Effect of Very Early Atorvastatin Initiation for Acute Myocardial Infarction on Creatine Kinase release

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Abstract

Background : It has been suggested that pre-treatment with a statin agent prior to myocardial infarction limits myocardial creatine kinase release, and thus may act to limit myocardial infarct size in humans.

Objective : To examine the effect of very early statin initiation for acute myocardial infarction (AMI), to the extent of myonecrosis as manifested by peak serum creatine kinase levels.

Methods : Patients with AMI admitted to Al-Kindy teaching hospital cardiac care unit from 1st February 2007 to 28th February 2008, who fulfilled the inclusion criteria cited in the present study, were randomly assigned into two study groups. The statin group patients have received a single oral dose of 40 mg atorvastatin at time of admission and repeated for the next days until discharge, patients not receiving statin were considered as controls, blood samples were obtained on admission and every 8 h for another three consecutive samples to identify peak creatine kinase levels.

Results : Patients who had statin therapy initiated immediately after hospital admission have similar peak creatine kinase concentrations as compared to those not receiving statin therapy (P= 0.332).

Conclusion : statin initiation in AMI patients fails to show any observable effect on creatine kinase release, the need of an extended period for the statin agent to achieve the predictable outcome may suggest the necessity of statin pretreatment in patients at high risk for AMI.

Keywords : Atorvastatin, Acute myocardial infarction , Creatine kinase , Infarct size.

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Introduction

Since the early notion that statins, an HMG-CoA reductase inhibitors, show evidence of pleiotrophic properties which are thought to be involved in cardiovascular protection including modulation of inflammation[1,2], inhibition of platelet activation and thrombosis[3-6], as well as improving endothelial function[7-9]. Several subsequent studies have suggested an association between the early administration of statins with enhanced short and long-term cardiovascular outcomes in patients presented with acute coronary syndromes [10-16]. The mechanisms by which statins award such early benefit in the setting of acute coronary syndromes have not been fully elucidated Elevated creatine kinase levels have been shown to be correlated with a bad prognosis in the setting of acute coronary syndromes [17]. Savonitto et al. [18] have shown that creatine kinase elevations greater than two to three times the normal reference limit, are associated with a significantly increased probability of death or re-infarction in the 6 months following acute myocardial infarction (AMI). Recently Bybee et al [19] have suggested that pre-treatment with a statin agent prior to myocardial infarction limits myocardial creatine kinase (CK) release, and thus may act to limit myocardial infarct size in humans. This finding was independent of serum cholesterol levels and may be related to the multitude of pleiotrophic effects of statins. The latter authors recommended that further study is needed to confirm their findings and to determine if very early statin initiation is beneficial in patients who are not on concomitant statin therapy We therefore, try in this study to examine the effect of very

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early statin initiation, immediately on hospital admittance for AMI, to the extent of myonecrosis as manifested by an increase in cardiac markers, namely peak serum CK levels [20, 21].

Methods

Patients with AMI, admitted to Al-Kindy teaching hospital cardiac care unit (CCU) from 1st February 2007 to 28th February 2008, who fulfilled the following criteria, were included in the present study: (1) not on concomitant statin therapy before admission; (2) no history of myocardial infarction; (3) normal serum CK level on admission, followed by elevation of CK to more than the upper limit of normal; (4) transfer-in and transfer-out patients were excluded to circumvent incomplete information with regard to first hours management and follow-up Diagnosis of AMI was established according to the WHO criteria [22]; abnormalities in ECG were implemented to ascertain the type of AMI [23]. Patients' cardiovascular history, risk factors (smoking status, history of hypertension, diabetes mellitus defined by insulin therapy or oral antidiabetic medications), history of drug intakes, and in-hospital therapeutic management were recorded. Patients were randomly assigned into two study groups based on whether statin was added to our CCU standard treatment policy (statin group), or not (control group). The statin group patients have received a single oral dose of 40 mg atorvastatin at time of admission and repeated for the next days until discharge. Measurement of peak CK values, during the time frame of the study, was not among the routine clinical practice of our CCU due to shortage in laboratory facilities. Hence blood samples were obtained upon admission and every 8 h for another three consecutive samples. Serum was separated as early as possible and aliquots were stored at -20 C until the time of measurement. Creatine kinase was measured by an optimized standard method according to the recommendations of the German society of clinical chemistry (Humazym M-Test Creatine Kinase) adopting the semi micro procedure at 25 C. Demographic and clinical frequency data were analyzed using chi-square tests or fisher test when chi square is not applicable. The Mann-Whitney test was used to compare peak creatine kinase levels, P values < 0.05 were considered to be statistically significant.

Results

Sixty consecutive AMI patients (68.3% men and 31.7% women) were enrolled in the present study, among whom 31(71% men and 29% women) have received atorvastatin, the other 29 (65.5% men and 34.5% women) were aimed to serve as controls. In 24 patients (11 from statin group and 13 from control group) serum CK levels on admission were higher than the upper normal limit (723 ± 503 and 777 ± 510 IU/L respectively), thus they were excluded from the study groups. There were no significant differences between the two groups with regard to baseline characteristics and treatment strategies utilized in the management of those patients (Table1). None of our patients had any sign of interfering noncardiac diseases, such as malignancy, infection, recent surgery, or trauma. Further, in our statin-treated AMI patients, no cases of rhabdomyolysis, muscle toxicity or apparent liver toxicity was noted.As presented in Table 2, patients who had statin therapy initiated immediately after hospital admission have similar peak CK concentrations as compared to those not receiving statin therapy (1020 ± 621 IU/L vs. 911 ± 591 IU/L ; P= 0.332). The mean time to peak CK was also comparable in both study groups (15.8 ± 3.5h vs. 15.6 ± 3.5h; P= 0.441). The normal range of CK in this study was 10-80 IU/L for males and 10 - 70 IU/L for females.

Discussion

The possible beneficial effect from concomitant or very early statin administration in patients with AMI was first proposed by the retrospective case study of Bybee et al [10], who demonstrated that statin-treated patients had a significantly lower rate of CK release and suggested smaller infarcts in those patients. The latter data were reanalyzed by the same group of investigators, in which subgroup analysis revealed that lower peak CK concentrations within the statin group were more likely to

occur in patients who were on a statin at the time of the index myocardial infarction, they literally stated that there was no significant difference in peak CK concentration between patients who had statin therapy initiated within the first 24 hours of hospital admission and those not receiving a statin [19].

More recently, Wright et al have utilized the Mayo Clinic Coronary Care Unit database to identify 3226 consecutive AMI patients admitted from 1993 to 2000, they observed reduced peak CK and CK-MB values among patients in whom statins were administered within the initial 24 h of hospitalization (n =220) as compared to those not receiving statin therapy (n =3006) [16]. Regardless of the influence of the retrospective observational nature of their data, the authors have not specify whether any of their patients have had been on a statin agent prior to the onset of AMI. To our knowledge, the present study is the first prospective randomized clinical trial conducted to investigate the effect of very early statin initiation to the extent of myonecrosis following AMI. The aforementioned inclusion criteria implemented for this study were aimed to optimize the reliability of our data and to allow the time necessary for the effect of the statin agent to come into action, before any cardiac marker turn out to be evident, unfortunately this was on the expense of our study size. Results from the present study fails to show any observable effect of statin initiation on CK release, as indicated by comparable peak CK levels in both study groups. Taking into consideration that peak CK values may superimpose myocardial infarct size [20, 21], it could be argued here that an early post-AMI initiation of statin can hardly reduce myocardial injury, this is in consonant with that of Bybee et al [19]. However, bearing in mind the growing body of evidence approving the cardioprotective effect of statins [10-16], our findings should not be interpreted as an opposition to the general trend that a statin should be administered as early as possible in those patients, which is beyond the aim of this study.

Lack of any significant effect in the current study, can be attributed to the need of an extended period for the statin agent to achieve the predictable outcome, suggesting the necessity of statin pretreatment in patients at high risk for AMI. Similar suggestions were reported by Bybee et al [19]. Support to this line of thinking may comes from the study of Herrmann et al [24], who demonstrated a more than 90% reduction in the incidence of postprocedural elevation of CK in patients with more than one week preprocedural statin treatment relative to patients without preprocedural statin therapy, suggesting a reduction in the extent of stenting-related myocardial injury. Additional support may be provided by experimental studies consistently demonstrated that administration of statins before induction of myocardial ischemia improves myocardial viability [25]. Our major study limitation is the small number of patients, obligated by the enrollment criteria. Further studies involving larger size and implementing the CK-MB measurement with more frequent samples to derive area under the curve may provide more insight to our findings.

Conclusion

Very early post-AMI initiation of statin can hardly reduce myocardial injury, mainly due to the requirement of an extended period for the statin agent to achieve the predictable outcome and suggesting the necessity of statin pretreatment in patients at high risk for AMI.

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Table 1: Baseline and Clinical Characteristics of study groups.

Characteristics	Statin (n=20)	control (n=16)	P- value
Age	54.3	55.3	0.876
Male/Female ratio	14/6	11/5	0.544
Diabetes mellitus	(n=7) 35%	(n=6) 37.5%	0.955
Hypertension	(n=8) 40%	(n=8) 50%	0.533
Current smoker	(n=13) 65%	(n=11) 68.8%	0.935
Mean time to hospital presentation	6.6 h	6.2 h	0.85
Type of infarction			
Inferior	(n=3)15%	(n=4) 25%	
Anteroseptal	(n=7)35%	(n=5) 31.3%	0.873
Anterolateral	(n=5)25%	(n=4) 25%	
Extensive	(n=5)25%	(n=3) 18.7%	
Primary reperfusion Thrombolytic	(n=11)55%	(n=7)43.8%	0.545
Other medication	(n=17)85 %	(n=13)81.3 %	
Beta blocker	(n=13)65 %	(n=11)68.8 %	0.734
ACE inhibitor	(n=18)90 %	(n=14)87.5 %	0.943
Aspirin	(n=13)65 %	(n=9)56.3%	0.902
Heparin			0.712

Table 2: Peak CK levels of study groups.

Parameter	Statin group (n=20)	Control group (n=16)	p-value
Peak CK level (IU/L)	1020 ± 621	911 ± 591	0.332
Mean time to peak CK (h)	15.8 ± 3.5	15.6 ± 3.5	0.441