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

Anand Rampure Vittal Rao¹, Santosh C Gudimani², Anand Kumar², Santosh Patil², Mithun V V² and Manjunath S Nekar³

¹ Department of Anesthesiology, Kannur Medical College, Kannur, Kerala, India.  
² Department of Surgery, Kannur Medical College, Kannur, Kerala, India  
³ Department of Community Medicine, Karnataka Institute of medical Sciences, Hubli, Karnataka, India

*Correspondence Info:  
Dr. Manjunath S Nekar  
Department of Community Medicine,  
Karnataka Institute of medical Sciences, Hubli, Karnataka, India  
E-mail: drmanjusn@gmail.com

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, whereas 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.¹²³. Though several risk factors have been attributed, an enhanced sympathetic tone and inflammation are the most relevant factors predisposing to POAF.⁴⁻⁶. Studies have reported that POAF is associated with increased early and late mortality, stroke, and prolonged hospital length of stay.⁴⁻⁶,⁷,⁸. Overall, the risk for death is increased by 9.7% (range 3–33.3%). 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.⁴⁻⁸,¹⁰,¹¹.  
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.⁷,₂⁻³,⁵⁻².  
Accumulating evidence suggests that statins may also reduce the risk of POAF. 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.⁶. 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. Current data, however do not emphatically answer the question whether the incidence of POAF is reduced with off pump surgery. 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 peroperatively, 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 dinitrite 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. On the first post-operative day, oral atorvastatin 40 mg OD was reinstituated and in patients who were on preoperative β 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 ± SD | Weight in kg Mean ± SD |
|----------|--------|------------------------|------------------------|
| Off Pump | Male   | 59.18 ± 10.98          | 66.9 ± 9.6             |
|          | Female | 68.21 ± 9.62           | 69.2 ±9.8              |
| On Pump  | Male   | 58.21 ± 9.62           | 69.2 ±9.8              |
|          | Female | 68.21 ± 9.62           | 69.2 ±9.8              |

P value: 0.79 for Age and 0.099 for weight

Other than more number of patients being on preoperative β 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 ± 0.12     | 0.56 ± 0.8     | 0.36    |
| Pre op use of β blockers | 34        | 46              | 0.01    |
| Aortic Cx-clamp time (min) | NA     | 155 ± 24      |         |
| No. of grafts        | 2.94 ± 0.65     | 3.46 ± 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

| Group       | None | 1st day | 2nd day | 3rd day | 4th 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 significant occurrence in the incidence 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  | 0.667                                               | 0.272      |
|             | 2    | 3.000  | 0.333                                               | 0.272      |
|             | 3    | 4.000  | 0.000                                               | 0.000      |
| On pump     | 1    | 1.000  | 0.750                                               | 0.217      |
|             | 2    | 2.000  | 0.500                                               | 0.250      |
|             | 3    | 3.000  | 0.250                                               | 0.217      |
|             | 4    | 4.000  | 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%4,6,9,11. 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%18.

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 surgery4,9,20. 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 CABG11. 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 POAF15. 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 β 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 statins4. 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 surgery9. Nonetheless, negative studies showing no benefit of statins on post-operative AF also exist12. Similarly, many contradictory studies are there regarding the POAF lowering effects of supplementation of Mg in the immediate postoperative period and allopurinol preoperatively9,10,11,12. 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 β 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.

References

1. Mathew JP, Fontes ML, Tudor IC, et al: A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004, 291(14):1720–1729.
2. Echahidi N, Pibarot P, O’Hara G, et al: Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008,51(8):793–801.
3. Solveig Helgadottir, Martin I Sigurdsson, Inga L Ingvarsdottir, David O Arnar and Tomas Gudbjartsson: Atrial fibrillation following cardiac surgery: risk analysis and long-term survival. J Card Surg 2012 7:87.
4. Bart Maessen, Jan Nijs, Jos Maessen, Maurits Allessie, and Ulrich Schotten : Post-operative atrial fibrillation: a maze of mechanisms. Europace. 2012 February; 14(2): 159–174.
5. Raja, Shahzad G, Dreyfus, Gilles D: Incidence of Atrial Fibrillation after Off-pump and On-pump Coronary Artery Surgery: Current Best Available Evidence. Internet Journal of Thoracic & Cardiovascular Surgery, 15240274, 2003, Vol, 6, Issue 2.
6. Diana Kaireviciute, Audrius Aidietis and Gregory. Atrial fibrillation following cardiac surgery: clinical features and preventative strategies. Eur Heart J 2009; 30: 410–425.
7. Alberto Zangrillo, Giovanni Landoni, Donatella et al. Perioperative Magnesium Supplementation to Prevent Atrial Fibrillation After Off-Pump Coronary Artery Surgery: A Randomized Controlled Study. Journal of Cardiothoracic and Vascular Anesthesia 2005; 19:723-728.
8. Lertsburapa K, White CM, Kluger et al. Preoperative Statins for the prevention of atrial fibrillation after cardiothoracic surgeries. *J Thorac Cardiovasc Surg* 2008; 135:405–411.
9. Nicole A Weimert, William F Tanke et al. Allopurinol as a Cardioprotectant during Coronary Artery Bypass Graft Surgery. *Ann Pharmacother* 2003; 37(11): 1708-1711.
10. Rashid HA, Williamolosson G. Influence of allopurinol on cardiac complications in open heart operations. *Ann Thorac Surg* 1991; 52:127-30.
11. Sachin Talwar, Janardhan Alamanda Sandeep et al. Effect of preoperative administration of allopurinol in patients undergoing surgery for valvular heart diseases. *Eur J Cardiothorac Surg* 2010; 38 (1): 86-90.
12. Kohno H, Koyanagi T et al. Three-day magnesium administration prevents atrial fibrillation after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2008; 135:405–411.
13. James T. Reston Meta-analysis of short-term and mid-term outcomes following off- pump coronary artery bypass grafting. *Ann Thorac Surg* 2003; 76:1510-1515.
14. Buffolo E, de Andrade CS, Branco JN, et al. Coronary arteries bypass grafting without cardiopulmonary bypass. *Ann Thorac Surg* 1996; 61: 63-66.
15. Turk T, Vural H, Eris C, Ata Y, Yavuz S. Atrial fibrillation after off-pump coronary artery surgery: a prospective, matched study. *J Intern Med Res* 2007; 35:134–142.
16. Lauer MS, Eagle KA, Buckley MJ, DeSanctis RW. Atrial fibrillation following coronary artery bypass surgery. *Prog Cardiovasc Dis* 1989; 5:367–36.
17. White HD, Antman EM, Glynn MA, Collins JJ, Cohn LH, Shemin RJ, Friedman PL. Efficacy and safety of timolol for the prevention of supraventricular arrhythmias after coronary artery bypass surgery. *Circulation* 1984; 70:479 –484.
18. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazur DC, Barash PG, Hsu PH, Mangano DT. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004; 291:1720 –1729.
19. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, Browner WS. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. *JAMA* 1996; 276:300-6.
20. Creswell LL, Schuessler RB, Rosenblloom M, Cox JL. Hazards of postoperative atrial arrhythmias. *Ann Thorac Surg* 1993 ;56:539-49.
21. Ozaydin M, Dogan A, Varok et al. Statin use before by-pass surgery decreases the incidence and shortens the duration of postoperative atrial fibrillation. *Cardiology* 2007; 107:117–121.
22. Liang Yin, Zhinong Wang, Yifeng Wang, Guanyu Ji, Zhiyun Xu. Review: Effect of Statins in Preventing Postoperative Atrial Fibrillation Following Cardiac Surgery. *Heart, Lung and Circulation*; 19(10):579-583.