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Original article

High versus low dose statin therapy in Indian patients with acute ST-segment elevation myocardial infarction undergoing thrombolysis

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ABSTRACT

Objectives: This study sought to compare high dose versus low dose statin therapy in Indian patients with ST-segment elevation myocardial infarction (STEMI) undergoing thrombolysis.
Background: Randomized trials have demonstrated that statin treatment reduced major adverse cardiac events (MACEs) in patients with stable angina pectoris and acute coronary syndrome. However, randomized studies of statin therapy in Indian patients with STEMI are scarce.
Methods: Of 1859 patients with acute STEMI, 1027 eligible patients were randomized to 80-mg (n = 512) or 10-mg (n = 515) atorvastatin. Primary end point was 30-day incidence of MACE (death from any cause, myocardial infarction, NSTE-ACS requiring readmission, ischemia driven revascularization, and stroke). Secondary end points included individual components of primary end point and ST-segment resolution at 90 min after thrombolysis.
Results: Two groups did not differ in primary endpoints of MACEs (8.79% in high dose vs 9.32% in low dose atorvastatin group, OR = 0.938, 95% CI = 0.612–1.436, P = 0.764). With 80 mg atorvastatin, there was insignificant reduction in rate of reinfarction, revascularization and death. Stroke and readmission for NSTE-ACS increased in 80 mg atrovastatin group, but was not statistically significant. ST-segment resolution was significantly higher in 80-mg atorvastatin arm (45.90% vs. 37.67%; p = 0.008). Myalgia was more in 80 mg statin group (18.06% vs 7.57%, p = 0.0001).
Conclusions: High-dose atorvastatin did not show significant difference of MACEs in STEMI patients undergoing thrombolysis but showed significant improvement in immediate coronary flow depicted by ST-segment resolution. This benefit of high dose statin is to be weighed against greater myalgia, drug discontinuation and cost in Indian patients.

1. Introduction

CAD burden in India is likely to increase exponentially due to changing lifestyle and urbanization of villages.1 Angiographic studies show that aggressive cholesterol reduction by a variety of methods, as opposed to dietary modifications alone, results in increased rates of plaque regression and stabilization.2 The results of the TNT and IDEAL trials established the important role for intensive statin therapy in the management of patients with stable CAD, and extend the observations from PROVE IT TIMI 22 in ACS patients to patients with stable disease.3–5 Atorvastatin 80 mg has been extensively used in management of ACS and stable CHD patients in the western world. Such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels. In the Indian context, there is limited data about usage of atorvastatin 80 mg either in ACS patients or stable CHD patients. This may be due to safety concerns of usage of higher dosage of statins in Indian patients.

2. Methods

2.1. Study population

It was a prospective double blind single centre study which included patients (18 years-70 years) admitted in coronary care unit from January 2014 to February 2015 with diagnosis of acute ST elevation myocardial infarction (STEMI) undergoing thrombolysis using fibrinolytic therapy after meticulous screening in the emergency department (ED). Patients with previous (within 3 months) or current treatment with statins; known allergy to heparin, aspirin, clopidogrel, active severe bleeding; pregnancy; history of major surgery or trauma; significant gastrointestinal or genitourinary bleeding (<6 weeks); history of cerebrovascular

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attack; and cardiogenic shock with mechanical ventilation, other contraindication to fibrinolytic therapy, suspected pulmonary thromboembolism, creatinine level of more than 2.0 mg per deciliter, obstructive hepatobiliary disease or other serious hepatic disease, known hypersensitivity to statin, chronic liver or muscle disease, history of treatment with drugs that are strong inhibitors of cytochrome P-450 3A4 within the month before randomization and those undergoing primary PCI were excluded from the study. Diagnosis was confirmed on the basis of ECG, serial CK-MB/troponin T measurements and echocardiography as per universal definition of myocardial infarction. STEMI was defined as a clinical syndrome with characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis. Diagnostic ST elevation in the absence of left ventricular (LV) hypertrophy or left bundle-branch block (LBBB) was defined as new ST elevation at the J point in at least 2 contiguous leads of $\geq$2 mm (0.2 mV) in men or $\geq$1.5 mm (0.15 mV) in women in leads V2–V3 and/or of $\geq$1 mm (0.1 mV) in other contiguous chest leads or the limb leads. New or presumably new LBBB at presentation, ST depression in $\geq$2 precordial leads (V1–V4) diagnostic of posterior wall STEMI; multilead ST depression with coexistent ST elevation in lead aVR were also included in STEMI group.[6]

2.2. Study protocol

All the patients received standard treatment for STEMI according to guidelines: thrombolytic therapy, heparin, nitrates, aspirin, clopidogrel, beta blockers, angiotensin converting enzyme inhibitor. Drugs with known or suspected interactions with statin were prohibited within five half-lives prior to inclusion and during the study.

2.3. Randomization

They were randomized in 1:1 manner using a table of randomized numbers containing double digits randomization codes (from 11 to 50) generated using computer program. Randomization codes were allotted to the enrolled patients by starting at random point in the table. Patients receiving code from 11 to 30 received low dose 10 mg atorvastatin (group A) and those with code from 31 to 50 received high dose 80 mg atorvastatin (group B). Randomization was performed at entry before starting any treatment. Adverse events were collected during the study period from selection to the end of follow-up at 30 days.

2.4. Endpoints

The primary end point was 30-day incidence of MACEs (death from any cause, myocardial infarction, documented Non ST elevation acute coronary syndrome [NSTE-ACS] requiring readmission, ischemia driven revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting, and stroke). Reinfarction within 18 h after initiation of fibrinolytic therapy should be based on recurrence of severe ischemic-type chest discomfort that lasts at least 30 min, usually but not always accompanied by recurrent ST-segment elevation of at least 0.1 mV in at least 2 contiguous ECG leads and re-elevation of CK-MB to more than the upper limit of normal or increased by at least 50% over the previous value and reaching at least >3 times the normal value, in association with ischemic symptoms. After 18 h, reinfarction was defined as new pathological Q waves or re-elevation of CK-MB to >3 times the normal value (24 h to discharge) or >2 times the normal value (after hospital discharge).[7] NSTE-ACS was defined as ischemic discomfort at rest for at least 10 min prompting rehospitalization, combined with one of the following: ST-segment or T-wave changes, cardiac-marker elevations that were above the upper limit of normal but did not meet the criteria for myocardial infarction, or a second episode of ischemic chest discomfort lasting more than 10 min and that was distinct from the episode that had prompted hospitalization. Secondary end points included individual components of the primary end point and ST-segment resolution at 90 min after thrombolysis.

2.5. Follow-up

A 30 days clinical follow-up was performed for all patients to evaluate MACEs (death from any cause, myocardial infarction, documented NSTE-ACS requiring readmission, ischemia driven revascularization and stroke.)

2.6. Statistical analysis

The statistical analysis was performed using IBM SPSS statistics version 20 (Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ SD, and categorical variables were presented as absolute number and proportion (%). Comparisons of categorical variables were made using the chi-square test and Fisher exact test, as indicated. Data were analyzed using the 2-tailed test to identify differences between groups and analysis of variance for repeated measures with Bonferroni correction for intragroup data. Nominal data were analyzed by the chi-square test. All efficacy analyses are based on the intention-to-treat principle. Event-free survival analysis was be analyzed by the Kaplan-Meier method with log-rank test group comparison. We considered 95% confidence intervals (CIs) that excluded unity, or, equivalently, $p < 0.05$, as statistically significant. Calculation of sample size was based on a 2-sample and 2-sided test. We assumed the incidence of MACEs might be similar between patients with STEMI treated with primary PCI or fibrinolytic therapy. Therefore, we calculated a sample size by analogy with the STATIN STEMI (Efficacy of High-Dose Atorvastatin Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction) study.[8] MACE in the STATIN STEMI study was 5.8% for high-dose (80-mg) atorvastatin arm versus 10.6% for conventional dose (10-mg) arm. Using a 2-sided alpha level of 0.05 and statistical power of 80%, we estimated the need for 511 patients in high-dose atorvastatin arm and 511patients in low dose arm, or a total of 1022 patients.

3. Results

Of 1859 patients with acute STEMI, 832 patients were excluded. Eligible patients (n = 1027) were randomized in 1:1 manner to 80-mg atorvastatin (n = 512) or 10-mg atorvastatin (n = 515) arms for pre-treatment before thrombolytic therapy and continued on the respective statin dose post thrombolysis (Fig. 1).

3.1. Baseline characteristics

Baseline demographic and clinical characteristics are displayed in Table 1. Mean age was 57.01 $\pm$10.65 years and 74.2% of the patients were men. Demographic characteristics did not differ significantly between the 2 groups. Mean left ventricular ejection fraction was 46 $\pm$ 8% in all patients and did not differ between the 2 groups. The pain-to-needle time and door-to-needle time were also not different between the 2 groups (4.9 $\pm$ 1.77 vs. 4.98 $\pm$ 1.88 h, P = 0.483 and 13.6 $\pm$ 4.76 min vs. 4.98 $\pm$ 1.88 min, P = 0.665, respectively). The proportion of patients taking medications after fibrinolysis was also similar between the 2 groups (Table 1). Peak CK-MB level was 243 $\pm$156 ng/dl in group A vs 253 $\pm$ 162 ng/dl in group B (P = 0.314).