Influence of statin therapy on circadian variation of acute myocardial infarction

Akut miyokart enfarktüsünün sirkadiyen ritmine statin tedavisinin etkisi

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ABSTRACT

Objective: Strong evidence has suggested that there is a circadian periodicity of acute coronary event. Beta-blockers, aspirin and angiotensin-converting enzyme inhibitors decrease the rate of acute myocardial infarction (AMI) and blunt the peak incidence in the morning. However, such effect has not been evaluated for statins. Accordingly, the present study aimed to evaluate the influence of statin therapy on circadian variation of AMI.

Methods: This retrospective study consisted of 451 consecutive patients with acute ST segment elevation AMI. The patients were divided into two group based on prior statin usage. In statistical analysis t test, Chi-square test and Mann Whitney U test were used for comparison of groups. We used harmonic regression models to evaluate the circadian variation of onset of MI symptoms in patients receiving statin and patients not receiving statin.

Results: In all study participants, the highest incidence of AMI was between 6.00 and 12.00; the odds ratio was 1.34 (95% CI 1.20 to 1.46, p<0.001). In the non-statin group, the highest incidence of AMI occurred between 0:00 A.M. and 06.00. There was still a peak incidence between 06.00 A.M. and noon in the statin therapy receiving group; the odds ratio was 1.61 (95% CI 1.34 to 1.80, p<0.001). Accordingly, there was no statistical difference between the statin and non-statin groups regarding circadian variation of AMI. Prior usage of statin did not blunt the peak incidence of AMI in the morning.

Conclusion: Prior usage of statin does not seem to play a role in the circadian periodicity of AMI. (Anadolu Kardiyol Derg 2010; 10: 429-33)

Key words: Acute myocardial infarction, circadian rhythm, statin, regression analysis

ÖZET


Yöntemler: Dört yüz üçü ardışık ST segment yükselmeli AMI hastası retrospektif çalışmaya kabul edildi. Hastalar, önceden statin kullanımı rehberinde iki grubu ayrıldı. İstatistiksel analizde gruplar arasında karşılaştırmaların t testi, Ki-kare testi ve Mann-Whitney U testi kullanıldı. Statin kullanan ve kullanmayan AMI hastalarının sirkadiyen ritmini değerlendirmede harmonik regresyon modeli kullanıldı.

Bulgular: Tüm hastalar değerlendirildiğinde en yüksek AMI görülme saatleri 06:00 ile 12:00 arasında oldu (%95 güven aralığına tabi olma olasılık oranı=1.34 [1.20-1.46], p<0.001). Statin almayan AMI oranının 06:00 ile 00:00 arası 1.61 (95% GAI 1.34-1.80, p<0.001) olarak tespit edildi. Akut miyokart enfarktüsünün sirkadiyen varyasyonu değerlendirildiğinde, statin alımayan AMI oranının 06:00 ile 00:00 arası 1.61 (95% GAI 1.34-1.80, p<0.001) olarak tespit edildi. Akut miyokart enfarktüsünün sirkadiyen varyasyonunu değerlendirildiğinde, statin kullanımı ile AMI'nin sabah saatlerinde görülme şeklini zirve yapması azalmamıştır.

Sonuç: Akut miyokart enfarktüsünün sirkadiyen ritminde, önceden statin kullanımı rolü gözlenmemiştir. (Anadolu Kardiyol Derg 2010; 10: 429-33)

Anahtar kelimeler: Akut miyokart enfarktüsü, sirkadiyen ritim, statin, regresyon analizi
Introduction

Strong evidence has suggested that there is a circadian periodicity of acute coronary event, with the highest rate between 8:00 A.M. and noon (1-3). This circadian variation is attributed to daily activities such as assuming the upright posture and performing different daily activities, which may trigger the onset of coronary thrombosis (3, 4). Such triggering may result from unfavorable alterations in the balance between the prothrombotic and antithrombotic properties of the blood. Accordingly, it has been shown that aspirin reduces the risk of infarction by inhibiting platelet aggregation during these critical periods (1-3).

Statins play an important role in risk reduction of cardiovascular diseases (CVD) based on the findings of large randomized trials of secondary and primary prevention of CVD (5). These favorable effects of statins are not only as a result of their lipid-lowering effects but also due to their pleotropic properties including the attenuation of the thrombotic process. Indeed, previous experimental and clinical studies have shown that usage of statin is associated with the reduced thrombosis burden, and diminished platelet activity (6). Moreover, statins also influence coagulation factors and fibrinolysis (5). The spectrum of direct antiatherogenic properties of statins includes maintenance of endothelial function, anti-inflammatory actions. Furthermore, following plaque disruption, statin influence thrombosis through variable inhibitory actions on platelet aggregation and activation, coagulation factors, and fibrinolysis (7). We sought that usage of statin could influence circadian variation of acute myocardial infarction (AMI). Although the benefit of statins has been shown to decrease AMI (9), their effects on the circadian periodicity of AMI have not been evaluated.

Taken together, the present study aimed to evaluate the influence of statin therapy on circadian variation of acute myocardial infarction (AMI).

Methods

Subjects

This retrospective study consisted of 451 consecutive patients with acute ST segment elevation AMI who were admitted to Coronary Care Unit of our University Hospital between January 2004 and July 2007. The diagnosis of AMI was determined from the presence of ≥30 minutes of continuous chest pain, ST-segment elevation >2.0 mm on ≥2 contiguous electrocardiographic leads and more than a two-fold elevation of creatine kinase-MB (CKMB) level. The time of the onset of AMI was determined by the attending physician on the basis of patients' self-reports. Patients without chest pain and those who were not remembering the onset of chest pain, patients with non-ST elevation AMI and unstable angina pectoris and patients experiencing MI after coronary bypass grafting or invasive cardiac procedures were excluded. The patients were divided into two group based on usage of statin.

The standard hourly profile of the onset of AMI was obtained over a 24-h period. Patients were then categorized into four 6-hour intervals according to the time that the symptoms had begun (00:00-05:59; 06:00-11:59; 12:00-17:59 and 18:00-23:59 hours). Clinical characteristics of the population in each group were assessed: previous history of coronary artery disease (CAD), family history of CAD, prevalence of male gender, obesity, diabetes mellitus (DM), hypertension, smoking and current medication. In each subject, blood pressure (BP) was measured in at least three separate days after 15 minutes of comfortable sitting and averaged. Individuals who had systolic BP ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg or prior use of antihypertensive agents were diagnosed as hypertensive. Smoking was defined as current regular use (any amount). Obesity was defined as a body mass index (BMI) ≥30 kg/m². Diabetes mellitus was defined by the patient's self-report of such history, use of insulin or hypoglycemic agents or a fasting plasma glucose level measured on three separate days in a week >126 mg/dL (7.0 mmol/L) or impaired oral glucose tolerance test: fasting plasma glucose <126 mg/dL (7.0 mmol/L) but 2-h plasma glucose after a 75-g oral glucose challenge >140 mg/dL (7.8 mmol/L).

Among the statin users, 42 were on atorvastatin (a dose of 10 to 40 mg/day), 6 on fluvastatin (a dose of 40 to 80 mg/day), 5 on pravastatin (a dose of 20 to 80 mg/day), 3 on rosuvastatin (a dose of 10 to 20 mg/day) and 5 on simvastatin (a dose of 10 to 40 mg/day). The mean time between initiation of statin and index AMI was 182±197 days. After discharge, statin was continued in the statin group and was started in the non-statin group if it was indicated according to Adult Treatment Panel III (8). A transthoracic echocardiogram was performed in each patient. Left ventricular ejection fraction (EF) was calculated using Simpson method, and mitral regurgitation was classified according to latest published guidelines.

All the patients were treated according to the latest published guidelines and clinical practice. No primary percutaneous coronary intervention is performed in our center. Therefore, thrombolytic treatment was used as reperfusion therapy.

Statistical analysis

All the analyses were performed using SPSS (SPSS Inc. Chicago, IL, USA). A p value of <0.05 (2-tailed) was considered significant. Continuous variables were expressed as mean±SD and categorical variables were presented as percentages. Continuous variables were compared with Student t test for normally distributed values and with Mann-Whitney U test for abnormally distributed values. We used harmonic regression models to evaluate the circadian variation of onset of MI symptoms in patients receiving statin and patients not receiving statin. For further analysis, we divided the day into four 6-h intervals from 0:00 to 5:59, 6:00 to 11:59, 12:00 to 17:59, and 18:00 to 23:59. The presence of circadian variation was tested using the Chi-square one degree of freedom goodness-of-fit test for uniform distribution. Difference in the circadian variation in the onset of MI was assessed using a Pearson Chi-square test.

Results

Clinical characteristics of the study population

The general characteristics, history and risk factors for CAD, hemodynamics, laboratory findings and prior medications of the
study population are presented in Table 1. Age, gender, smoking status, and heart rate were similar within the groups. Body mass index was significantly higher (p<0.05) in the statin therapy group as compared to non-statin group. The frequency of hypertension, diabetes, heredity and history of CAD were significantly higher (p<0.05 for all) in patients receiving statin therapy. Systolic and diastolic BPs were significantly higher (p<0.05 for both) in statin therapy group than those in non-statin group. As expectedly, total cholesterol, low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol levels were significantly lower (p<0.05 for all) in the statin therapy group because of ongoing statin therapy. However, triglyceride and HDL cholesterol levels did not differ between the groups. Peak CK-MB level was different between the groups, but this difference did not reach statistical significance (p>0.05). Usage of aspirin, beta-blockers, and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) was significantly frequent (p<0.05 for all) in the statin therapy group. Fibrinolytic therapy use was similar in each group.

Analyses of the echocardiographic measurements and angiographic findings

Left ventricular EF was similar between the groups. The frequency of mitral regurgitation was significantly higher (p<0.05) in the statin therapy group. Presence of left main coronary artery (LMCA) lesion was more frequent (p<0.05) in the statin therapy group. However, other angiographic findings did not differ between the groups. Choice of treatment base on angiography results and frequency of heart failure and major cardiac events during hospitalization were similar in the groups (Table 2).

Analysis of circadian variation of acute myocardial infarction

In all study participants, the highest incidence of AMI was between 6.00 and 12.00 (Fig. 1); the odds ratio was 1.34 (95% CI 1.20 to 1.46, p <0.001). In the non-statin group, the highest incidence of AMI occurred between 00.00 A.M. and 06.00. There was still a peak incidence between 6.00 A.M. and noon in the receiving statin therapy group; the odds ratio was 1.61 (95% CI 1.34 to 1.80, p <0.001). Accordingly, there was no statistical difference between the statin and non-statin groups regarding circadian variation of AMI (Fig. 2).

Discussion

The present study confirmed that there was a circadian periodicity, with the highest rate of AMI between 00.00 A.M. and noon. However, prior usage of statin did not impact circadian periodicity of AMI.

Previous studies have reported that there is a circadian periodicity in the onset of AMI over a 24-hour period with peak event rates between 0.00 A.M. and noon, especially between 6.00 A.M. and noon (1, 9-11). Although morning peak of the onset of AMI is very common, especially western countries, several studies reported a secondary peak at noon (12, 13). Lunch is usually the main meal of the day in some countries including Turkey.
Pathologic studies have revealed that plaque rupture and subsequent thrombosis is one of the major causes of acute AMI (2, 16, 17). Therefore, the hypothesis that increased physiologic activities in the morning hours may trigger plaque disruption has been proposed (18). Confirming these reports, Tanaka et al. recently reported that the circadian variation of acute AMI was the result of a morning increase in the incidence of plaque rupture identified by intravascular ultrasound (19). Several physiological factors have been proposed in the morning increased incidence of plaque rupture accounts for the characteristic circadian rhythm of AMI, such as changes in catecholamine levels, an arterial pressure surge accompanied by an increased heart rate, increased vascular tone and impaired endothelial function (3, 20-23). During the plaque rupture, the contents of lipid core that from the most thrombogenic components of the plaque may be released into the lumen and participate the thrombosis cascade. Increased platelet aggregability and activity, increased blood viscosity, and the minimal level of fibrinolytic activity may further contribute to thrombosis in this setting during the morning hours. The efficacy of beta-blockers, aspirin and ACE inhibitors in preventing AMI supports the idea that these physiological factors may play an etiological role in plaque rupture and resultant thrombosis (24-26).

Statins influence critical pathways that regulate plaque stability and thrombosis, and these properties extend beyond LDL lowering. The spectrum of direct antiatherogenic properties of statins includes maintenance of endothelial function, anti-inflammatory actions. Furthermore, following plaque disruption, statin influence thrombosis through variable inhibitory actions on platelet aggregation and activation, coagulation factors and fibrinolysis (7). Based on these data, we sought that usage of statin could influence circadian variation of AMI. However, in the present study we found that prior usage of statin did not impact on circadian periodicity of AMI. These unexpected

**Figure 1.** Circadian periodicity in the onset of chest pain in all patients with AMI: harmonic regression models

AMIC - acute myocardial infarction

**Figure 2.** Comparison of the time of AMI onset within a 24-hour period in patients receiving and not receiving statin therapy: harmonic regression models

AMIC - acute myocardial infarction

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients receiving statin therapy (n=61)</th>
<th>Patients not receiving statin therapy (n=390)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiographic findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular EF, %</td>
<td>38.1±10.0</td>
<td>38.0±8.9</td>
<td>0.91</td>
</tr>
<tr>
<td>Mitral regurgitation, n (%)</td>
<td>41 (61)</td>
<td>194 (50)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mild, n (%)</td>
<td>22 (36)</td>
<td>117 (30)</td>
<td></td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>15 (25)</td>
<td>62 (16)</td>
<td></td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>4 (7)</td>
<td>15 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Angiographic findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of LMCA lesion, n (%)</td>
<td>6 (10)</td>
<td>10 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Two vessels disease, n (%)</td>
<td>16 (26)</td>
<td>125 (32)</td>
<td>0.26</td>
</tr>
<tr>
<td>Multi vessels disease, n (%)</td>
<td>19 (31)</td>
<td>89 (23)</td>
<td>0.34</td>
</tr>
<tr>
<td>Presence of LAD lesion, n (%)</td>
<td>42 (69)</td>
<td>243 (62)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Angiographic decision</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical treatment</td>
<td>13 (21)</td>
<td>74 (19)</td>
<td>0.33</td>
</tr>
<tr>
<td>PCI</td>
<td>25 (40)</td>
<td>179 (46)</td>
<td>0.39</td>
</tr>
<tr>
<td>CABG</td>
<td>23 (39)</td>
<td>137 (35)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure during hospitalization, n (%)</td>
<td>3 (5)</td>
<td>26 (7)</td>
<td>0.68</td>
</tr>
<tr>
<td>MACE during hospitalization, n (%)</td>
<td>8 (13)</td>
<td>51 (13)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values are means±SD or proportions (percentages)

*p*Mann-Whitney U and Chi-square tests

CABG - coronary artery by-pass graft surgery, EF - ejection fraction, LAD - left anterior descending artery, LMCA - left main coronary artery, MACE - major cardiac event, PCI - percutaneous coronary intervention

**Table 2.** Echocardiographic and angiographic findings of the study groups, and follow-up results

**Table 3.** Echocardiographic and angiographic findings of the study groups, and follow-up results

**Figure 3.** Comparison of the time of AMI onset within a 24-hour period in patients receiving and not receiving statin therapy: harmonic regression models

AMIC - acute myocardial infarction
results of the present study could be explained by existence of higher risk patients, especially diabetics, in statin group as opposed to non-statin group. Accordingly, it has been shown that the circadian morning peak of AMI symptom onset is attenuated in patients with type 1 or type 2 diabetes for 5 or more years, suggesting a role of autonomic dysfunction (27). In the present study, percentage of diabetes was also higher in statin group as compared to non-statin group.

Study limitations
The study was not a prospective and randomized clinical trial. Therefore, any unmeasured potential factors, which affects on the circadian periodicity of AMI and might be distributed unequally between two groups, might affect the results. There are some differences in demographic and clinical parameters. In order to overcome this problem, we used harmonic regression models to minimize the effects of confounding factors.

Conclusion
In conclusion, the present study showed that prior usage of statins did not influence the circadian variation of AMI.

Conflict of interest: None declared.

References