CK is still widely used in developing countries like Pakistan for confirming the diagnosis of AMI. Recent clinical data have suggested that CK concentration in serum at the time of presentation (admission CK) is an independent predictor for the short and long term cardiac outcomes.[3-5] However, most of the studies on CK related to prognosis have been reported from the West. Reports from the developing world, especially from South Asian region, regarding the prognostic value of CK in AMI are scarce. Apart from one small study in India and another one from the Aga Khan University Hospital (AKUH), Karachi, Pakistan, there is hardly any report on prognostic significance of admission CK in AMI patients in this part of the world.[6,7]

The purpose of this study was to examine the relationship of admission CK level in serum and its prognostic value in Pakistani patients suffering from AMI, and to find out if CK along with troponin T (TnT) could be of added value in predicting prognosis of the disease.

Patients and Methods

One hundred and eighty six consecutive AMI patients (146 males; 40 females; mean age 56 ± 0.8 years) requiring thrombolytic therapy with streptokinase (SK) were included in this prospective cohort study. They were admitted to the Coronary Care Unit of AKUH from October 1998 to October, 2001. AMI was diagnosed on the basis of clinical history, electrocardiogram (ECG) and biochemical data. All these patients were offered SK treatment (1.5 million units over a period of 60 minutes). After discharge from the hospital, a follow up from 18 months to 30 months was carried out.

The study had been approved by the Ethics Review Committee of the Institution.

Blood collection:

At the time of admission, 10 ml blood was collected and half of it was transferred to a plain vacutainer tube and the rest to another tube containing 3.8% sodium citrate as anti-coagulant. Plasma and serum were removed by centrifugation of two tubes at 1500xg.

Determination of CK and troponion t (TnT):

CK activity in serum and plasma concentration of TnT were determined using commercially available kits (Roche Diagnostic Ltd, Sussex, UK). While CK values were described as IU/l (normal values for males ≤ 174 IU/l and for females ≤ 140 IU/l), TnT values were reported as TnT positive if the value was above 0.1ng/ml, or TnT negative when the value it was below 0.1 ng/ml.

Clinical outcomes:

Follow up information was collected by telephone and review of the medical records of patients with a mean ± SD follow up of 24.12 ± 3.75 months. The primary end point was information regarding mortality, reinfarction, or revascularization. For analysis, any one of these events was recorded as a cardiac event, however, mortality was included in the analysis as an independent outcome as well. Forty-five patients were lost to the follow up.

Statistical analysis:

Statistical analyses were done with the help of SPSS® (Statistical Package for Social Sciences) version 13.0 for Windows® (Apache Software Foundation, USA). Means were expressed as means ± S.E. (standard error). Comparison of distribution of frequencies of cardiac events and mortality with respect to normal and above-normal levels of CK was carried out by test of association using chi square. Independent samples t-test was used to compare distribution of CK levels between patients with cardiac event and patients with no cardiac event during the follow up. Similarly, mean values regarding distribution of time from symptoms to SK treatment between patients experiencing a cardiac event and those experiencing no cardiac event during the follow up were compared using Independent samples t-test. Logistic regression was used to relate above-normal and normal levels of CK and TnT positivity and TnT negativity with clinical outcomes. A P-value less than 0.05 was considered significant.

Results

Of the 186 patients studied, there were 146 males and 40 females. The mean age was 56 ± 08 years. Prior history of MI was present in 75% patients. The mean time interval between onset of symptoms and thrombolytic treatment was 188 ± 9 minutes. Regarding MI location, 40% had anterior, while 35% had inferior and/or posterior location. The other 25% were those where ECG changes were not confined to any one territory.

Distribution of frequencies of cardiac events and mortality in AMI patients with normal and above-normal levels of CK is shown in Table-1. A comparison of these outcome frequencies in two groups of patients (one group with normal CK levels and another group with above-normal CK levels) revealed that this marker of myocardial necrosis is associated with both cardiac events as well as mortality.

To study the association (if any) between time from onset of symptoms to SK treatment and admission CK levels, the mean time values in group of patients with normal CK and the group of patients with above-normal CK were statistically analyzed by Independent samples t-test. The mean time (224 ± 20 minutes) in the group with above-normal CK was higher ($P<0.001$) than the mean time (156 ± 8 minutes) in the group with normal CK. Strength of association was further analyzed by Spearman's correlation test (non-parametric correlation),

Table-1: Distribution of frequencies of cardiac events and mortality in patients with AMI with normal and above-normal levels of CK.

Clinical outcome	Normal CK* (n=88) Number (%)	Above-normal CK* (n=53) Number (%)	P**
Cardiac event (n=92)	50(57)	42(79)	0.01
Mortality (n=20)	8(40)	12(60)	0.044

*CK values were adjusted for gender.
**Based on test of association using chi-square.

Table-2: Distribution of serum concentrations of admission CK in AMI patients with and without cardiac event.

Mean ± SE

AMI patients	N	CK (admission) (IU/l)	P*
With no cardiac event	49	197 ± 42	0.04
With cardiac event	92	434 ± 82	

*P-value was obtained by comparing means values in the group of patients experiencing no cardiac event vs those who experienced a cardiac event by Independent samples t-test.

It is important to mention that though some of the patients experienced more than one cardiac event (reinfarction, revascularization or mortality), yet for analysis purposes, for each patient these were entered as at least one cardiac event. Therefore, 65.2% of AMI patients (n=92) had at least one cardiac event. Mortality was taken as an independent outcome as well and 14.2% of patients (n=20) died over a mean follow up of 24 months.

Mean admission CK level, however, in patients with at least one cardiac event was found to be significantly higher than the mean level in patients who experienced no cardiac event during the follow up time (P = 0.04; Table-2). This suggests that admission CK could be of prognostic value at least in terms of future risk of a cardiac event.

To see if the admission TnT levels add to the prognostic value of admission CK, the values of admission TnT and admission CK versus clinical outcome (in terms of cardiac event and mortality) were analyzed in a logistic regression model. The logistic regression model included 121 patients of which both admission CK and admission troponin t values were available. Table-3 shows that although TnT is a

Table-3: Odds ratios (OR) and 95% confidence interval (CI) of cardiac event and mortality by admission CK and admission troponin T.

Variable	Clinical outcome at follow up					
	Subjects with cardiac event (n) (n = 73)	Subjects with no cardiac event (n) (n = 48)	OR* (95% CI)	Mortality (n) (n=18)	No Mortality (n) (n=89)	OR* (95% CI)
CK						
- Above-normal (n = 43)	33	10	3.46(1.37-8.78)	10	28	1.44**(0.44-4.69)
- Normal (n = 78)	40	38	1(Ref)	8	61	1(Ref)
Troponin T						
-Positive (n=32)	21	11	0.78**(0.3-2)	11	20	4.62(1.4-15.1)
-Negative (n=89)	52	37	-	7	69	1(Ref)

*OR and CI were determined by applying logistic regression.
**Non-significant.
Note: A cardiac event refers to mortality or reinfarction or revascularization in one patient.
Logistic regression model included those subjects with both values of admission CK and admission TnT (n=121).

and a mild association between admission CK and time between onset of symptoms to SK treatment was found (correlation coefficient "r"=0.23). This indicates that greater the time interval before treatment, higher would be the levels of admission CK.

The relationship of time from onset of symptoms to SK treatment with clinical outcome (both cardiac event and mortality) in AMI patients, showed that the mean time interval from onset of symptoms to SK treatment was higher in the group of patients who died (219 ± 32 min) than the time interval in the group which experienced at least one cardiac event (197 ± 13 min). However, the two values when compared by Independent samples t-test were not found to be statistically significant (P = 0.093).

better prognostic marker for mortality (odds ratio 4.6), but CK was a better predictor of any cardiac event (odds ratio 3.46). The two biochemical markers together did not add to the prognosis of the disease.

Discussion

CK is a sensitive marker of myocardial necrosis. Compared to other biochemical markers, it is widely used for diagnostic purposes in many developing countries due to its high sensitivity and being more cost-effective than others.[1] It has been reported earlier that TnT is an independent risk predictor of future deaths and MI in acute coronary syndrome.[7,8] The mean follow up times in both of these studies were 13 months and 18 months, respectively. In the

present study, the focus was on admission CK along with admission TnT for their prognostic role in AMI patients over a mean follow up time of nearly 2 years. This current data not only substantiates the previous findings regarding role of admission TnT in predicting cardiac death, but also provides evidence towards the role of admission CK in predicting the risk of future cardiac events, such as reinfarction, requirement of revascularization and mortality.

Gender was not identified to be associated with clinical outcome (cardiac event or mortality). This is in line with an earlier report from our hospital.[8] A mild positive association between admission CK levels and time interval between onset of symptoms to SK treatment is indicative of degree of cell damage (reflected by CK release) as a function of time. It also points towards a better prognosis if the time interval between onset of symptoms to SK treatment is reduced as it would be accompanied by lower levels of CK.

Results of this study indicate that admission TnT is a better predictor of mortality (OR 4.62) and conforms well with those reported by Ohmen et al,[9] who have also showed that TnT levels were strongly associated with mortality (P<0.001) compared to CK-MB (P=0.03).

Savonitto et al[3] in a large study on 11,725 patients with a 6-month follow up have reported that even minor CK elevations appear to have important and independent prognostic implications. Pierard et al[10] have emphasized that even a low peak serum level of CK would be associated with higher mortality over a follow up of 3 years. All these reports point towards the prognostic significance of CK in AMI. Results of the present study corroborate well with these reports and admission CK does appear to have a prognostic value in Pakistani AMI patients.

Combination of markers of myocardial necrosis, such as admission TnT (or troponin I) along with admission CK would be expected to have more prognostic information compared to a single marker. In a recent study, Szmanski et al[5] have shown that mortality at 30 days in acute coronary syndrome was higher in patients with all three markers increased than in patients with other combinations. Similarly, in a large study on 970 patients with non-ST elevation acute myocardial syndromes with elevated CK along with positive TnT, showed worst prognosis compared to those with one positive biomarker.[11] In the present study, we did not find any additional benefit of including admission TnT to admission CK values in predicting mortality or future cardiac events in AMI patients over a mean follow up of 24.12 ± 3.75 months. However, a prospective study using a large sample size over a long follow up time would be required to clarify whether combination of markers would be superior to a single marker in predicting the risk of future cardiac events in AMI patients.

Conclusion

Admission CK is a better prognostic marker for a combined end point of mortality, repeat MI and revascularization, whereas admission TnT is a stronger predictor of mortality in AMI patients over a mean ± SD follow up of 24.12 ± 3.75 months. Together, they do not improve predictability of adverse cardiac event.

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