Statins Reduce Incidence of Early Perioperative Complications and Length of in-Hospital Stay after Coronary Artery Bypass Graft Surgery

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Abstract

Background: Coronary artery bypass grafting (CABG) is associated with several perioperative complications that may significantly prolong length of in-hospital stay, increase costs and provide worse long term outcome. The 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, or statins, exert anti-inflammatory and vascular protective effects. We hypothesized that pre-operative statin therapy may reduce incidence of early perioperative complications and length of in-hospital stay following CABG.

Methods: We retrospectively enrolled 103 patients (age 67±3; 18 females), who underwent CABG. Patients were allocated into 2 groups: 57 patients on statin therapy prior to CABG (St Group) and 46 patients not on statin therapy (n-St group). Demographic and clinical features, pre-operative medications use and the incidence of early adverse postoperative events were collected. Pre-operative risk of death using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) was also calculated. The primary end-point was the composite of early complications occurring after surgery, including infections, bleedings, sustained ventricular and supra-ventricular tachyarrhythmias, cardiogenic shock, myocardial infarction and mortality. As secondary end-points single perioperative complications were considered. In-hospital stay length was also evaluated.

Results: Clinical features, cholesterol levels and EuroSCORE were similar between two groups. Statin therapy and EuroSCORE emerged as predictors of the composite adverse outcome. n-St patients had a significant higher rate of early complications if compared with St patients: the primary endpoint occurred in 18 St patients (31%) versus 25 (54%) n-St patients (p=0.019). Multivariate analysis confirmed pre-operative statin therapy and EuroSCORE as independent predictors of the primary endpoint (OR=0.307, 95% CI=0.123-0.766, p=0.011 and OR= 2.114, 95% CI= 1.213-4.407, p= 0.002 respectively) showing a protective role of the statin therapy.

The incidence of secondary end-points did not differ significantly between the groups, while in-hospital stay was longer in n-St group if compared with St group (7.7±3.9 days vs 5.6±1.8 days; p=0.001).

Conclusion: Our data suggest that statin therapy may reduce early perioperative complications after coronary artery bypass grafting. This effect is independent from cholesterol basal levels, thus supporting pre-operative statin use in patients undergoing CABG.

Keywords: Statins; CABG; Prevention

Abbreviations: CABG: Coronary Artery Bypass Grafting; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; MI: Myocardial Infarction; ICU: Intensive Care Unit; EuroSCORE: European System for Cardiac Operative Risk Evaluation; UTI: Urinary Tract Infection; BP: Blood Pressure; LBBB: Left Bundle Branch Block; CPR: C-Reactive Protein; SAA: Serum Amyloid A

Introduction

Despite the improvements in the surgical technologies, coronary artery bypass grafting (CABG) associated mortality is a considerable medical and socioeconomic problem, with estimates ranging as high as 2% to 4%. Moreover, perioperative major cardiovascular events including myocardial infarction (MI), major bleeding, atrial fibrillation, stroke, renal failure, infections, need for inotropic support may significantly prolong length of stay in Intensive Care Unit (ICU) with increased costs and severe long term complications [1].

Statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzym A reductase, are powerful inhibitors of cholesterol biosynthesis. Beyond their lipid-lowering actions, statins are known to exert multiple pleiotropic effects including improvement of endothelial function, plaque stabilization, decrease of inflammatory markers, and attenuation of myocardial ischaemia-reperfusion injury that can offer direct organ protection and contribute to improve clinical outcome in the early postoperative course [2-4].

Long-term lipid-lowering therapy with statins prevents progression of atherosclerotic coronary artery and vein graft disease [5]. Statins were found to be associated with a reduced incidence of perioperative mortality in patients undergoing major non-cardiac vascular surgery [6,7]. However, in patients undergoing cardiac surgery results are conflicting [8-12].

Powell et al observed that in patients undergoing first-time isolated CABG, pre-operative use of lipid-lowering therapy was associated with improved survival to hospital discharge [8]. Retrospective cohort studies, moreover, showed that statins pre-operative therapy was associated with a significant reduction in the risk of 30-day mortality.
and morbidity [9-10]. On the other hand, large observational studies failed to demonstrated a beneficial effect of pre-operative statin use on in-hospital mortality or major morbidity following cardiac surgery [11,12].

In view of the limited clarity of available data, we conducted an observational retrospective cohort study of consecutive patients undergoing primary CABG surgery to determine if statins could reduce early post-CABG mortality and decrease the incidence of major postoperative adverse events in ICU (Figure 1).

Materials and Methods

Study design

A retrospective cohort study of all consecutive patients (age 67±3; 18 females) undergoing primary isolated on-pump CABG surgery from January 1, 2008, to April 30, 2008 at our Institution was performed. Patients with history of atrial arrhythmias (atrial flutter, fibrillation, and supraventricular tachycardia) as well as combined CABG and valve or other cardiac surgery (eg, atrial septal defect repair, ventricular aneurysm resection) were excluded from the analysis. Patients were classified into 2 groups: patients receiving pre-operative lipid-lowering therapy and patients not receiving pre-operative lipid-lowering therapy at admission. Patients were considered as taking statins if on treatment with this class of drugs continuously from at least 1 month before CABG surgery. Commercially available statins screened for in this study included simvastatin, atorvastatin, and rosuvastatin.

Data collection

Patients' demographic variables, pre-operative risk factors, co-morbid conditions, pre-operative medications use (including statin therapy, ACE-inhibitors, β-blockers and aspirin) and the incidence of adverse perioperative events, in the first 7 post-CABG days, were collected.

For each patient, the pre-operative risk of death using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [13] was also calculated.

The primary end-point was the composite of early complications occurring after surgery during stay in ICU and in Sub-Intensive Care Unit. Measured adverse outcomes included: postoperative infections; reoperation for bleedings; sustained ventricular and supra-ventricular tachyarrhythmias requiring medical treatment or DC shock, including atrial fibrillation; cardiogenic shock needing inotropic support; Myocardial Infarction (MI) and mortality. A diagnosis of postoperative infection was made if one of the following occurred: pneumonia, deep sternal wound infection, sepsis, Urinary Tract Infection (UTI) with bacteremia. A diagnosis of cardiogenic shock was made if systolic blood pressure (BP) was < 70 mmHg or cardiac index was < 2.2 L/min/m², needing for inotropic support (including Intra-Aortic Balloon Pump counterpulsation, adrenaline or dobutamine infusion). According to current guidelines, a diagnosis of MI was made if there was elevation of troponin greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium [14]. As secondary end-points single perioperative complications were considered. In-hospital stay duration was also evaluated.

Statistical analysis

According to current literature [15], for sample size calculation we hypothesized a 20% risk reduction of composite adverse outcome in patients on statin therapy. On the basis of a mean number of 150 isolated CABG interventions performed in our Cardiac Surgery ward in a four-months period, we calculated a sample size of about 50 patients for each subgroup in order to detect a statistically significant difference between the two groups with a 95% power and a type I error of 0.05. Comparison among groups for discrete categorical variables was carried out by determining chi² statistic, using Fisher's exact test as appropriate. Continuous variables not normally distributed were presented as median and interquartile range (IQR) and compared by Mann-Whitney U-test. Predictors of combined outcome were assessed using a stepwise multivariate logistic regression model to estimate the odds ratio (OR) and corresponding 95% confidence interval (95% CI). Univariate analysis was performed including demographic variables, cardiovascular risk factors and relevant co-morbidities, known to be related to adverse outcome on the basis of current evidence. Variables showing statistical differences at p≤0.20 were included into a multivariate backward binary logistic regression model. Finally p < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 software (SPSS Inc, Chicago, IL, USA).
Results

A total of 150 patients undergoing primary on-pump CABG surgery were screened. According to the prespecified exclusion criteria, 22 patients were excluded for concomitant valve surgery and 25 for history of atrial arrhythmias. We finally enrolled 103 consecutive patients (age 67±3; 18 females), classified into 2 groups: patients
receiving pre-operative lipid-lowering therapy (St, n=57, 55%) and patients not receiving pre-operative lipid-lowering therapy (n-St, n=46, 45%) on admission. The pre-operative characteristics of study population are summarized in Table 1. Among St Patients, 27 were on atorvastatin (mean dose 11, 42 mg/day), 27 on simvastatin (16.66 mg/day) and 3 on rosuvastatin (mean dose 5 mg/day). No significantly statistical differences were observed between groups with respect to age, gender, presence of diabetes, history of myocardial infarction, smoke habit, hypertension, presence of three-vessel disease, cerebrovascular and pulmonary disease, renal failure, and EuroSCORE. Only a higher prevalence of family history of coronary artery disease was observed in St group. Of note, the cholesterol levels were similar between St- and n-St patients (Figure 2).

At univariate analysis, only statin therapy and EuroSCORE emerged as predictors of the composite adverse outcome. Age, presence of three vessels disease and history of pulmonary disease showed a weak trend for statistical significance.

Multivariate analysis confirmed pre-operative statin therapy and EuroSCORE as independent predictors of the primary endpoint (OR=0.307, 95% CI=0.123-0.766, p=0.011 and OR= 2.114, 95% CI= 1.213- 4.407, p= 0.002 respectively) (Table 2). n-St patients had a significant higher rate of early complications if compared with St patients: the primary endpoint occurred in 18 St patients (31%) versus 25 (54%) non-St patients (p=0.019) (Table 3). The incidence of secondary end-points did not differ significantly between the groups. Of note, in-hospital stay was longer in n-St group if compared with St group (7.7±3.9 days vs 5.6±1.8 days; p=0.001).

Discussion

Despite progress in surgical techniques, cardiac surgical morbidity and mortality is still a problem of significant medical and socioeconomic significance. Our study suggests that pre-operative statin therapy may reduce the occurrence of perioperative adverse events after CABG.

We studied retrospectively a population of 103 patients, all of whom had undergone primary CABG surgery, of whom 57 on statin therapy (St group) and 46 not (n-St group). In our population, pre-operative statin therapy and EuroSCORE emerged as the only predictors of early post-CABG complications and of in-hospital stay duration. Of note, pre-operative statin therapy had a beneficial effect on outcome which was independent of cholesterol levels.

Statins exert their primary effect on cholesterol metabolism reducing cholesterol levels. Long-term statin administration in ambulatory patient populations with hypercholesterolemia has been previously associated with a reduced risk of adverse cardiovascular events, including death, MI, stroke, and renal dysfunction [16]. Furthermore, many randomized clinical trials have shown a beneficial effect of long-term statin administration in primary and secondary prevention of adverse cardiovascular outcomes even in patients with mild hypercholesterolemia and with normal total and low-density lipoprotein cholesterol levels [17,18]. All these data strongly support the use of statins for primary and secondary prevention of coronary artery disease, as recommended by current guidelines.

Moreover, statin therapy has been shown to exert an early beneficial effect on outcome in patients undergoing percutaneous coronary interventions [19-21].

Recent evidence suggests that pre-operative statin therapy in patients undergoing non-cardiac surgery improves the post-operative outcome by reducing adverse cardiovascular events and all-cause mortality [6,7]. However, in patients undergoing cardiac surgery, results are conflicting.

Some studies failed to show a beneficial effect of statins on perioperative adverse events after CABG, while others suggest that pre-operative statin therapy may reduce the occurrence of these end-points [8-12].

Our data are largely consistent with those of recently published meta-analysis [15,22] on the topic, that have demonstrated a substantial improvement in early clinical outcome for statin pre-treated patients undergoing cardiac surgery, in particular reducing the short-term mortality and the incidence of atrial fibrillation and stroke.

Although the exact mechanisms linking pre-operative statin therapy with reduced cardiac surgical mortality are unclear in the present study, we can hypothesize that this finding may be due, more than to their lipid lowering effect, to their pleiotropic, anti-inflammatory effects. A significant increase in inflammatory markers, including C-reactive protein (CRP), serum amyloid A (SAA), TNF-α, IL-6, has been shown during by-pass circulation, suggesting an activation of inflammation during the procedure [23]. Furthermore, statins have consistently been demonstrated to decrease inflammation in both in vitro and in vivo. Statins have been shown to be protective against tissue injury in multiple models of ischemia/reperfusion, including heart, lung, brain, kidney, and gut. In patients with acute coronary syndromes or idiopathic dilated cardiomyopathy, statin therapy has been shown to reduce serum inflammatory marker levels, including CRP, SAA, tumor necrosis factor-α, interleukin-6, and brain natriuretic peptide [24-26]. Indeed, data from JUPITER trial [27] suggest that in apparently healthy subjects, CRP screening might be an effective method to identify subjects who are more or less likely to benefit from statin therapy for cardiovascular risk reduction, regardless of cholesterol levels. Taken together these findings may represent the theoretical framework for the reduction in perioperative complications observed in our study.

Our study has several limitations. First of all, it is an observational retrospective study, with inability to control all confounding factors such dosage of statin therapy. Second, the small sample size probably influenced the results concerning the secondary end-points. Third, we can only speculate about the mechanism underlying the beneficial effect of statins; it might be due to their inflammatory properties but we failed to collect blood samples to measure inflammatory biomarkers levels in order to assess differences between groups.

Conclusions

Our study, despite the limitations discussed above, demonstrates that statin therapy may reduce early perioperative complications after CABG and that this effect is independent from cholesterol levels, thus supporting pre-operative statin use in patients undergoing CABG. However, larger prospective studies are needed to investigate this important and interesting topic.

References


