International Journal of Research in Medical Sciences
Dhaulta P et al. Int J Res Med Sci. 2019 Jun;7(6):2078-2083
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20192155

Original Research Article

Inflammation modulatory effect of perioperative high-dose statin in prevention of post-operative atrial fibrillation in patients undergoing coronary artery bypass grafting

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Received: 27 April 2019
Accepted: 14 May 2019

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ABSTRACT

Background: Atrial fibrillation (AF) is one of the most common complications after coronary artery bypass grafting (CABG), occurring in 20% to 40% of patients. Statins exert pleiotropic effects which are largely independent from their lipid-lowering properties. The objective of this study was based on to affirm the evidence that perioperative statins have a significant role in preventing early postoperative AF in patients undergoing CABG.
Methods: A prospective, randomized, cohort study of all consecutive patients who underwent primary isolated on pump CABG surgery was performed. Patients were divided into two groups -statin and non-statin groups - to examine the influence of statins on early postoperative prevention of AF.
Results: In total, 127 patients who underwent isolated CABG were included in the study and were analysed. There were no significant differences in age, gender, history of cardiac infarction, concomitant diseases (hypertension, smoking, PPCI, hyperlipidaemia), cardiac functional grading (NYHA III-IV), electro- cardiograms, and preoperative medication. There were no significant differences in the average number of grafts where the left internal mammary artery was used as a bypass conduit, the surgical procedure or total cardiopulmonary bypass time, or aortic cross-clamping (ACC) time. In addition, there were no significant differences in the postoperative mechanical ventilation duration time, length of ICU stays or length of hospitalization between the two groups. The incidence of AF following CABG in the statin group was significantly lower than that in the non-statin group.
Conclusions: Oral atorvastatin 40 mg/d, initiated at least 1 week before the scheduled CABG and continued in the early postoperative period, significantly decreases the risk of post-operative AF.

Keywords: Atorvastatin, Atrial fibrillation, Coronary artery bypass grafting, Statin

INTRODUCTION

Coronary artery bypass grafting (CABG) is one of the landmark cardiac surgery that rescued millions of people afflicted by coronary artery disease (CAD). It has been shown to be an effective therapy for prolonging life and decreasing symptoms in appropriately selected patients with CAD.[1,2] Atrial fibrillation (AF) is one of the most common complications after CABG.[3-6] Although this arrhythmia is usually benign and self-limiting, it may result in hemodynamic instability and increases the risk of congestive heart failure (CHF), longer ICU stays and longer hospital stay, hence increased healthcare costs.[4-6]

AF following CABG is also a risk factor for post-operative thromboembolic event like stroke.[7]

One of the possible patho-physiological mechanisms highlighted behind AF is inflammation, which, in return, causes atrial structural remodeling. In conditions such as post-surgery, ischemic heart disease or myocarditis, pronounced inflammatory response takes place.[8-10] It was shown in recent meta-analysis, that the level of C-reactive protein (CRP) is connected to AF recurrence.[11] AF is also connected to cellular calcium overload in atrial myocites.[12] Several studies showed a possible interplay between increased intracellular calcium concentration and inflammatory molecules such as CRP, C3 and C4 and components of the complement system C3 and C4. Other possible mechanism highlighted in the pathophysiology of AF is involvement of increased renin-angiotensin-aldosterone (RAAS) activation in atrial structural remodeling and involvement of reactive oxygen species.[13]

Statins, in addition to its lipid lowering action, exerts pleiotropic effects, which are largely independent from their lipid-lowering properties. Reported effects include: decreased levels of high-sensitivity CRP (hs-CRP), decreased plaque area in coronary arteries, reduced number of cardiac events after CABG, myocardial protective effects after ischemic reperfusion injury, AF preventive effects after CABG.[14] Keeping all this in view the present study was conducted to affirm the evidence that perioperative statins has a significant role in preventing early postoperative AF in patients undergoing CABG.

METHODS

This study was performed at a tertiary care center in North India. A prospective, randomized, cohort study of all consecutive patients undergoing primary isolated on pump CABG surgery. Study was conducted from 1st May 2017 to 31st December 2018.

Inclusion criteria

- Patients were divided into two groups to examine the influence of statins on early postoperative prevention of AF.
- Group A (Statin group, n=68) included patients in which statin therapy was started from first postoperative day,
- Group B (Non-statin, n= 59) included patients in which statins were not started in immediate post-operative period.

All patients received pre-operative lipid-lowering therapy continuously from at least 10 days before CABG surgery. In addition, patients with in two groups were studied to determine the independent predictors for postoperative AF. Commercially available statins screened for in this study included atorvastatin 40mg OD.

Exclusion criteria

- Patients with history of atrial arrhythmias (atrial flutter, fibrillation, and supraventricular tachycardia),
- Combined CABG and valve or other cardiac surgery (eg, atrial septal defect repair, ventricular aneurysm resection),
- Patient not willing to participate in the study.

Study methods

Patients' demographic variables, pre-operative risk factors, comorbid conditions, pre-operative medications use (including statin therapy, ACE-inhibitors, β-blockers and aspirin) and the incidence of adverse perioperative events, in the first 5 post-CABG days, was be collected. Clinical data including the data of physical examinations, laboratory investigations on all included patients were obtained during their hospital treatment in pre and postoperative periods. The time-dependent change of CRP levels and TLC count was be recorded preoperatively and on 1st 2nd 3rd 4th and 5th postoperative days. CRP was measured by the immunoturbidimetric assay with a detection limit of 0.06mg/L. All patients underwent preoperative electrocardiography (ECG), and selective coronary angiography examination. All patients signed a consent form before operation. All surgeries were performed through a median sternotomy using either an on-pump or off-pump technique. Cardiopulmonary bypass (CPB) was conducted using ascending aortic cannulation and bicaval cannulation or retrograde cannulation accordingly, mild hypothermia (32°C), and using cold blood cardioplegic arrest.

Study endpoint

Post-operative atrial fibrillation (POAF) event after CABG was the endpoint of the study. AF episode occurring in the 5-day period after CABG was defined as a POAF event. In accordance to the treatment protocol, all patients were kept under 24 hours bedside ECG and blood pressure (BP) monitoring for the first 72 hours after the surgery. After 72 hours following the surgery, ECG was used every day until the day of discharge from the ICU.

Statistical analysis

Data was entered in Microsoft excel spread sheet and cleaned for errors and was analyzed using SPSS software version 20.0. Quantitative variables were described in mean and standard deviation. Qualitative variables as frequencies and percentages.

Fisher's exact/chi-square test was used to check the association between qualitative variables. Independent t-test was used to compare means of qualitative variables between different groups. A two-sided p-value<0.05 was considered as statistically significant.

RESULTS

Baseline characteristics

A total of 147 patients underwent CABG during the study period but fourteen patients with preoperative AF and 6 patients with concomitant valve surgery were excluded from this study. Thus, 127 patients who underwent isolated CABG were included in the study and were analyzed. Table 1 describes baseline characteristics in two groups.

Table 1: Baseline characteristics.

Parameters	Group A (statin)	Group B (Non-statin)	P-value
Age	56.97±7	56.68±8	0.37
Smoking	57 (83.8%)	48 (81.4%)	0.815
Hypertension	57 (83.8%)	47 (79.7%)	0.646
Diabetes mellitus	18 (26.5%)	7 (11.8%)	0.034
PPCI	14(20.6%)	17(28.8%)	0.307
NYHA > III-IV	6(8.8%)	4 (6.8%)	0.75
PRE MI	18 (26.5%)	17 (28.8%)	0.461
Calcium channel blocker	12 (17.6%)	7 (11.9%)	0.255
Angiotensin receptor blockers	10 (14.7%)	15 (25.4%)	0.179
Beta blocker	68 (53.5%)	59 (46.5%)	-
LVED	46.19	46.76	0.703
LVES	31.66	32.85	0.506
EF	56.9	53.42	0.163
CHL	144.75	140.6	0.684
TG	158.96	146.86	0.302

Preoperative and perioperative variables

Preoperative and perioperative variables included older age (age over 65), gender, diabetes, hypertension, hypercholesterolemia, smoking recent myocardial infarction, chronic obstructive pulmonary disease (COPD), previous percutaneous coronary intervention (PCI), preoperative congenital heart failure (NYHA class III or IV), left ventricular ejection fraction (LVEF) >0.5, left atrial diameter >45mm, left ventricle diameter >55 mm, left main disease, multivessel coronary artery disease, preoperative administration of oral atorvastatin, β-blockers, calcium antagonists, and angiotensin-converting enzyme inhibitors (ACEI), postoperative CRP levels above the median value, post-operative TLC values. In present study it was observed that there were no significant differences in age, gender, history of cardiac infarction, concomitant diseases (hypertension, smoking, PPCI, hyperlipidemia), cardiac functional grading (NYHA III-IV), ECG, and preoperative medication. The perioperative characteristics of the two groups are shown in Table 2. There were no significant differences in the average number of grafts where the left internal mammary artery was used as a bypass conduit, the surgical procedure or total cardiopulmonary bypass time, or aortic cross-clamping (ACC) time. In addition, there were no significant differences in the postoperative mechanical ventilation duration time, length of ICU stays, or length of hospitalization between the two groups.

Table 2: Perioperative characteristics in two groups.

Perioperative characteristics	Group A (Statin)	Group B (Non-statin)	P-value
CPB time	2.31	3.1	0.267
X-clamp time	1.34	1.81	0.301
Number of grafts ≥4	36 (52.9%)	38 (64.4%)	0.228

Postoperative atrial fibrillation

As shown in Table 3, there were 7 (5.5%) cases with atrial fibrillation. The incidence of atrial fibrillation following CABG in the statin group was significantly lower than that in the non-statin group (1.5% versus 10.2%, P =0.049).

Table3: Incidence of postoperative atrial fibrillation in the two groups.

Groups	AF		Total
	Yes	No	
Statin	1 (1.5%)	67 (98.5%)	68
Non-statin	6 (10.2%)	53 (89.8%)	59
Total	7	120	127

Time course of changes in serum CRP levels

Baseline CRP levels (preoperative CRP levels) were not different between the two groups (1.768 mg/L in the statin group versus 1.658 mg/L in the control group, P = 0.0632). CRP levels increased sharply after operation, reaching a peak within 3 days, followed by a slow decline (Table 4). CRP levels in the statin group at various observation points after surgery were significantly lower on 3rd 4th and 5th post-operative days than those in the control group. Mean peak CRP level following CABG in the statin group was significantly lower than that in the non-statin group (178.89±24.3 mg/L versus 217.55±32.5 mg/L, P <0.0001). Patients with postoperative AF had significantly higher peak CRP levels than those without AF (251.14±29.1mg/L versus 193.61±19.6mg/L respectively, P<0.0001).

DISCUSSION

AF always remains a major concern among patients undergoing CABG, it occurs in 20% to 40% of patients with the arrhythmia usually occurring between the second and fourth postoperative days with peak incidence on second postoperative.[3-6] Prevention or minimization of new-onset AF after cardiac surgery either

pharmacologically or non-pharmacologically is a reasonable goal for patients undergoing CABG. Its proportions represent a significant burden to healthcare systems and efforts have been made to reduce AF occurrence along with its consequences. In this regard, there is a growing amount of evidence which suggests that, beside conventional antiarrhythmic treatment, therapies aiming at the reversal of atrial tissue derangement could be of some benefit. The main focus is oriented towards drugs such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), polyunsaturated fatty acids and statins. However, these so-called 'upstream therapies' act through different mechanisms, so their antiarrhythmic properties largely differ. From the accumulation of clinical and experimental data it is now clear that the effect of these drugs depends heavily on the clinical background in which AF occurs.[15]

Table 4: Time course of changes in serum CRP levels.

Time course	Statin	Non-statin	P-value	AF	Non-AF	P-value
Pre-op CRP	1.7685	1.6586	0.50	1.86	1.68	0.632
1st day	167.031	172.903	0.569	212.43	167.26	0.044
2nd day	244.065	257.075	0.206	323.43	245.72	<0.01
3rd day	209.535	264.71	<0.01	300.43	231.31	<0.01
4th day	155.616	219.002	<0.01	243.57	181.58	0.013
5th day	118.22	174.09	<0.01	175.86	142.18	0.096
Mean	178.893	217.556		251.14	193.61	

Statins have anti-inflammatory, antioxidant, coronary plaque regressive and antiarrhythmic effects and also play a role in extracellular matrix modulation. They also modulate inflammation, act on endothelial function and interfere with coagulation.[16-20] They interfere with the activation of matrix metalloproteinase (MMPs) and hence with the progression of tissue derangement and fibrosis.[15] They modulate the renin-angiotensin-aldosterone system, probably via the reduction of oxidized LDLs.[21] The other possible mechanism by which statins can affect AF is through modulation of membrane protein receptors. The net effect of this is the alteration of transmembrane ion conductance and thus reduction of ectopic atrial activity.[20] All these concepts, however, suggest, that the antiarrhythmic effect of these drugs tends to be more pronounced in already damaged atrial tissue, such as in patients with coronary disease, after cardiac surgery or in heart failure and especially in patients with diagnosed AF.

In clinical studies, statins were considered effective in preventing AF after cardiac surgery, in patients with CAD, and in patients with left ventricular dysfunction.[22] Statins are known to lower the levels of acute-phase proteins independently of their effects on cholesterol.[22] Also, the antifibrotic effects, modulation of matrix metalloproteinases, interaction with peroxisome receptors that regulate proliferation, and endothelial nitric oxide synthase protect atrial myocardium during ischemia. For these reasons, statins may be able to decelerate or even reverse structural remodeling in patients with AF. It would thus seem intuitive to suppose that if AF is indeed linked to inflammation, then statins would offer a potentially preventative role in AF. Therefore, statin therapy may provide an effective treatment strategy for AF because of its potent anti-inflammatory and antioxidant properties.

In present study, statin therapy was started in the preoperative period or the patients were already receiving statin therapy preoperatively. With the fact that, there are more patients undergoing CABG very early after coronary angiography and patients being already on medical management including statins, in this study, impact of statin therapy was assessed in the immediate early postoperative period. It was observed that, statin reduced the risk of postoperative AF, with an incidence of 1.5% in the statin group versus 10.2% in the non-statin group, which is statistically significant. Most of the data for the primary prevention of AF comes from retrospective and observational studies or studies that were primarily designed for different end points. In a large registry examining the patients with left ventricular dysfunction, lipid-lowering agents, which were mainly statins, reduced AF prevalence for a relative risk of 31% compared to patients not taking lipid lowering agents. The effect was larger than the effect of RAAS inhibitors or beta blockers and was largely independent of the lipid-lowering effect of the drugs.[23] For the GISSI-HF trial, patients were randomly assigned to treatment with statins or a placebo. During 3.7 years of follow-up, AF was reported in 13.9% of the statin group and in 16% of the placebo group, after adjustment for other covariates it became significant ($p = 0.038$).[24]

Several retrospective studies have shown the beneficial effect of statin therapy in patients after cardiac surgery.[25-28] Randomized control trials (RCT) have also given promising results. The ARMYDA-3 trial showed significant reduction of in-hospital AF in patients treated

with atorvastatin compared to a placebo.[29] Another study in which patients were randomly assigned to atorvastatin or placebo prior to CABG also showed significant reduction in postoperative AF.[30] Recently published meta-analysis of RCTs also supports the role of statins in this clinical setting, showing a significant reduction of postoperative AF occurrence, when compared with the control (19% vs. 35.6%, p<0.0001).[31] In another retrospective study, Sakamoto et al. evaluated the effects of statins on postoperative AF in 203 patients (77 of whom received preoperative statins) who underwent isolated CABG. They concluded that preoperative statin treatment reduced the risk of postoperative AF by 67%, with an incidence of 16% in the statin group versus 33% in the non-statin group.[32] Kourliouros A et al, reported in a retrospective study of 680 patients who underwent CABG surgery and/or aortic valve replacement that statin treatment reduces the incidence of AF after cardiac surgery. Higher-dose statins have the greatest preventative effect.[33] Subramaniam K et al, in an observational cohort study of 2,497 adult patients who underwent isolated CABG with statin therapy vs. no statins therapy groups concluded that preoperative statin intake did not reduced the frequency of major perioperative morbid events after isolated CABG.[34]

CRP is a marker of systemic inflammation in clinical settings.[22,35,36] In this study, the postoperative mean peak CRP level was higher in patients who developed postoperative atrial fibrillation. This study further confirmed the importance of inflammation in the development of atrial fibrillation following CABG. Preoperative CRP levels (baseline CRP levels) were not different between the two groups, but the post- operative peak CRP level in the statin group was significantly lower than that in the control group, which suggested early post-operative administration of oral atorvastatin reduced inflammatory reactions caused by surgical trauma. This study showed atorvastatin may reduce the risk of atrial fibrillation following CABG through reductions in inflammation. However, the incidence of AF was much lower in present study in comparison to the literature, possible explanation to this could be because all the patients included in present study were already taking oral statins prior to surgery.

CONCLUSION

The present study showed a statistically significant decrease in postoperative new-onset AF and a significant decrease in CRP levels in patients undergoing isolated CABG. Thus, preoperative administration of oral atorvastatin 40 mg/d, initiated at least 1 week before the scheduled coronary artery bypass grafting with cardiopulmonary bypass and continued in the early postoperative period, may significantly decreases early postoperative atrial fibrillation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Dhaulta P, Panwar V. Inflammation modulatory effect of perioperative high-dose statin in prevention of post-operative atrial fibrillation in patients undergoing coronary artery bypass grafting. Int J Res Med Sci 2019;7:2078-83.