Low-dose Versus High-dose Statin Therapy for Prevention of Post-operative Atrial Fibrillation in Off-pump Coronary Artery Bypass Grafting - A Prospective, Randomized, Control Trial

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Abstract

Background: Statins are commonly used medications during a post-operative period for off-pump coronary artery bypass grafting cases. American College of Cardiology/American Heart Association guidelines specifically address the issue with recommending use of post-operative statin. However, do not mention specific dosages. The role for prevention of long-term mortality secondary to cardiovascular events is well studied, though dosages are unclear. We tried to address this issue looking specifically whether low-dose or high-dose statins are useful for prevention of post-operative atrial fibrillation (AF).

Aims and Objectives: To assess the impact of the use of low-dose versus high-dose statin for prevention of AF in immediate post-operative period in patients undergoing off-pump coronary artery bypass grafting.

Materials and Methods: This was prospective, randomized, control trial conducted for 1 year between tertiary care cardiac surgical units. A total 120 patients were enrolled in the study; both the groups received similar pre-operative medications. Intraoperative patients were randomized to receive low-dose (20 mg) versus high-dose (80 mg) atorvastatin. From second post-operative day, the same dose was continued until the end of the 1st month. The primary outcome variable was the incidence of post-operative AF. Secondary outcome variables were major adverse cardiac and cerebrovascular events and persistence of AF at 1 month.

Result: A total of 120 patients included in the study. Demographic profile and risk factors were similar in both the groups. Post-operative AF was observed in 2 patients in Group A and 3 patients in Group B with non-significant P values. Major cardiac adverse effects were observed in 1 patient in each group. While no patient continued to have post-operative AF at the 1st month follow-up.

Conclusion: Both low-dose and high-dose statins are equally effective in treating post-operative AF.

Key words: Atorvastatin, Atrial fibrillation, Low dose, Off-pump coronary artery bypass grafting, Statins

INTRODUCTION

Atrial fibrillation (AF) is one of the types of supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with ensuing worsening of cardiac function. Post-operative AF (POAF) is more common than before due to the greater than before number of cardiac surgeries being performed in Indian patients. This consecutively is associated with an increased incidence of post-operative complications, length of hospital stay, and later increase in the cost of hospitalization. Therefore, preventing and/or minimizing AF by pharmacological or non-pharmacological means is a reasonable objective.1,2 AF has been reported in up to 5-40% of patients in the early post-operative period following coronary artery bypass graft (CABG).3,4 AF worsens patient’s hemodynamic status and increases the risk of congestive heart failure, embolic events, and longer Intensive Care Unit stays.
Statins are highly effective in lowering serum cholesterol concentrations through 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibition and thus are vital to the primary and secondary prevention of cardiovascular disease. More than 50% of patients undergoing major vascular surgery and 80% undergoing cardiac surgery are on chronic statin therapy. Statins also exert numerous lipid-independent or “pleiotropic” effects that were not expected during drug development due to their ability to inhibit the inflammatory response, reduce thrombosis, enhance fibrinolysis, decrease platelet reactivity, inhibit cell growth, reduce ischemia-reperfusion injury, and restore endothelial function. These beneficial effects result mainly from the modulation of the complex interplay between the pathologic triad of inflammation, dynamic obstruction, and thrombosis.6

2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline for coronary artery bypass graft surgery. A report of the ACCF/AHA Task Force on Practice Guidelines states that all patients undergoing CABG should receive statin therapy unless contraindicated (level of evidence is A). These guidelines do not mention the dose of statin. Various dosages of atorvastatin are in use which range from low dose 20 mg/day to high dose which is 80 mg/day. ACC/AHA does not recommend any dose because exactly at what dose benefit occurs is still obscure.

In view of high morbidity with the development of AF, the treatment of it is constantly evolving with multimodal approach, and still, it is not possible to control it precisely. Many studies with statin therapy in Western scenario show conflicting results and overall trend toward protection. However, because of obvious epidemiological reasons, the same cannot be generalized for Indian patients, and there are no studies which compare dose of atorvastatin for Indian population for prevention of AF, so we decided to conduct a randomized control trial for the same in Indian population (Table 1).

**MATERIALS AND METHODS**

This was prospective, double-blind, parallel group, randomized, clinical trial of assessment of high-dose atorvastatin (80 mg) versus low-dose atorvastatin (20 mg) on post-operative AF in 120 cases who underwent elective off-pump CABG. The study protocol was approved by the Ethical Committee of the Institute (Table 2). Written valid and informed consent was obtained from all the patients before the procedure. Inclusion criteria included all patients posted for elective off-pump coronary artery bypass surgery. Exclusion criterion included active liver disease.

**Table 1: Patients characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (80 mg)</th>
<th>Group B (20 mg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>56±10</td>
<td>57±12</td>
<td>0.4</td>
</tr>
<tr>
<td>Male sex</td>
<td>56</td>
<td>54</td>
<td>0.332</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>52±12</td>
<td>51±10</td>
<td>0.102</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td>2.4</td>
<td>2.2</td>
<td>0.874</td>
</tr>
</tbody>
</table>

**Table 2: Risk factor of the patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (80 mg)</th>
<th>Group B (20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA grade 2 angina</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>Diabetes</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td>Old cerebrovascular accident</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

NYHA: New York Heart Association

Patients were identified by primary investigator 1 day before surgery in pre-anesthesia clinic. Aspirin and clopidogrel were stopped 5 days before surgery while calcium channel blockers, angiotensin-converting enzyme inhibitor or angiotensin receptor blockers were stopped 1 day before surgery as per institutional protocol. Beta blockers and nitrroglycerines were continued. All pre-operative dose of atorvastatin was continued which is 20 mg as institutional protocol.

Intraoperatively, after bypass grafting is over, 80 mg atorvastatin was given in one group of patients (Group A) while no atorvastatin was given in Group B through Ryles tube. After extubation, from 2nd day, Group A patients received atorvastatin 80 mg/day while Group B received atorvastatin 20 mg/day. Demographic characteristics of the patients were collected.

Primary outcome variable was the incidence of post-operative AF. Secondary outcome variables were major adverse cardiac and cerebrovascular events, and persistence of AF at 1 month.

**Statistical Analysis**

Data expressed at mean ± standard deviation. Student’s t-test was applied to compare study Groups A and B. Paired t-test was used to compare variable before and after the intervention value <0.05 was considered significant. SPSS 19 was used for statistical analysis.

**RESULTS**

A total of 120 patients included in our study which was done from June 2015 to June 2016. Mean age in years was 56 ± 10 years in Group A while Group B it was 57 ± 12 years. 56 were male in Group A while 54 were
male in Group B. Mean ejection fraction was 52 ± 12 in Group A while 51 ± 10 in Group B. Number of diseased vessels in Group A was 2.4 versus 2.2 in Group B.

When we compared risk factors, New York Heart Association class 2 angina was present in 50 cases in Group A while in 54 cases in Group B. Hypertension was present in 72 cases in Group A while in 74 cases of Group B. Previous myocardial infarction was present in 42 cases in Group A while 46 cases of Group B. Previous cerebrovascular accident was present in 10 cases of Group A while 12 cases of Group B. P values are shown in respective tables and are non-significant.

POAF occurred in 2 cases in Group A while it occurred in 3 cases in Group B. The p value was 0.23 which is non-significant. One case each of major adverse cardiac event occurred in each group with a non-significant P value. While no patient persisted with AF at the end of 1 month.

**DISCUSSION**

The use of statins in perioperative period now is mandatory as supported by various trials and suggested by ACC/AHA guidelines. Statins have got additional beneficial effects which include anti-inflammatory effects, plaque stabilization effect, and antioxidant effect. Advanced data also suggest beneficial effect on mortality and morbidity. The question remains unanswered is what is exact dose? Are low-dose statins useful or high-dose statins should be given? Our prospective, randomized, control trial shows that the incidence of post-operative AF, major adverse cardiac event, and AF at the end of the 1st month is equal in low-dose versus high-dose statin group indication efficacy for even a lower dose of atorvastatin in the 1st month postsurgery.

Two studies specifically look after low-dose versus high-dose atorvastatin therapy after coronary artery bypass grafting. Compared with the less aggressively treated patients, those in the atorvastatin 80-mg group experienced a 27% reduction in major cardiovascular events and a 30% reduction in repeat coronary revascularization (either CABG or percutaneous coronary intervention) during a mean follow-up of 4.9 years. The number needed to treat with 80 mg compared with 10 mg to prevent 1 of these events was 16 in both the studies.

Although above studies look at different parameters after cardiac surgery, no study specifically looks at AF prevention which is the primary goal of our study (Table 3).

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative AF</td>
<td>2</td>
<td>3</td>
<td>0.23</td>
</tr>
<tr>
<td>Major adverse cardiac events</td>
<td>1</td>
<td>1</td>
<td>0.383</td>
</tr>
<tr>
<td>Persistence of AF at 1 month</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

AF: Atrial fibrillation

by both the low-dose and high-dose statins effectively. However, when we see from a broader perspective in view of reduction in long-term mortality and morbidity, it should be concluded that higher doses are safer in view of secondary beneficial effects, while initial period for prevention of hospital costs and patient morbidity, both dosages can be used.

**CONCLUSION**

Low-dose and high-dose statins are equally effective for immediate prevention of post-operative AF.

**LIMITATION OF THE STUDY**

The study has got several limitations. First, it specifically looked into a single parameter, i.e., AF in view of hospital costing as a post-operative morbidity rather than taking a holistic approach for post-operative mortality reduction. The second limitation is data are not collected regarding cholesterol levels of the patients.

**REFERENCES**


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