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Intensive atorvastatin improves endothelial function and decreases ADP-induced platelet aggregation in patients with STEMI undergoing primary PCI: A single-center randomized controlled trial

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ABSTRACT

Background: Intensive atorvastatin may be beneficial for patients with ST segment elevated myocardial infarction (STEMI). However, its effects on endothelial and residual platelet function remain uninvestigated in these patients.

Methods: This single-center single-blinded prospective randomized controlled trial included STEMI patients undergoing PCI, aiming to investigate the acute effects of intensive atorvastatin (40 mg) vs. standard atorvastatin (20 mg) on serum endothelin-1 (ET-1) and ADP-induced platelet clot strength (MA-ADP), which were measured before and after 7 days of atorvastatin treatment respectively. MA-ADP was measured by thromboelastography. The tolerance and safety of intensive atorvastatin therapy in these patients were also observed.

Results: A total of 120 patients (60 patients in the intensive group and 60 patients in the standard group) with STEMI, who are undergoing primary PCI, were included into this study (mean age, 63.5 years). Patients from these two groups were matched for baseline characteristics. Atorvastatin did not significantly affect the serum level of LDL-C or CRP in either the standard or intensive group. Furthermore, ET-1 did not significantly change following treatment with atorvastatin in the standard group. However, intensive treatment with atorvastatin significantly reduced ET-1 serum level (0.65 ± 0.38 pmol/L vs. 0.49 ± 0.21 pmol/L, $P < 0.05$) and achieved a greater reduction of MA-ADP (49.2 ± 12.1 vs. 38.4 ± 17.4 mm, $P < 0.05$). In addition, although not statistically significant, patients assigned to the intensive group appeared to suffer from less major adverse cardiovascular events.

Conclusions: Periprocedural intensive atorvastatin is associated with improved endothelial function and platelet inhibition, and is well-tolerated in STEMI patients undergoing PCI.

1. Introduction

Acute coronary syndrome (ACS) remains one of the most important causes of mortality and morbidity for people from both developed and developing countries [1]. ST segment elevated myocardial infarction (STEMI), characterized by the acute rupture of vulnerable plaque in the coronary artery and subsequent ischemic necrosis of the myocardium by acute coronary thrombosis, has been considered to be the most severe subtype of ACS [2]. Although emergent revascularization such as primary percutaneous coronary intervention (PCI) has been well recommended as the most effective treatment strategy for patients with STEMI, the prognosis for these patients still needs to be improved [3].

Previous evidence of clinical trials and observational studies have confirmed the potential benefits of statins, a class of medications for lowering low-density lipoprotein cholesterol (LDL-C), for the primary and secondary prevention of cardiovascular (CV) diseases [4]. Since relationships among elevated LDL-C levels and risks for coronary artery disease (CAD) and acute CV events have been well-established [5,6], subsequent clinical studies have indicated the potential benefits of intensive statin therapy, compared with moderate statin therapy, in patients with CAD [7,8]. For patients with ACS undergoing PCI, intensive statin therapy has also been associated with reduced risk of incidences of myocardial infarction (MI) and CV death [9,10]. However, potential mechanisms underlying the acute benefits of intensive statin therapy in patients with STEMI have not been exactly determined.

Endothelial function impairment is involved in the pathogenesis of ACS [11]. Endothelial dysfunction may cause contractions or even spasms in the coronary artery, which may lead to the deterioration of coronary blood flow [12]. Subsequent activated platelet and inflammatory responses may accelerate the pathologic process of myocardial ischemia [13]. Clinical evidence has also demonstrated that endothelial dysfunction may be a prognostic factor for patients with STEMI, and treatment strategies that target endothelial dysfunction may improve

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clinical outcomes in patients with STEMI [14–16]. Moreover, despite the application of standard antiplatelet medications, residual platelet aggregation has been well-recognized as a risk factor for the incidence of perioperative and long-term CV events for patients with STEMI undergoing primary PCI [17,18]. Previous studies have suggested the pleiotropic benefits of statins, despite its LDL-C lowering effect such as anti-inflammation, anti-oxidative, stabilization of venerable plaques, improvement of endothelial function, as well as the inhibition of platelet activation [19,20]. Therefore, we hypothesized that the benefits of the intensive treatment of atorvastatin, a potent statin, may be related to its effects on endothelial function and platelet aggregation. In this single blinded prospective randomized controlled trial (RCT), we evaluated the acute effects of periprocedural intensive atorvastatin therapy on endothelin-1 (ET-1) serum levels [15], a marker of endothelial dysfunction, and platelet aggregation, which was measured by thromboelastography (TEG), in patients with STEMI undergoing primary PCI. Moreover, the tolerance and safety of intensive atorvastatin therapy in these patients were also observed.

2. Methods

This study was designed as a single-center single-blinded prospective RCT. Patients with STEMI, who underwent primary PCI, were included in to this study. The acute effects of intensive atorvastatin on serum ET-1 and ADP-induced platelet clot strength (MA-ADP), which was measured by TEG within 7 days, were investigated and compared with standard atorvastatin. This study protocol was approved by the Ethics Review Board of Beijing Chaoyang Hospital, and written informed consent was obtained from all patients before they were enrolled into this study. This study was designed and performed in accordance with the rules for good clinical practice (GCP), and the study process was performed under the supervision of the GCP Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University.

2.1. Inclusion and exclusion criteria of the study patients

Patients who were diagnosed with STEMI, underwent primary PCI, and admitted to the Department of Cardiology of our hospital were included in the present study. STEMI was diagnosed based on the Chinese Guideline for the diagnosis and treatment of Acute STEMI in 2010 [21] and the American College of Cardiology (ACC) and the American Heart Association (AHA) STEMI Guidelines [22]. The determination and performance of primary PCI were conducted through the consensus of at least two attending interventional cardiology physicians, based on the recommendations of the Chinese Guidelines for PCI [23]. Patients who fulfill either of the following criteria were excluded from the present study: (1) patients with complications of cardiogenic shock or cardiac systolic dysfunction (left ventricular ejection fraction [LVEF] <40%, detected by echocardiography); (2) patients who have been taking statins prior to enrollment into this study; (3) patients with severe renal or hepatic dysfunction; (4) patients with confirmed diagnosis of malignant tumor; (5) patients who are allergic to contrast materials; (6) patients with comorbidities of skeletal muscular disease such as polymyositis; and (7) patients who are pregnant or in their lactation period. The enrollment of these study patients was performed from August 1, 2012 to February 29, 2014.

2.2. Randomization and assignment

Patients with STEMI were randomly assigned to the following groups using a computer generated random number: (1) standard group, in which the patients received 20 mg of atorvastatin per night from the day of primary PCI and 6 days after (for a total of 7 days); and (2) intensive group, in which the patients received 40 mg of atorvastatin per night from the day of primary PCI and 6 days after. Patients included in this study were blinded to the groupings. Other medications for STEMI such as aspirin, clopidogrel and low molecular weight heparin were administered in accordance with the recommendations of the Chinese Guidelines for STEMI and PCI [21,24]. The primary PCI process was performed in accordance with the recommendations of Chinese Guidelines and the judgment of PCI strategy; and perioperative medications (such as Tirofiban) were used, based on the consensus of at least two attending interventional cardiology physicians. Blood samples were obtained from each of the included patients for further analysis.

2.3. Measurement of serum endothelin-1 (ET-1)

ET-1 serum levels were measured before and 7 days after atorvastatin treatment by radioimmunoassay (RIA) using the Test Kit provided by the Northern Biotechnologic Institute (Beijing, China), according to manufacturer's instructions.

2.4. Platelet-fibrin clot strength measurement by thromboelastography

The strength of the platelet fibrin clot was analyzed using the TEG Hemostasis System (Haemoscope Corporation, Niles, IL, USA) before and 7 days after atorvastatin treatment, as previously described [25]. In brief, the blood clots were linked to a stationary pin suspended in an oscillating cup that contains the whole blood sample. The strength of the clot was measured through the amplitude of pin rotation. During the testing process, heparin is added to eliminate thrombin activity in the sample. Adenosine diphosphate (ADP) was used as an agonist for platelet aggregation, and was added to measure the contribution of P2Y12 receptor to clot formation. The TEG Hemostasis System automatically generated the maximum amplitude (MA) to reflect the platelet-fibrin clot strength. MA-ADP was applied, which was the ADP-induced clot strength used to measure the effect clopidogrel on platelet aggregation.

2.5. Follow-up outcomes

After the seven-day treatment with different dosages of atorvastatin, all patients were prescribed with 20 mg of atorvastatin for the secondary prevention of MI. Patients visited our clinic for further follow-up every month from the time of hospital discharge. Although this study was not designed to investigate clinical outcomes, the influence of different acute atorvastatin dosages in these patients on middle-term clinical outcomes were observed, including the incidences of unstable angina (UA), nonfatal MI, stent restenosis, stent thrombosis, repeat revascularization, stroke, CV death, and target lesion revascularizition (TLR). The definitions of the above outcomes and events were in accordance with previously published RCTs [26,27].

2.6. Statistical analyses

Continuous data were presented as mean ± standard deviation (SD), and categorical data were presented as numbers and frequencies. Each set of data was subjected to a normality distribution test. Differences of continuous and categorical data between these two groups were analyzed using student's t-test or chi-square analysis. Spearman correlation analysis was performed to evaluate the relationship between serum ET-1 and MA-ADP at 7 days after atorvastatin treatment in patients in the intensive group. Statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

3. Results

Overall, a total of 120 patients (60 patients randomized to the intensive group, and the remaining 60 patients randomized to the standard group) with STEMI, who underwent primary PCI, were included in our study. All patients above completed the seven-day acute treatment