

Independent Effect of Digoxin in Preventing Atrial Fibrillation in High Risk Patients after CABG Surgery

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Abstract

Background: Atrial fibrillation (AF) is one of the most common arrhythmias after coronary artery bypass graft (CABG) surgery. AF can result in hemodynamic instability, thromboembolic events, increase the perioperative myocardial infarction, congestive heart failure, stroke, more length of hospital stay (LOHS) and cost of treatment. The aim of this study was to evaluate the independent effect of digoxin in preventing AF after CABG in patients who had a predictor for AF and had already been on other anti-arrhythmic drugs.

Methods: In a prospective randomized clinical trial, using alternate randomization, 239 patients categorized into three different groups. Group one consisted of 72 patients who had at least one predictor for developing AF after CABG. Group two consisted of 67 patients with the same predictors who received 0.5 mg intravenous digoxin after disconnecting from bypass pump followed by 0.25 mg intravenous digoxin one hour and four hours later. Oral daily digoxin (0.25 mg) was continued from the first post operation day to the 14th day with 2 days off per week. One hundred patients without those predictors for AF were randomly allocated in group three to confirm the impact of those predictors on developing AF.

Results: AF occurred in 16 patients (22.2%) in group 1, six patients (8.8%) in group 2, and seven patients (7%) in group 3. The duration of AF was 6.43 ± 4.23 min in group 1, 1.2 ± 1.41 min in group 2, and 47.18 ± 67.29 min in group 3.

Conclusion: Intraoperative digoxin can independently decrease the incidence of AF after CABG surgery in patients with high risk factors for AF.

Iran J Med Sci 2007; 32(4): 193-197.

Keywords • Digoxin • coronary artery bypass • atrial fibrillation

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias after coronary artery bypass graft (CABG) surgery. It is one of the major causes of morbidity after heart surgeries and can increase the healthcare resource utilization, which can be more significant in developing countries with low per capita incomes. Its incidence has been reported about

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30-50% in various studies.¹ AF can result in hemodynamic instability, thromboembolic events, increase the perioperative myocardial infarction, congestive heart failure, stroke,²⁻⁴ more length of hospital stay (LOHS),⁵ and a higher treatment cost.

Many studies have been conducted to find suitable drugs to prevent AF after CABG. Various medications have been used in this regard.⁶⁻¹¹ But the role of digoxin in controlling this arrhythmia is controversial.¹²⁻¹⁶

The aim of this study was to evaluate the independent effect of digoxin in preventing AF after CABG in high risk patients who had a predictor for AF.

Patients and Methods

In a prospective randomized clinical trial, history, physical examination, electrocardiography (ECG), and echocardiography were used to evaluate all patients who were scheduled for the first, elective, isolated CABG in the period of January to October 2005. Using alternate randomization, 239 patients were selected and categorized into three different groups.

Group one consisted of 72 patients who had at least one predictor for developing AF after CABG (age > 65, congestive heart failure (CHF) or ejection fraction \leq 35%, chronic obstructive pulmonary disease (COPD), right atrial enlargement, use of intra-aortic balloon pump, and previous AF now presenting sinus rhythm).¹⁻³

We also enrolled 67 patients with the same predictors in group two to receive 0.5 mg intravenous (iv) digoxin after disconnecting from bypass pump followed by 0.25 mg iv digoxin one hour and four hours later. Oral daily digoxin (0.25 mg) was continued from the first post operation day to the 14th day with 2 days off per week.

One hundred patients without those predictors for AF were randomly allocated in group 3 to confirm the impact of those predictors on developing AF.

We excluded the patients with renal failure, atrioventricular block, sinus bradycardia, preoperative treatment with anti arrhythmic drugs, and those with hypo or hyperthyroidism.

For those patients who received beta blockers, calcium channel blockers or angiotensin receptor blockers preoperatively, the drugs were continued postoperatively to prevent the adverse effect of withdrawal of these medications.

We recorded all possible confounding factors such as diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, previous myocardial infarction (MI), history of smoking or opium consumption, wean off time, aortic cross clamp time, and post operative intubation time. AF rhythm and duration, history of reoperation, episodes of

reintubation, and the specific types of beta or calcium channel blockers were also recorded.

The study was done in Shiraz Central hospital (MRI center) and Ordibehesht hospital and the ethical committee of the hospitals approved the study. After getting informed consent from all 239 patients, a single surgeon performed all surgeries.

Surgical procedure

Midazolam (50 mic/kg) and morphine (0.2 mg/kg) was used as premedication for all patients and anesthesia was induced by infusion of propofol (50-100 mic/kg/min) and remifentanyl (0.25 mic/kg/min). Pavulon was used (0.1 mg/kg for induction and 0.05 mg/kg for maintenance) as muscle relaxant. Peripheral intravenous catheters, arterial line, and central venous pressure (CVP) catheter were inserted in the operating room. Hemodynamic parameters such as arterial pressure, heart rate, central venous pressure, and arterial blood gases were monitored during the operation. The patients were intubated endotracheally and ventilated with 100% oxygen. Using standard median sternotomy, we exposed the heart and harvested the left internal mammary artery for all patients. Cardiopulmonary bypass with mild hypothermia was used for all operations. We performed cardioplegia by using cold blood.

Post op course

All the patients had special nurses in the ICU who continuously checked the electrocardiographic changes by regular monitor checks. Pulse oximetry was also performed using finger probes for 5 days. Full time physician of critical care unit diagnosed the AF, then all 12-lead electrocardiograms were reviewed by an attending cardiologist to verify the rhythm abnormality and AF episodes.

Data analysis

Baseline clinical variables, intraoperative data, and post operative course including the development of AF or any other serious complications were recorded by trained special nurses. Data were expressed as the mean \pm standard deviation.

Chi-square test was used for comparing the variables mentioned in table 1 in the three groups. Fisher exact test was used to compare some variables in table 1 for two groups. One-way ANOVA with Scheffe multiple ranges test was used for comparing the variables in table 2 in the three groups, and Kruskal-Wallis and Mann-Whitney U test were used for assessing the duration of AF. SPSS software version 11.5 was used for statistical analysis and $p < 0.05$ was considered significant.

Table 1: Baseline patients' characteristics and the risk factors between groups 1&2 and the differences with group 3

	Group 1	Group 2	P(G ₁ VsG ₂)	Group 3	P(between groups)
No of patients	72	67		100	
Gender (male)	57	54	1.000	70	0.257
HTN	44	35	0.307	51	0.368
DM	18	21	0.457	30	0.647
Atrial enlargement	1	1		0	0.474
Hyperlipidemia	25	30	0.300	49	0.156
Opium consumption	13	11	0.825	9	0.196
Smoking	38	30	0.316	26	0.001
CHF	8	13	0.343	2	0.002
COPD	45	53	0.181	86	0.000
Age	65.04±11.42	64.38±10.42	0.921	52±6/83	0.000
EF	47.28±13.3	43.1±12.64	0.110	54/12±6/52	0.000
History of MI	19	29	0.51	24	0.028
Re-operation	2	0	0.489	1	0.274

HTN=hypertension, DM=diabetes mellitus, CHF= congestive heart failure, COPD= chronic obstructive pulmonary disease, EF= ejection fraction, MI= myocardial infarction

Table 2: Perioperative variables in the three groups

	Group 1	Group 2	Group 3	P
Cross clamp time(min)	33.62±9.48	31.35±7.76	30.92±6.84	0.110
Bypass-time(min)	54.42±12.45	51.41±9.69	51.84±12.34	0.184
*Intubation time(hour)	10.44±3.7	9.36±2.73	7.86±2.54	0.000
IABP (No.)	1	2	0	0.244

*The difference between groups 1&2 was not significant (P. value= 0.13), IABP=intra-aortic balloon pump

Results

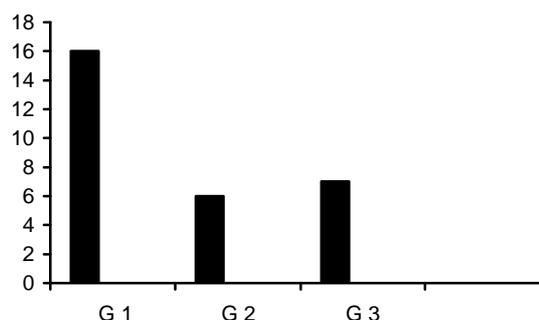
Gender, incidence of HTN, DM, hyperlipidemia, atrial enlargement, and history of opium consumption, and reoperation were similar in the three groups (table 1). Also age, ejection fraction (EF), incidence of smoking, and history of CHF and COPD were similar in groups 1 and 2. The patients in group 3 who were chosen from those without AF predictors had significant differences with the patients in groups 1 and 2 regarding these variables (table 1).

Perioperative variables such as cross clamp time, pump time, use of IABP, and wean off time were also similar in the three groups. The intubation time had not significant difference between the patients in groups 1 and 2. But it was significantly shorter in group 3 compared with groups 1 and 2 (table 2).

The antihypertensive drugs used by the patients before the operation such as beta blockers, calcium channel blockers, and an-

giotensin receptor blockers were compared between the groups, which showed no statistical differences (table 3).

AF occurred in 16 patients (11.52%) in group 1, six patients (8.8%) in group 2, and seven patients (7%) in group 3 (figure). The duration of AF was 6.43±4.23 min in group one, 1.2±1.41 min in group two, and 47.18±67.29 min in group three (table 4).

**Figure:** Incidence of AF between the three groups.**Table 3:** Preoperative medications consumed by the patients in the three groups

Drug	Group1	Group2	Group3	P
Inderal	23	34	49	0.53
Atenolol	12	13	15	0.756
Metoral	3	0	3	0.264
*Angiotensin receptor blocker	8	3	1	0.011
Ca-channel blocker	13	15	23	0.723

*The difference between groups 1&2 was not significant (p=0.21)

Table 4: The number and duration of AF between the three groups

	Group 1	Group 2	P(G ₁ VsG ₂)	Group 3	P(between groups)
AF (number)	16	6	0.019	7	0.002
Duration of AF (min)	6.43±4.23	2±1.41	0.033	47.18±67.29	0.043

In those patients who developed AF, normal sinus rhythm was maintained by additional antiarrhythmic drug (amiodarone 300 mg bolus infusion followed by 1mg/kg/min for 6 hours and 0.5 mg/kg/min for another 6 hours) or by cardioversion.

The relationship between AF and age, DM, HTN, cross clamp time, atrial size, and hyperlipidemia, was studied by using multiple regression analysis, which showed that risk of developing AF in group one was 3.62 times more than the other group.

Discussion

AF is the most frequent arrhythmia after CABG.² It has a multi-factorial phenomenon and is associated with increased early and late mortality risk.⁴ Hypoxia, hypovolemia, post-operative electrolyte imbalance, and structural changes due to HTN and age are responsible factors.¹⁷ Several drugs have been used to prevent AF after CABG.⁶⁻¹¹ Beta blockers, digoxin, and amiodarone are the most frequent ones. Beta blockers are the most acceptable drugs to reduce post operative AF.⁹ Discontinuing the beta blockers prior to operation may lead to withdrawal arrhythmia. In this study we allowed the patients to continue their preoperative medications to prevent such side effects.

In this study we found that using intraoperative digoxin can independently decrease the incidence of AF in patients with high risk factors for AF. Since the other drugs such as beta blockers or calcium channel blockers, which can affect the incidence of AF were similarly used by the patients in the three groups, we concluded that the decrease in the incidence of AF can be independently attributed to digoxin.

In our study a combination of drugs such as beta blockers and calcium channel blockers, which were used by the patients prior to operation and digoxin were used. This is in accordance with the study done by Tokmakoghlu et al who used the combination of digoxin and metoprolol and compared the effects with amiodarone as an effective drug for prevention of AF. They showed that both groups of drugs were effective in prevention of post operative AF.¹⁶ Yazicioglu et al compared the effects of combined digoxin and atenolol with digoxin and atenolol separately. They found that the combination is effective in lowering the incidence of AF at CABG.¹⁷ A similar result was reported by Kowey in 1997.¹³

Rubin et al compared the effects of beta blockers and digoxin. They showed that incidence of AF in CABG patients was much higher in digoxin-treated than propranolol-treated

patients.¹⁴

Digoxin has been one of the first drugs used for prevention of AF. Some studies showed that preoperative and postoperative use of digoxin had been effective in preventing AF,¹⁸ while other studies showed that digoxin alone could not prevent AF,¹⁹ should not be used routinely,²⁰ and its use prior to surgery could even increase the incidence of post operative AF.⁵

A meta-analysis in the year 2005 reviewed 10 trials that had used digoxin to lower post operative AF. In two studies combined beta blockers and digoxin had been used. The meta-analysis attributed the efficacy of treatment to beta blockers rather than digoxin.⁹ This finding is different from ours, because in our study beta blockers were uniformly distributed between the patients. So decreased incidence of AF in group 2 can independently attributed to digoxin.

Calcium channel blockers are the other antiarrhythmic drugs have been used to prevent AF post CABG. Tisdale et al compared diltiazem and digoxin. They showed that diltiazem could control AF more rapidly than digoxin but the difference was not significant after 24 hours.¹⁵

Amiodarone is another widely used drug to prevent AF after CABG.²¹ Its effect has been reported superior to beta blockers in some studies,¹⁰ while it had similar effect comparing with combined digoxin and metoprolol.¹⁶ None of the patients in our study used amiodarone prior to operation so we could not evaluate the independent effect of digoxin in patients using amiodarone.

In our study digoxin could lower the heart rates in those patients developed AF but this decrease was not significant ($p=0/0501$). In group 1, 22.2% of patients developed AF post CABG, which is slightly lower than previous reports.^{8,4} This can be in part due to other antiarrhythmic drugs have been used by the patients prior to operation.

In group 3 whose patients had not any predictor for developing AF post operation, the incidence of AF was 6% indicating that how the risk factors such as age, CHF, etc can be important in developing AF.

In this study we tried to consider most of the known variables associated with post operative AF but other unmeasured factors may influence the outcome.

Conclusion

Having considered the independent effect of digoxin in preventing AF, we recommend that digoxin can be used for those patients who have several risk factors for developing AF after CABG surgery.

Acknowledgement

We would like to thank Dr Tabatabaee from Shiraz University of Medical Sciences for the statistical analysis.

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