

**Research Article**

**Effect of prophylactic supplementation of allopurinol, magnesium and statin on the incidence of atrial fibrillation in off pump and on pump coronary artery surgery**

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**Abstract**

**Background:** Postoperative atrial fibrillation (POAF) is an adverse event after coronary artery bypass grafting (CABG). Various studies have reported, POAF is associated with increased early and late mortality, stroke, and prolonged hospital length of stay.

**Objective:** To evaluate the combined effect of prophylactic supplementation of allopurinol in the immediate preoperative period, magnesium in the immediate post operative period and atorvastatin perioperatively.

**Methods:** This was an observational, prospective study. A total of 120 patients, underwent elective CABG surgery were allocated to off pump group or on pump group depending on whether surgery was planned off pump or on pump. Primary outcome evaluated was the incidence of AF of 5 minutes duration or longer (by rhythm analysis on ECG) requiring therapy in the first six days of postoperative period in all the patients under study and also we evaluated if there was any difference in its occurrence between off pump and on pump CABG.

**Statistical Analysis:** Continuous variables were compared by means of student's unpaired t test and categorical variables were compared by Fischer's exact test. Kaplan-Meier analysis was used to compare the probability of atrial fibrillation in the Off pump and on pump groups.

**Results:** Overall 12 patients (10%) developed AF in the postoperative period. In that, 7 patients (11.6%) were from on pump group, where as 5 patients (8.3%) were from off pump group (P=0.20) and there was no statistical difference in the incidence of AF between the two groups.

**Conclusion:** Off pump CABG has no advantage over on pump CABG on occurrence of POAF, but perioperative supplementation of allopurinol, statin and Mg in combination may have some beneficial role in reducing the overall incidence of POAF.

**Keywords:** Postoperative atrial fibrillation, coronary artery bypass grafting, allopurinol, magnesium, atorvastatin, off pump, on pump

**1. Introduction**

Postoperative atrial fibrillation (POAF) is a frequent adverse event (20-40%) after coronary artery bypass grafting (CABG) and has potentially deleterious consequences<sup>1,2,3</sup>. Though several risk factors have been attributed, an enhanced sympathetic tone and inflammation are the most relevant factors predisposing to POAF<sup>4,5</sup>. Studies have reported that POAF is associated with increased early and late mortality, stroke, and prolonged hospital length of stay<sup>4,6,7,8</sup>. Overall, the risk for death is increased by 9.7% (range 3-33.3%)<sup>6</sup>. In addition, other complications following cardiac surgery have been found associated with POAF in various studies: myocardial infarction, persistent congestive heart failure, respiratory failure, various infectious complications, renal failure, severe hypotension and shock, multisystemic failure, and cardiopulmonary arrest. POAF is therefore associated with increased hospital and healthcare costs as well.

Effective prophylaxis can considerably reduce morbidity, hospital stay and resource utilization. Multiple studies with various doses of allopurinol on outcomes in CABG patients have found that allopurinol can reduce in-hospital mortality, improve cardiac performance, reduce incidence of arrhythmias, reduce markers of ischemia and free-radical generation, and reduce the need for inotropic support. However, these findings were not consistent between all studies<sup>9,10,11</sup>.

Magnesium (Mg) is also shown to be highly effective in the reduction of POAF. Indeed, Mg levels should be corrected in the same manner as potassium levels because they have definitively an impact on the incidence of AF. Decreased levels of Mg post operatively are associated with a higher risk of AF occurrence after cardiac surgery. Trials have demonstrated that Mg replacement can attenuate the perioperative fall in serum Mg, but most of the previous studies investigating the relationship between serum Mg and AF after CABG have produced inconsistent results<sup>7,12</sup>.

Accumulating evidence suggests that statins may also reduce the risk of POAF<sup>8</sup>. The antiarrhythmic mechanism of statins can possibly be explained by their effects on inflammation, antioxidant effects, antiarrhythmic effects due to ion channel stabilization, a role in extracellular matrix modulation, an inhibition of synthesis of isoprenoids that are significant for the posttranslational modification of such signalling molecules as Rho, Rac, and Ras, and an ability to reverse angiotensin II mediated atrial structural remodelling<sup>6</sup>. While the current evidence evaluating the use of statins to prevent POAF is encouraging, definitive conclusions cannot be drawn. However, because of statins are

widely used in cardiac patients for other indications and are not associated with the risks inherent to antiarrhythmic drugs, their value as an adjunct to current preventive strategies for POAF deserves further study.

There is speculation that off pump CABG may reduce the incidence of POAF through reduced trauma, ischaemia and inflammation<sup>13,14</sup>. Current data, however do not emphatically answer the question whether the incidence of POAF is reduced with off pump surgery<sup>15</sup>. The evidence from both observational and randomised studies is conflicting.

Our objective was to evaluate the combined effect of prophylactic supplementation of allopurinol in the immediate preoperative period, Mg in the immediate post operative period and atorvastatin perioperatively, in reducing the incidence of atrial fibrillation in all patients undergoing elective CABG surgery, as well as to compare its incidence between off pump and on pump CABG.

## 2. Materials and Methods

This was an observational, prospective study done in our institute between January 2011 to June 2012. A total of 120 patients who underwent elective CABG surgery were included after approval from the ethical committee and written informed consent taken from all the study subjects. Patients were allocated to off pump group or on pump group depending on whether surgery was planned off pump or on pump. Patients with history of AF in the past, myocardial infarction (MI) less than 1 month before surgery, a previous stroke, thyroid disorder, with preoperative renal dysfunction, left ventricular ejection fraction (LVEF) < 40%, whose left atrial size was large and patients with a history of previous heart surgery and/or undergoing valvular heart surgery were excluded from the study. Patients in the off-pump group who converted to on-pump CABG during surgery were also excluded from the study.

Primary outcome evaluated was the incidence of AF of 5 minutes duration or longer (by rhythm analysis on ECG) requiring therapy in the first six days of postoperative period in all the patients under study and also we evaluated if there was any difference in its occurrence between off pump and on pump CABG.

As an institutional protocol, all patients were started on oral atorvastatin 40 mg once daily (OD), 7 days before the scheduled day of surgery. All cardio vascular medications and bronchodilators if any, were continued till the day of surgery. Premedication with oral diazepam 5 mg, the night before surgery, fentanyl 100 mcg administered intramuscular 30 minutes before and sublingual isosorbide dinitrate 5 mg just before shifting the patient to the operation theatre. Patients were given oral allopurinol 600 mg, the night before and in the morning of surgery.

During the surgery, all patients received Mg 2 gm as an infusion, as well as supplemented with the same dose as slow infusion during the Post operative day 1 to 3<sup>12</sup>. On the first post-operative day, oral atorvastatin 40 mg OD was reinstated and in patients who were on preoperative  $\beta$  blocker, appropriate dose of metoprolol was also restarted depending on the clinical situation.

For On pump cases, a systemic temperature between 30 °C and 32 °C was induced. Myocardial protection was achieved by antegrade infusion of blood cardioplegia with St Thomas' solution.

All persistent arrhythmias were confirmed with 12-lead ECG. After 72 hr, trained nurses performed clinical observation every 4 hr. If there was any clinical suspicion of arrhythmia, an ECG was performed, and continuous ECG monitoring was restarted in cases of documented arrhythmia. Potassium levels were monitored and deficiencies were treated promptly to maintain the electrolyte balance within the normal range. Intra and postoperative adverse events and complications were recorded.

### 2.1 Statistical Analysis

Continuous variables were compared by means of student's unpaired t test and categorical variables were compared by Fischer's exact test. Kaplan-Meier analysis with the log rank test was used to compare the probability of atrial fibrillation in the Off pump and on pump groups. After an episode of atrial fibrillation or after the sixth postoperative day, the patient was withdrawn from the analysis.

## 3. Results

The demographic characteristics were similar in both the groups (Table 1).

**Table 1: Gender, age and weight distribution of the patients**

Group	Gender		Age in years Mean $\pm$ SD	Weight in kg Mean $\pm$ SD
	Male	Female		
Off Pump	44	16	59.18 $\pm$ 10.98	66.9 $\pm$ 9.6
On Pump	46	14	58.21 $\pm$ 9.62	69.2 $\pm$ 9.8

P value: 0.79 for Age and 0.099 for weight

Other than more number of patients being on preoperative  $\beta$  blockers in the on pump group (P=0.01), there was no statistical difference in the characteristics of the patients between the 2 groups (Table 2).

**Table 2: Clinical Characteristics of the patient**

Parameters	Off Pump (N=60)	On Pump (N=60)	P Value
Previous MI (no)	11	15	0.12
Systemic Hypertension (no)	36	32	0.11
Diabetes Mellitus (no)	23	28	0.09
COPD (no)	12	14	0.16
LVEF	0.59 $\pm$ .12	0.56 $\pm$ .08	0.36
Pre op use of $\beta$ blockers	34	46	0.01
Bypass time (min)	NA	155 $\pm$ 24	
Aortic Cx-clamp time (min)	NA	92 $\pm$ 23	
No. of grafts	2.94 $\pm$ 0.65	3.46 $\pm$ 0.96	0.09

NA - Not Applicable

Overall 12 patients (10%) developed AF in the postoperative period. In that, 7 patients (11.6%) were from on pump group, where as 5 patients (8.3%) were from off pump group (P=0.20). (Table 3)

**Table 3: Incidence of AF Postoperatively**

	None	1 <sup>st</sup> day	2 <sup>nd</sup> day	3 <sup>rd</sup> day	4 <sup>th</sup> day	Total
Off pump	55	0	2	2	1	60
On pump	53	1	3	2	1	60

**Kaplan Meier Analysis:** (Table no: 4): According to Kaplan Meier Analysis, there was no statistically significance in occurrence of the AF in cases and controls.

**Table 4. Survival Table**

Group	Time	Status	Cumulative Proportion Surviving at the Time		
			Estimate	Std. Error	
Off pump	1	2.000	2	0.667	0.272
	2	3.000	2	0.333	0.272
	3	4.000	1	0.000	0.000
On pump	1	1.000	1	0.750	0.217
	2	2.000	3	0.500	0.250
	3	3.000	2	0.250	0.217
	4	4.000	1	0.000	0.000

Log Rank (Mantel-Cox) Chi square test Value: 0.254 P value: .614 (Not Significant)

#### 4. Discussion

Though there was no statistical difference in the incidence of AF between the two groups, the overall incidence of AF (10%) in our study was much less when compared to most of the studies reported. The incidence of AF after elective CABG surgery has been reported in a very wide range, from 5–70%<sup>6,16,17</sup>. A large, prospective, observational, international, multicentre study of 4657 patients published in 2004 found the occurrence of POAF in 32.2% of patients undergoing isolated CABG surgery. Interestingly, this seems to vary between different regions: for example, the USA - 33.7%, Canada - 36.6%, Europe - 34.0%, the UK - 31.6%, Europe -41.6%, South America - 17.4%, and Asia - 15.7%<sup>18</sup>.

Almost all AF episodes are said to occur within the first 6 days following cardiac surgery, with the highest incidence on the second or third post-operative day, which coincides with a peak of systemic inflammation caused by surgery<sup>5,19,20</sup>. In our study as well, the incidence of AF was mainly observed in second and third day (4/5 cases in off pump group and 4/ 7 in on pump group).

There is some contradictory evidence concerning the advantage of off pump over conventional CABG with cardiopulmonary bypass in reducing the rate of POAF. Some meta-analyses showed that off-pump CABG significantly lowers incidence of POAF compared with on-pump. The meta-analyses of length of hospital stay, AF, and wound infection exhibited heterogeneity, however random-effects meta analyses showed a statistically significant reduction in these three outcomes among patients receiving off pump CABG<sup>13</sup>. Turk *et al* reported a prospective study of off pump vs on-pump CABG on the occurrence of POAF, and did not find any significant difference between these operative techniques in preventing POAF<sup>15</sup>. Our study also did not have any significant difference between the groups, but the possibility of the combined effect of the prophylactic medications taken in our study may have obfuscated any obvious benefit that off pump group could have had. Also, we had significantly more patients on preoperative  $\beta$  blockers in on-pump group, which may also have had an influence on the outcome.

Several observational studies have documented the benefit of perioperative supplementation with statins<sup>5</sup>. One RCT reported a significant reduction in the risk of POAF and reduced length of hospital stay in patients given preoperative atorvastatin beginning 7 days before surgery<sup>21</sup>. Nonetheless, negative studies showing no benefit of statins on post-operative AF also exist<sup>22</sup>. Similarly, many contradictory studies are there regarding the POAF lowering effects of supplementation of Mg in the immediate postoperative period and allopurinol preoperatively<sup>7,9,10,11,12</sup>. However, we supplemented all these three drugs perioperatively to observe if there was any benefit in giving these drugs in combination.

Also, as per the American Heart Association guidelines as well as the European Association for Cardio-Thoracic Surgery guidelines, which strongly recommend beta-blockers as first choice for the prevention of POAF in all the patients undergoing cardiac surgery, unless they are contraindicated, we reinstated  $\beta$  blockers postoperatively at the earliest, as the clinical situation permitted, especially for those who were already on it preoperatively.

We can conclude from this study that off pump CABG has no advantage over on pump CABG on occurrence of POAF, but perioperative supplementation of allopurinol, statin and Mg in combination may have some beneficial role in reducing the overall incidence of POAF.

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