Prophylactic Effect of a Single Intravenous Dose of a Combination of Digoxin, Hydrocortisone, and Amiodarone on Atrial Fibrillation after Off-Pump Coronary Artery Bypasses Graft Surgery

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Abstract

Objective:
Postoperative atrial fibrillation (POAF) is the most common complication after coronary artery bypass graft surgery (CABG) and a major cause of increased hospital costs. Dispersed atrial refractoriness is thought to be the primary mechanism, whereas myocardial inflammation has an important role in altering atrial conduction. We evaluated the preventive effect of an intravenous combination of Digoxin, Hydrocortisone, and Amiodarone as anti-inflammatory and anti-arrhythmic agents on AF after off-pump CABG.

Material and Methods:
One hundred fifty patients who underwent off-pump CABG between March 2010 and April 2011 and met our inclusion criteria were enrolled. The patients were randomized into two groups: the study group received 300 mg Amiodarone, 0.5 mg Digoxin, and 200 mg Hydrocortisone before the induction of anesthesia, but the control group did not. Surgical and anesthetic techniques were identical in both groups.

Results:
Patient characteristics and surgical variables were similar in both groups (p value<0.05). POAF was observed in 6 (8%) patients in the case group and in 18 (24%) of the controls. There was a significant difference between the two groups in the prevalence of new-onset POAF (p value=0.03).

Conclusion:
A preoperative dose of a combination of Digoxin, Hydrocortisone, and Amiodarone is a safe and feasible method to reduce POAF prevalence, produce a better outcome, and reduce the duration of hospital stay and hospital costs. ***(Iranian Heart Journal 2012; 13(3):33-38)*** **.**

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Introduction

Postoperative atrial fibrillation (POAF) is the most frequent complication after coronary artery bypass graft surgery (CABG), with a prevalence of 20–50% [1]. POAF is typically seen between the second and fourth post-CABG days, with the highest incidence being on the second postoperative day [2, 3], and can be associated with significant morbidity and mortality, particularly in elderly patients and those with left ventricular dysfunction. POAF is a major factor allied to increased hospital costs and should be treated appropriately [4, 5].

The pathophysiology of POAF is incompletely understood, but the mechanisms are thought to be multifactorial [6]. The main risk factors that increase the prevalence of POAF after CABG are: hypertension; withdrawal of ß-blockers; hematoma; over-manipulation of the right atrium; electrolyte imbalance; and respiratory problems. Several mechanisms are thought to be causative, including systemic inflammation, local inflammation of the pericardium and myocardium, autonomic imbalance, and excessive release of catecholamines. These factors may result in the dispersion of atrial refractoriness and slow atrial conduction. Multiple re-entry wavelets resulting from altered atrial refractoriness are believed to be the main cause of POAF [7].

We hypothesized that eliminating any of the aforementioned mechanisms may lead to a decrease in the POAF prevalence. We used Hydrocortisone as an anti-inflammatory agent in addition with Amiodarone and Digoxin as anti-arrhythmic agents. The aim of the present study was to evaluate the effect of the administration of a single intravenous dose of Digoxin, Amiodarone, and Hydrocortisone on the POAF prevalence after off-pump CABG

Materials and Methods

The protocol of this randomized clinical study was approved by the local ethics committee, and written informed consent was obtained from all the patients.

One hundred fifty patients who underwent off-pump CABG between March 2010 and April 2011 and met our inclusion criteria were enrolled. The patients were randomized into two groups of 50 cases and 50 controls.

The inclusion criteria were off-pump CABG surgery, and the exclusion criteria were patients who: underwent re-operation; had concomitant valve surgery, ventricular aneurysm resection or other major cardiac procedures; had a history of hypertension or sensitivity to Digoxin, Amiodarone, or hydrocortisone; had been treated with anti-arrhythmia drug classes I or III; or had thyroid disorders, renal failure, bradycardia, or atrioventricular block. Patients who required emergency conversion to on-pump CABG were excluded from the study as well. Two patients were excluded from the study because of intraoperative AF, so the final study subjects consisted of 95 patients.

The patients of the case group received 200 mg Hydrocortisone, 0.5 mg Digoxin, and 300 mg Amiodarone 15 minutes before anesthesia induction; the controls did not receive any of these drugs. Premedication included Lorazepam, Morphine, Promethazine, and Ranitidine prescribed in both groups. After surgery, all the patients were observed for AF up to 48 hours in the Intensive Care Unit (ICU) and then in the post-ICU ward until hospital discharge.

The anesthetic and surgical techniques were identical and carried out by the same anesthesiologist and surgeon in both groups. The left internal mammary artery was used as an arterial graft and a temporary epicardial pacing wire was placed in all the patients of both groups. In the ICU, standard twelve-lead electrocardiography (ECG) was done every 12 hours. Vital signs along with

specific symptoms such as chest pain, palpitation, and dyspnea were recorded every 4 hours. AF occurrence >5 minutes on monitoring or occurrence of the above-mentioned specific symptoms followed by ECG-confirmed atrial tachyarrhythmia was defined as "new-onset POAF".

Statistical Analysis

The data were analyzed with SPSS software using frequency tables, chi-square test, and Student *t*- test. A p value≤0.05 was considered statistically significant.

Results

The patients' characteristics are shown in Table 1. There was no significant difference between the two groups with respect to age distribution, sex, weight, ejection fraction (EF), left atrial size, pattern and number of involved coronary arteries, use of calcium channel blockers or ß-blockers, diabetes, recent myocardial infarction, hypertension, and hyperlipidemia. POAF was observed in 6 (8%) patients in the case group and 18 (24%) of the controls. There was a significant difference between the two groups in the prevalence of new-onset POAF (p value=0.03).

Table 1. Characteristics of patients before off-pumpCABG.
*MI: myocardial infarction

	Study group (n=48)	Control group (n=47)	P value
Age (mean±SD, year)	60.75±2.32	55.95±2.49	NS
Gender (male/female)	36/12	34/13	NS
Hypertension (%)	23.1%	12.2%	NS
Heart rate (bpm)	75.0±1	75.4±1	NS
Recent MI* (%)	23.9%	18%	NS
Systolic dysfunction (%)	51.3%	40%	NS
Diastolic dysfunction (%)	92.3%	82.5%	NS
Preoperative beta-blocker use (%)	35%	30%	NS
Preoperative beta- calcium channel blocker use (%)	11%	16%	NS
Diabetes mellitus (%)	11%	14%	NS
Left atrial enlargement (%)	15.4%	7.5%	NS
The mean number of grafts	2.52±1	2.99±0	NS
Mitral valve disease (n)	13	13	NS
Left ventricular ejection fraction (mean±SD)	53.45±11.25	54.80±8.75	NS

Discussion

AF is the most common complication of CABG and a major cause of increased hospital costs; patients complicated by postoperative AF stay 13 hours longer in the ICU and 2 days longer in the ward [7]. This type of arrhythmia rarely causes death, but can significantly increase postoperative morbidity [8]. Administration of ß-blockers before and after surgery can decrease the prevalence of POAF [9] as well as other preventive medical treatments such as calcium channel blockers, Digoxin; magnesium, Amiodarone, amid procaine, and corticosteroids, and a combination of glucose, insulin, and potassium [10-14].

Mathew et al. reported that advanced age, male sex, previous history of AF, heart failure, preoperative heart rate >100 bpm, and the use of cardiopulmonary bypass (CBP) are the main risk factors for POAF after CABG [12], but the mechanism of POAF is not precisely known. Systemic and myocardial inflammation is believed to be one of the most important underlying causes of POAF. In the study performed by Chiappini et al. in 2004, histological myocardium findings were observed in patients with AF [13]. Many studies have reported the effects of corticosteroid drugs such as Methylprednisolone and Dexamethasone for short periods in the prevention of AF after coronary artery surgery [13-14].

Digoxin has no anti-fibrillatory effect, but keeps the heart rate under control and improves hemodynamic status in patients with depressed myocardium. Different results have been reported after the sole use of Digoxin as a preventive drug for POAF, but Digoxin in combination with ß-blockers are reported to prevent AF after CABG [15–16].

Amiodarone is a class-III anti-arrhythmic drug which also has α- and β-adrenergic-blocking properties that may regulate sympathetic overstimulation during and after surgery. In a large study by Mitchell et al. in 2005, a 13-day preoperative course

of oral Amiodarone was well tolerated and effective in preventing atrial tachyarrhythmia after cardiac surgery [17]. Several studies have been carried out using different drugs to reduce the prevalence of POAF after CABG. B-blockers were first studied in 1990 and had the most effect on AF prevention compared with other drugs. This medical method was recently accepted as a standard preventive treatment: AF prevalence has decreased by up to 50% with β-blocker use. The important role of Sotalol has recently been described, but its use has been limited due to side effects such as tachycardia, asthma, and renal disorders [18-20]. Gediki et al. reported a significant increase in the levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6 in patients with new-onset and chronic AF, which supports the role of the inflammatory response in the pathogenesis of AF [21]. Km and Tan carried out a meta-analysis on 3323 patients from 50 clinical trials and reported the efficacy of low-dose and high-dose corticosteroids in reducing POAF risk after adult cardiac surgery [22]. Oral administration of prophylactic drugs is less acceptable due to problems related to pharmacokinetics and the time required for maximal effect. We evaluated a preventive method, i.e. a single intravenous dose before anesthesia induction which rapidly reaches the maximal effect. Some studies have reported the efficacy of Digoxin, Hydrocortisone, and Amiodarone alone. It is unlikely that a single dose of corticosteroids can increase complications such as bleeding, infection, and delayed wound healing [7, 12]. In the present study, POAF was considerably reduced in the study group. This strongly supports our hypothesis of POAF prevention by eliminating the inflammatory mechanisms and anti-arrhythmic therapy via a combination of Digoxin, Amiodarone, and Hydrocortisone.

Conclusion

The present study suggests that a preoperative combination of Digoxin, Hydrocortisone, and Amiodarone is a safe and feasible method to reduce POAF prevalence, improve outcome, and reduce the duration of hospital stay and hospital costs.

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References

1. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol. 2008; 51 (8): 793–801.

2. Selvaraj R. Prevention of postoperative atrial fibrillation - a stitch in time. Indian Pacing Electrophysiol J. 2011 Feb 7;10(12):526-8.

3. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM, Massumi A. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol. 2004; 43:742–8.

4. Rollo P. Villareal, Ramesh Hariharan, Brant C. Liu, Biswajit Kar, Vei-Vei Lee, MacArthur Elayda, J.Alberto Lopez, Abdi Rasekh, James M. Wilson, Ali Massumi, Postoperative atrial fibrillation and mortality after coronary artery bypass surgery, Journal of the American College of Cardiology, Volume 43, Issue 5, 3 March 2004, Pages 742-748.

5. Perkerson KA, Gillespie EL, White CM, et al. Impact of prophylactic amiodarone on length of hospital stay, stroke, and atrial fibrillation after

cardiothoracic surgery. Pharmacotherapy 2005; 25:320-4.

6. Hogue CW, Hyder ML. Atrial fibrillation after cardiac operation: risks, mechanisms, and treatment. Ann Thorac Surg. 2000; 69:300–6.

7. Almassi GH, Pecsi SA, Collins JF, Shroyer AL, Zenati MA, Grover FL. Predictors and impact of postoperative atrial fibrillation on patients' outcomes: a report from the Randomized On Versus Off Bypass trial. J Thorac Cardiovasc Surg. 2012 Jan;143(1):93-102. Epub 2011 Nov 4.

8. Chelazzi C, Villa G, De Gaudio AR.Postoperative atrial fibrillation. ISRN Cardiol. 2011;2011:203179. Epub 2011 May 22.

9. Zhu J, Wang C, Gao D, Zhang C, Zhang Y, Lu Y, Gao Y.Meta-analysis of amiodarone versus beta-blocker as a prophylactic therapy against atrial fibrillation following cardiac surgery.Intern Med J. 2012. 1445-5994.

10. Yazicioglv L, Eryilmaz S, Sirlak M, et al. The effect of preoperative digitalis and atenolol combination on postoperative atrial fibrillation incidence. Eur J cardiothorac surg 2002;22:397-40.

11. Kaplan M, Kut MS, Icer UA, et al. Intravenous magesium sulfate prophylaxis for atrial fibrillation after CABG surgery. J Thorac cardiovasc surg 2003;125:344-52.

12. Mathew JP, Parks R, Savino JS, et al. Atrial fibrillation following CABG surgery: Predictors, outcomes and resource utilization. JAMA 1996; 276: 300-306.

13. Chiappini B, Deone O, Bracchetti G, et al. The role of corticosteroid therapy following surgery for atrialfibrillation. J card surg 2004; 19:232-4.

14. Prasongsukarn K, Able JG, Jamieson WR, et al. The effects of steroids on the occurrence of postoperative atrialfibrillation after CABG surgery. J Thorac cardiovasc surg 2005;130:93-98.

15. Pharmacologic prophylaxis of postoperative atrial fibrillation in patients undergoing cardiac surgery: beyond beta-blockers.Pharmacotherapy. 2010 Jul;30(7):749, 274e-318e. Davis EM, Packard KA, Hilleman DE.

16. A hospital perspective on the cost-effectiveness of beta-blockade for prophylaxis of atrial fibrillation after cardiothoracic surgery. Gillespie EL, White CM, Kluger J, Sahni J, Gallagher R, Coleman CI. Clin Ther. 2005 Dec;27(12):1963-9.

17. Mitchell LB, Exner DV, Wyse DG, Connolly CJ, Prystai GD, Bayes AJ, Kidd WT, Kieser T, Burgess JJ, Ferland A, MacAdams CL, Maitland A. Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair: PAPABEAR: a randomized controlled trial. JAMA. 2005 Dec 28;294(24):3093-100.

18. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. Europace. 2011 Mar;13(3):329-45.

19. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F, Boehmer JP, Carlson MD, Frantz RP, McNulty SE, Rogers JG, Anderson J, Johnson GW, Walsh MN, Poole

JE, Mark DB, Lee KL, Bardy GH. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. Circulation. 2009 Dec 1;120(22):2170-6.

20. Bagshaw SM, Galbraith PD, Mitchell LB, Sauve R, Exner DV, Ghali WA.Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg. 2006 Nov;82(5):1927-37.

21. Gedikli O, Orem C, Baykan M, Karahan C, Kucukosmanoglu M, Sahin S, Korkmaz L, Yilmaz H, Celik S. Association between serum C-reactive protein elevation and atrial fibrillation after first anterior myocardial infarction. Clin Cardiol. 2008 Oct;31(10):482-7.

22. Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. Circulation. 2009 Apr 14;119(14):1853-66.