Prophylactic effect of amiodarone in atrial fibrillation after coronary artery bypass surgery; a double-blind randomized controlled clinical trail

Moshiri Esmail1, Dadashpoor Nilufar2, Golestani-Eraghi Majid3, Taheri-Nejad Mohammad Reza4, Mohammadbeigi Abolfazl5*

1Assistant Professor, Department of Anesthesiology, Arak University of Medical Sciences, Arak, Iran
2Department of Anesthesiology, Resident of Anesthesiology, Arak University of Medical Sciences, Arak, Iran
3Fellowship of Intensive care, Department of Anesthesiology, Arak University of Medical Sciences, Shahid Beheshti, Iran
4Department of internal medicine, General Practitioner, Arak University of Medical Sciences, Arak, Iran
5Department of Epidemiology and Biostatistics, School of Health, Qom University of Medical Sciences, Qom, Iran

ABSTRACT

Introduction: Atrial fibrillation is the most common complication after coronary artery bypass surgery. It’s known that increases morbidity and mortality after Coronary artery bypass graft (CABG) surgery and also leads to increased length of stay in the ICU and the hospital. The purpose of this study is to evaluate the prophylactic effect of amiodarone in reducing the incidence of atrial fibrillation after coronary artery bypass surgery. Materials and Methods: In this randomized clinical trial study, 124 elective patients scheduled for CABG surgery were enrolled based on inclusion and exclusion criteria and randomly divided into two equal groups. Patients of intervention group before anesthesia, intravenously received 300 mg amiodarone medication and the control group received normal saline. Up to 24 hours after coronary artery bypass surgery, the incidence of atrial fibrillation in the two groups was observed. Results: The incidence of atrial fibrillation after CABG in intervention group was 16 people and in the control group was 35 people. The prevalence of atrial fibrillation compared between two groups using chi-square analysis showed that there is a significant difference between two groups (p=0.037) and the incidence of atrial fibrillation in control group was significantly lower than the intervention group. Conclusion: Although in the study the amiodarone medication was used with lower dose and duration compared with other studies, but the results of this study showed that even with the same protocol it is possible to use amiodarone for prevention of atrial fibrillation after coronary artery bypass surgery.

Key words: Amiodarone, Arrhythmia, Atrial Fibrillation, Coronary Artery Bypass, Prevention Clinical Trial.

INTRODUCTION

Atrial tachyarrhythmias are common in early recovery period after cardio-thoracic surgery. The problem is seen in 11-40% of patients after Coronary Artery Bypass Graft surgery (CABG). Advances in surgery and anesthesia, as well as changes in myocardial preservation techniques have reduced the incidence of tachyarrhythmias after surgery.1 After surgery, Atrial Fibrillation (AF) is often seen during the first 5 days(1) but its peak incidence is during the first 48 hours after open heart surgery which indicates the importance of after surgery monitoring2 and it is known that it increases the morbidity and mortality after CABG surgery and also will lead to an increase in the ICU and hospital length of stay.3 Although AF in the early postoperative period is often sudden and self-limiting, but can be continued for weeks and leads to increased morbidity, cardiac loss, embolic complications

*Corresponding address:
Mr. Mohammadbeigi Abolfazl
Department of Epidemiology and Biostatistics,
School of Health, Qom University of Medical Sciences,
Qom, Iran.
E-mail: beigi60@gmail.com

DOI: 10.5530/jcdr.2015.1.2
and the need for pacemaker. The most common known risk factors include aging, heart valve disease, atrial enlargement, preoperative atrial dysrhythmia and chronic lung disease. Also beta-blocker withdrawal, right coronary artery occlusion, reduced left ventricular function or left ventricular hypertrophy are risk factors, as well. However the aging is a constant independent predictor for the incidence of AF after CABG.

Many of the medications have been used to prevent postoperative AF. Since sympathetic activation is essential in the pathogenesis of AF after surgery, using beta-blockers such as propranolol, metoprolol, and atenolol is a good option for prophylaxis. The use of intravenous magnesium sulfate before surgery also reduces the incidence of AF after cardiac surgery. Patients who are digitalized in before the surgery are less likely to have postoperative AF.

Preoperative prescription of amiodarone is an interventional method which may reduce the incidence of AF after cardiac surgery. Amiodarone is a unique drug that belongs to the class III anti-arrhythmic agents. This medication is used to treat supraventricular and ventricular arrhythmias, and dysrhythmias associated with acute myocardial infarction. Using low-dose intravenous or oral administration for 3-5 days before and after CABG surgery has reduced the incidence of AF.

Amiodarone has been widely used for clinical purposes. Despite its antiarrhythmic characteristic, the use of this drug as a prophylactic agent against the occurrence of postoperative AF is uncommon and yet the use of amiodarone as prophylaxis in patients undergoing CABG is not routine. On the other hand, the role of amiodarone in reducing the post-CABG AF is controversial. Therefore, this study is to investigate the effect of amiodarone in reduction of post-CABG AF.

**MATERIALS AND METHODS**

In this randomized, double-blind, placebo-controlled study, 124 patients scheduled for non-emergency CABG referred to the Amir-Kabir hospital of Arak city, were randomly divided into two groups (62 subjects in each group) using a random number table. Details of study plan presented to the patients and they were enrolled after obtaining their consents. All patients were CABG candidates and all were ASA II and III. All of the subjects were candidates for 2 or 3 grafts and patients who needed more than three grafts were excluded.

Patients received preoperative premedication consisting of oxazepam at surgery night and morphine 3-5 mg and promethazine 15-25 mg in the surgery morning and entered the operating room. All of them received 3 to 5 cc/kg crystalloid serum. Patients were monitored for SPO₂, pulse rate, and electrocardiogram in the operating room and were prepared for IBP monitoring after taking 1-2 ml sufentanil. After performing arterial line, intervention group received 300 mg amiodarone as iv bolus within 20-30 minutes and the control group received the same amount 0.9% normal saline in the same period.

Researcher and patients were not aware of the type of medication and the drugs prepared formerly by another anesthesiologist and were given to the chief assistant to prescribe to patients, according to research group. Then, the anesthesia was induced by 5-10 µg/kg sufentanil, midazolam 0.1 mg/kg, and pavulon 10-12 mg. After intubation and endotracheal tube fixation, patients were prepared for CV line catheterization from the internal jugular vein. Then, medications include muscle relaxants, opioids, benzodiazepines and propofol was given to them.

Eventually the cardiopulmonary pump was used for all patients to perform CABG on-pump. Then based on patient’s condition and stability after CABG the pump was separated. All patients were taken to the ICU intubated with stable hemodynamic.

Then, the patients in the first group after receiving the bolus dose of amiodarone within the first 24 hours after surgery, received the iv infusion; 1 mg/kg in the first 6 hours and 0.5 mg/kg in the next 18 hours. During this period, the control group received the same volume of placebo (NS 0.9%).

In case of arrhythmias including AF, ventricular tachycardia (VT), and ventricular fibrillation (VF) in the placebo group, patients were treated with routine anti-arrhythmic treatment and were excluded from the study. Also by occurring other arrhythmias in the amiodarone group (unless AF) these patients were excluded too. Forty eight hours later, the incidence of postoperative AF was recorded in the patients. Chi Square, t-test and analysis of variance for repeated measurement were used.

**RESULTS**

The mean age of patients was 67.1±10.9 years old in the control group and 63.3±8.7 years in the intervention group. The average number of patients’ grafts in the
control group was 2.24±0.43, and 2.23±0.47 in the intervention group (p=0.322). The baseline measurement Table 1 for adequacy of random allocation showed that two groups are the same regarding to some of important confounding variables including sex, taking 2 grafts, history of arrhythmia, and arrhythmia after induction, after removing pump, and in the ICU entrance, and hemodynamic parameters including heart rate, primary systolic and diastolic blood pressure.

The analysis of variance for repeated measurement (Table 2) did not showed any significant difference between two groups regarding to heart rate, systolic and diastolic blood pressure (P>0.05). However, the overall trend of heart rate, systolic and diastolic blood pressure was decreasing after CBAG surgery.

After induction of anesthesia, one patient in intervention group and four patients in the control group had AF. One patient with VF was excluded from the intervention group. After removing the pump from patients, the arrhythmia was evaluated. At this point, 2 patients with AF and 3 patients with VF were excluded from the intervention group. Also 2 patients with AF were excluded from the control group.

Then the patients were sent to the intensive care unit. At ICU admission, five patients were excluded from the control group and also four patients had AF in the amiodarone group. Six hours after admission to the ICU, one patient also affected by VT and was excluded from the study and five other patients with AF were excluded from the control group. Twelve hours after admission to the ICU, 10 other patients by AF were excluded from the control group.

In general, evaluating the incidence of AF, VF and VT in both groups (overall incidence of other arrhythmias in patients after excluding also been considered), the results showed that 15 patients in the intervention group and 21 patients in the control group had arrhythmias in this study. Chi-square analysis showed no significant difference between the groups in the incidence of arrhythmias (p=0.323). But if we consider arrhythmias such as PVC and sinus bradycardia, 38 patients in the intervention group and 40 patients in the control group as a whole were experiencing various arrhythmias. Chi-square analysis showed no significant differences between the groups in the incidence of arrhythmias (p=0.853).

The trend of AF (Table 3) in the treatment group was significant and showed a decreasing trend after CBAG surgery but this event in placebo group was not significant. Also the incidence of AF in different times after surgery tested by Chi square and our results showed that the

**Table 1: Baseline measurement for adequacy of random allocation in two intervention groups.**

<table>
<thead>
<tr>
<th></th>
<th>Treatment group n (%) or Mean(SD)</th>
<th>Placebo group n (%) or Mean(SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>39(62.9)</td>
<td>34(54.8)</td>
<td>0.362</td>
</tr>
<tr>
<td>History of Arrhythmia</td>
<td>10(16)</td>
<td>18(29)</td>
<td>0.086</td>
</tr>
<tr>
<td>Arrhythmia After Induction</td>
<td>18(29)</td>
<td>25(40.3)</td>
<td>0.187</td>
</tr>
<tr>
<td>Arrhythmia After Removing Pump</td>
<td>26(41.9)</td>
<td>22(35.5)</td>
<td>0.461</td>
</tr>
<tr>
<td>AF Arrhythmia in ICU</td>
<td>7(10)</td>
<td>4(9.5)</td>
<td>0.616</td>
</tr>
<tr>
<td>Two grafts</td>
<td>42(67.7)</td>
<td>47(75.8)</td>
<td>0.318</td>
</tr>
<tr>
<td>Baseline Systolic Blood Pressure</td>
<td>139.3(17.7)</td>
<td>139(19.7)</td>
<td>0.924</td>
</tr>
<tr>
<td>Baseline Diastolic Blood Pressure</td>
<td>86(10)</td>
<td>82.3(11.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline Heart Rate</td>
<td>73.3(7.8)</td>
<td>73.3(9)</td>
<td>0.975</td>
</tr>
</tbody>
</table>

**Table 2: Hemodynamic parameters of patients, before, immediately after the onset and after the surgery**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Immediately</th>
<th>ICU0</th>
<th>ICU6</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td>Treatment</td>
<td>139±18</td>
<td>125±15</td>
<td>118±16</td>
<td>128±16</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>139±20</td>
<td>123±16</td>
<td>113±17</td>
<td>119±18</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>Treatment</td>
<td>86±10</td>
<td>76±10</td>
<td>75±11</td>
<td>81±10</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>82±12</td>
<td>74±9</td>
<td>68±11</td>
<td>72±12</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Treatment</td>
<td>73±8</td>
<td>74±8</td>
<td>74±14</td>
<td>75±13</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>73±9</td>
<td>72±10</td>
<td>78±10</td>
<td>79±16</td>
</tr>
</tbody>
</table>
incidence in treatment group is significantly lower than placebo group (p=0.037).

**DISCUSSION**

The results showed the incidence of atrial fibrillation was over 50% lower in patients who received amiodarone. AF after cardiac surgery is common and its incidence is estimated to be between 30-50%. Although the postoperative AF is intermittent and self-limiting, it can continue for several weeks and can lead to increased mortality, cardiac arrest, embolic complications and the need for pacemaker. So the atrial fibrillation can increase the length of hospitalization and increases health care costs. Despite the advances in surgical techniques, the incidence of AF after cardiac surgery has not been decreased, especially in the elderly.

It seems that several underlying pathophysiologic mechanisms are responsible for the high incidence of postoperative AF. Preoperative factors such as aging, hypertension, chronic obstructive pulmonary disease (COPD), more grafts, poor left ventricular function, discontinuation of beta blockers before surgery and history of AF are considered as predictors of AF. Studies have shown that post-CABG AF is associated with sympathetic activity.

Although the long-term complications of postoperative AF are unusual but more length of hospitalization and increased costs are the most common problems. Therefore, any action to reduce the incidence of postoperative AF is economically beneficial. A variety of pharmaceutical strategies are available in prevention of postoperative AF but still there are disagreements about the risks and benefits of these strategies.

Principles of treating post-CABG AF include ventricular rate control, using anticoagulants, and change to sinus rhythm. Amiodarone increases refractory period of atrial and ventricular muscle and AV node. In addition to act as a class III antiarrhythmic drug, amiodarone has a mild activity in beta- and calcium channel blocking. It is effective in acute AF as well as chronic AF. Based on these characteristics, amiodarone has been studied for prevention of AF after cardiac surgery.

The amiodarone has been applied orally and intravenously to prevent AF. Amiodarone was prescribed between 2 to 15 days in most of these studies but the drug was used intravenously for 24 hours.

Review articles show that amiodarone reduces major cardiovascular complications such as ventricular tachyarrhythmias and neurological events. The investigation of 19 studies showed that prescription of prophylactic amiodarone reduces the length of stay by 0.6 day. Although it is a short term but if the number of annual heart surgeries be considered, it is clear that use of the drug saves health care costs.

Redle and colleagues study indicated that oral amiodarone (2 grams per day for 1 to 3 days before surgery and 400 mg per day for 7 days after CABG) cannot significantly decrease the incidence of AF after CABG. In contrast to our study, the oral amiodarone was used. Aasbo et al mentioned that although amiodarone reduces AF but should not be used as a routine therapy. They recommended further clinical studies to determine the exact impact of concomitant use of amiodarone beta blockers. This observation supports the hypothesis that amiodarone should be applied in patients in whom beta blockers are contraindicated or have AF risk factors such as valvular disease, left atrial enlargement, or supraventricular tachyarrhythmia’s.

The study by Yagdi et al demonstrated that amiodarone reduces the incidence of AF more than 50% in patients who received amiodarone. Although the results are quite consistent with our study but in this study the patients were prescribed amiodarone postoperatively and received 10 mg/

---

Table 3: Incidence of atrial fibrillation in two groups in different times after CABG

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Placebo</th>
<th>RR (CI of RR)</th>
<th>Chi Square P value*‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>After induction</td>
<td>18(29)</td>
<td>25(40.3)</td>
<td>0.77(0.51-1.2)</td>
<td>0.129</td>
</tr>
<tr>
<td>In entry to ICU</td>
<td>26(41.9)</td>
<td>24(38.7)</td>
<td>1.07(0.75-1.5)</td>
<td>0.427</td>
</tr>
<tr>
<td>ICU 6th hours</td>
<td>19(30.6)</td>
<td>22(35.5)</td>
<td>0.894(0.61-1.3)</td>
<td>0.351</td>
</tr>
<tr>
<td>ICU 12th hours</td>
<td>14(22.6)</td>
<td>23(37.1)</td>
<td>0.686(0.435-1.1)</td>
<td>0.058</td>
</tr>
<tr>
<td>ICU 24th hours</td>
<td>7(11.3)</td>
<td>20(32.3)</td>
<td>0.457(0.336-0.991)</td>
<td>0.004</td>
</tr>
<tr>
<td>Overall atrial fibrillation</td>
<td>10(16.1)</td>
<td>21(33.9)</td>
<td>0.577(0.36-0.97)</td>
<td>0.019</td>
</tr>
<tr>
<td>Friedman P value</td>
<td>&lt;0.001*</td>
<td>0.845*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Friedman test, ‡ Chi Square test
kg/day in the first 48 hours, oral amiodarone 600 mg per
day three times a day for 5 days, 400 mg per day twice
a day for the following 5-day period, and 200 mg per
day in a single dose for the last 20 days for a total of 30
days, while in our study the patients received amiodarone
infusion for only 24 hours after surgery. The same results
achieved by Hohnloser and colleagues.\textsuperscript{26} They acclaimed
that amiodarone significantly reduce the incidence of
post-CABG AF. They used more doses in longer period
(four days).

It seems that prophylactic amiodarone prescribed for a
longer period is more effective. Daoud et al who used
amiodarone as prophylaxis for AF after CABG or valve
surgery, or both, showed that the use of prophylactic oral
amiodarone at least one week before surgery leads to a
reduction in postoperative AF.\textsuperscript{10} The results are partially
consistent with the our results, however, a heterogeneous
population of patients (CABG and/or heart valve surgery)
were enrolled in their study.

The systematic review by Bagshaw and colleagues evaluated
19 randomized clinical trial studies examined the effects
of amiodarone in the prevention of atrial fibrillation in
patients undergoing cardiac surgery.\textsuperscript{4} The results showed
that amiodarone should be considered as the first-line
therapy and routine prophylaxis of AF after cardiac
surgery. According to the study, the most effective protocol
for the prescription of amiodarone is unclear, but briefly
the prophylactic use of amiodarone causes a significant
reduction in the incidence of AF after cardiac surgeries.

There is no consensus about the optimal dose and mode of
prescription of amiodarone. In most studies, amiodarone
was prescribed intravenously at a dose of 10-20 mg/kg/day
for 2 to 8 days.\textsuperscript{13,16,18,21,22,26,27} An advantage of prophylaxis
by intravenous amiodarone is the shorter treatment period
compared to that of oral. Studies have shown that between
7 to 20 days of oral amiodarone therapy is needed to control
arrhythmia\textsuperscript{26,29} Moreover, the superior antiarrhythmic
effect of ranolazine–amiodarone combination against
postoperative atrial fibrillation is established in Simopoulos
and et al study\textsuperscript{30} and in current study the amiodarone alone
effect was assessed.

Before routine prescription of amiodarone for AF
prophylaxis, side effects must be considered. Although
there are evidence on it’s relative safety and patients’
tolerance,\textsuperscript{31,32} retrospective studies indicate an increased
risk of pulmonary toxicity, and acute respiratory distress
syndrome in patients receiving amiodarone.\textsuperscript{33,34} However,
some other studies have failed to link between short-
term low-dose amiodarone and acute respiratory distress
syndrome.\textsuperscript{33,35} The results of our study did not show severe
complications of the medication, although the patients were
followed up for only 24 hours after the operation, while
other studies have examined patients for at least one week.

Lack of evaluation of the duration of hospitalization was
one of the limitations of this study. Also the mortality rate
was not recorded in our study.

In conclusion the results of our study showed that
using prophylactic intravenous amiodarone significantly
decreases the post-CABG AF, however we used lower
doses and duration than other studies.

\textbf{CONCLUSION}

Although in the study the amiodarone medication was used
with lower dose and duration compared with other studies,
but the results of this study showed that even with the same
protocol it is possible to use amiodarone for prevention
of atrial fibrillation after coronary artery bypass surgery.

\textbf{CONFLICTS OF INTEREST}

The authors declare that they have no conflicts of interests.

\textbf{ACKNOWLEDGMENTS}

This study has been done as PhD thesis of anesthesia and
sponsored by vice chancellor for research of Arak
University of Medical Sciences.

\textbf{REFERENCES}

1. Naqvi S, Hussain SA. Amiodarone prophylaxis for Atrial fibrillation after
125-31.
2. Tiryakioğlu O, Demirtas S, Ari H, Tiryakioğlu SK, Huysal K, Selimoglu O,
et al. Magnesium sulphate and amiodarone prophylaxis for prevention
of postoperative arrhythmia in coronary by-pass operations. Journal
2009/02/24.
al. Amiodarone prophylaxis for atrial fibrillation of high-risk patients after
coronary bypass grafting: a prospective, double-blinded, placebo-controlled,
randomized study. European heart journal 2006; 27(13): 1584-91. Epub
2006/06/09.
Prophylactic amiodarone for prevention of atrial fibrillation after cardiac
Mohammadbeigi, et al.: Prophylactic Effect of Amiodarone in Atrial Fibrillation


