How Should We Use the Amiodarone After Coronary Bypass Surgery? Prophylactic or Therapeutic?

Koroner Baypas Sonrası Amiodaronu Nasıl Kullanmalıyız? Profilaksi mi, Tedavi mi?

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ABSTRACT Objective: The aim of this study was to assess the efficacy and side effects of postoperative administration of amiodarone as a prophylaxis for or treatment of new onset atrial fibrillation after coronary artery bypass grafting surgery. **Material and Methods:** Between January 2010 and January 2012, we conducted a retrospective analysis on consecutive patients who underwent coronary artery bypass grafting surgery. Patients were grouped according to whether they received amiodarone for prophylaxis or for treatment of atrial fibrillation. In Group 1, amiodarone was given after new onset atrial fibrillation for treatment (Group 1; n=595; 378 males, 217 females; mean age 62.16±4.72 years; range 43-78 years). Group 2 received amiodarone for prevention of postoperative atrial fibrillation (Group 2; n=500; 344 males, 156 females; mean age 61.43±6.12 years; range 41-81 years). The patients were followed-up for arrhythmias and left ventricular function using electrocardiography and echocardiography. **Results:** Preoperative patient characteristics and operative variables were similar in two groups. Patient recovery was significantly slower in Group 1. Postoperative atrial fibrillation occurred in 595 patients among 3500 patients (17%) who underwent coronary bypass surgery without amiodarone, and in 27 patients (5.40 %) receiving amiodarone as prophylaxis (p=0.0001). Mean pulmonary and liver function tests were not significantly different between two groups. Group 2 patients had shorter hospital stays compared to Group 1 patients (Group 2: 4.9+3.6 days vs. Group 1: 6.2+5.8 days, p=0.001). The in-hospital mortality was not different between the two groups (1.5% vs. 1.2%, p=0.176, respectively). **Conclusion:** Postoperative prophylactic amiodarone therapy in patients undergoing coronary bypass surgery is well tolerated and significantly reduces the incidence of postoperative atrial arrhythmias while not affecting left ventricular function.

Key Words: Coronary artery bypass; amiodaron; prevention and control

ÖZET Amaç: Bu çalışmanın amacı, koroner arter baypas operasyonlarından sonra başlayan atriyal fibrilasyonda, amiodaronun tedavi amaçlı veya proflaktik amaçlı kullanımının etkinlik ve yan etkilerini değerlendirmektir. **Gereç ve Yöntemler:** Ocak 2010 ile Ocak 2012 tarihleri arasında ardışık olarak koroner arter baypas cerrahisi uygulanan hastaların verileri geriye dönük olarak değerlendirildi. Hastalar atriyal fibrilasyonun tedavisi veya proflaktik amaçlı amiodaron kullanımına göre iki gruba ayrıldı. Yeni başlayan atriyal fibrilasyonun tedavisi amacıyla amiodaron uygulanan hastalardan elde edilen veriler Grup 1 içinde değerlendirildi (Grup 1; n=595; 378 erkek, 217 kadın; ortalama yaş 62,16±4,72 yıl; dağılım 43-78 yıl). Atriyal fibrilasyon gelişmeden proflaktik olarak amiodaron verilen hastalardan elde edilen veriler de Grup 2 içinde değerlendirildi (Grup 2; n=500; 344 erkek, 156 kadın; ortalama yaş 61,43±6,12 yıl; dağılım 41-81 yıl). Hastalar elektrokardiyografi ve ekokardiyografi ile aritmi ve ventrikül fonksiyonları bakımından değerlendirildi. **Bulgular:** Her iki gruptaki hastalar, hasta özellikleri ve operatif veriler açısından benzerdi. Hastaların iyileşme süreci Grup 1'de anlamlı şekilde daha yavaştı. Amiodaron verilmeyen hastalarda atriyal fibrilasyon görülme oranı %17 iken (3500 hastadan, 595 hasta), proflaktik olarak amiodaron verilen hastalarda bu oran %5,4 idi (27 hasta) (p=0,0001). Akciğer ve karaciğer fonksiyonlarına ait ortalama değerler her iki grupta da benzerdi. Grup 2'deki hastaların hastanede kalış süreleri, grup 1'e göre daha kısaydı (Grup 2; 4,9+3,6 gün iken, Grup 1; 6,2+5,8 gün, p=0,001). Hastane içi mortalite iki grupta da benzerdi (sırasıyla, %1,51 ve %1,2, p=0,176). **Sonuç:** Koroner baypas cerrahisi uygulanan hastalarda postoperatif dönemde proflaktik amiodaron uygulaması iyi tolere edilir, postoperatif atriyal aritmi riskini anlamlı şekilde azaltır ve sol ventrikül fonksiyonlarını da etkilemez.

Anahtar Kelimeler: Koroner arter baypas; amiodarone; önleme ve kontrol

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Coronary artery bypass grafting (CABG) was introduced as a treatment for ischemic atherothrombotic coronary disease more than 40 years ago. In the early postoperative period of coronary bypass surgery, the direst complication increasing the risk of morbidity and mortality is arrhythmia, especially in patients with impaired left ventricular function.[1] The incidence of these arrhythmias in the early period of post-coronary artery bypass graft surgery varies between 11-40%.[2,3] The most frequently seen type of arrhythmia is atrial fibrillation (AF), and the first agent to be selected during therapy is amiodarone.[4,5] Although this agent is used after AF has developed, there are publications in literature recommending utilization of this agent in prophylaxis, before AF develops.[1,4] However, prolonged use of amiodarone is known to have some adverse effects on the liver, lungs, and thyroid gland. In the literature, it is unclear whether amiodarone must be used in the prophylaxis or for the treatment of new-onset AF. In this study, we compared the effects of amiodarone given after development of AF postoperatively and its use as a prophylactic agent during the early postoperative period.

MATERIAL AND METHODS

We reviewed the medical charts of two hospitals of Sifa University Medical Faculty retrospectively. Patients who underwent coronary bypass surgery in Cardiovascular Surgery Clinic of Sifa University Medical Faculty between January 2010 and January 2012 were enrolled in this study. They were divided into two groups. Group 1 consisted of 595 patients who had undergone coronary bypass surgery and received therapeutic amiodarone after development of atrial fibrillation (n=595; 378 males, 217 females; mean age 62.16±4.72 years, range 43-78 years). In the same time period, 500 patients operated on by another surgical team in the other hospital and given amiodarone as a prophylactic agent before development of atrial fibrillation comprised Group 2 (n=500; 344 males, 156 females; mean age 61.43±6.12 years, range 41-81 years). All patients were evaluated with postoperative electrocardiography, echocardiography, AST, ALT and blood gases. These two groups' preoperative and postoperative data were compared.

All study procedures were approved by the Hospital Ethics Committee before initiation of the study. Patient informed consent forms disclosed in patient files were reviewed prior to study enrollment; and if the consent forms were lacking, the patients were excluded from the study. Individuals who had arrhythmias during preoperative period, met criteria for a paroxysmal AF attack in the past, had a drug-dependency, a history of temporary or permanent pacemakers or ventricular arrhythmias in the preoperative or postoperative period, advanced chronic liver disease, elevated liver enzyme levels, impaired thyroid function, undergone cardiac surgery for any reason, used amiodarone and digoxin during preoperative period, or received CABG+valve surgery were excluded from study. A total of 87 patients were excluded from the study because of these exclusion criteria.

SURGICAL TECHNIQUE

All patients were on 5 mg intramuscular midazolam and 1 g intravenous cefazolin before the operation, and continued to use them in repeated doses (two times a day) until chest tube removal. Cardiopulmonary bypass (CPB) was initiated by using a Sarns roller pump (Sarns, Fort Myers, FL, USA) 2.4-2.6 L/m^2, and mild-medium hypothermia was achieved (esophageal 26-28^{o}C). For oxygenation, a membrane oxygenator (Dideco, Mirandola, Italy) was used throughout the CPB. Preoperative and operative processes were the same in both groups. During the postoperative period, in the first 24-48 hours, patients were followed-up constantly with electrocardiography (ECG) and, subsequently, with ECG record-taking device twice a day to assess cardiac rhythm.

ADMINISTERED DOSES

After AF started, amiodarone was initiated in a 300 mg/30 min intravenous (IV) loading dose and continued as 900-1200 mg/24 hours as IV maintenance therapy in Group 1. Later, it was given as 400 or 600 mg/day for five days, according to the heart rate. Again, according to heart rate, patients were

provided an amiodarone dose of 200-400 mg/day for at least three weeks. In Group 2, two hours after the patient was moved into the intensive care unit, IV amiodarone was initiated as 10 mg/kg/day. Until the patient received amiodarone orally, it was given IV, at least at a dose of 1200 mg. As post-IV therapy, all patients received an oral amiodarone dose of 400-600 mg for five days, and subsequently, a dose of 200 mg/day was continued for 21 days. Dose differences were due to dose adjustments according to heart rate. During the first three-month period, patients were followed-up by monthly follow ups, and then by telephone interviews. Three and six months after surgery, the follow up of the patients were done with echocardiography (Hewlett-Packard ultrasound imaging system-Hewlett-Packard Company, Palo Alto, CA, USA), wherein their left ventricular ejection fraction (LVEF) values and ECG records were studied. These values were compared with preoperative values. Patients who used beta blockers during the preoperative period had continued to use them.

STATISTICAL ANALYSIS

Continuous data are displayed as means and standard deviations. Categorical data are expressed as proportions. All data were evaluated using Student's t-tests and Chi-square test. In all studies, p values less than 0.05 were considered statistically significant.

RESULTS

There were no statistical differences ($p>0.05$) between groups in terms of mean age, gender, morbid obesity, use of tobacco, diabetes mellitus, or chronic hepatic and renal diseases. Using the New York Heart Association's (NYHA) classification system, no significant differences ($p>0.05$) were

TABLE 1: Demographic, clinical and procedural data of the study patients.

Parameters	Group 1, n=595 (Amiodarone after AF) Patient Number/Characteristic	%	Group 2, n=500 (Amiodarone as a prophylactic agent) Patient Number/Characteristic	%	p value
Age (Mean±SD)	62.16±4.72		61.43±6.12		0.062
Female Gender, n	217	36.47	156	31.2	0.371
BSA (Mean± SD)	1.82±0.2		1.83±0.31		0.520
Preoperative beta blocker use, n	131	22	120	24	0.076
-Acute MI, n	32	5.3	29	5.8	0.893
-Heart Failure, n	127	21.3	119	23.8	0.822
- Three vessel disease, n	482	81.0	473	79.5	0.052
LMCA disease, n	59	9.91	51	10.2	0.612
RCA disease, n	351	59	363	61	0.075
Risk Factors					
- Smoking, n	302	50.75	296	59.2	0.203
- Hypertension, n	395	66.38	393	68.6	0.076
- Morbid Obesity, n	142	23.86	121	24.2	0.964
- Dyslipidemia, n	281	47.22	269	53.8	0.186
- Family story, n	161	27.05	156	31.2	0.509
- Peripheral vascular disease, n	47	7.89	42	8.4	0.401
Co morbidity					
- DM, n	161	27.05	155	31	0.509
- COLD, n	89	14.95	85	17.0	0.736
- CRF, n	82	13.78	78	15.6	0.891
B,C Hepatitis, n	117	19.66	104	20.8	0.986
NYHA Class (Mean±SD)	2.9±3.2		2.8±1.8		0.535

AF: Atrial fibrillation; SD: Standard deviation; BSA: Body surface area; MI: Myocardial infarction; CHF: Congestive heart failure; LMCA: Left main coronary artery; RCA: Right coronary artery; DM: Diabetes mellitus; COLD: Chronic obstructive lung disease; CRF: Chronic renal failure; NYHA: New York Heart Association.

found between the groups in terms of using medications due to functional capacity, hepatic and pulmonary problems, blood cholesterol levels, family history, or accompanying peripheral vascular diseases (Table1). Groups were compared for operative data. There were no significant differences ($p>0.05$) between groups for mean cross clamp time, CPB time, cerebrovascular events, and the number of bypasses performed. The number of anastomoses per patient were 3.39±5.6 in Group 1 and 3.37±6.2 in Group 2; differences between the groups were not significant ($p=0.615$). The ventricular arrhythmia rate encountered during the postoperative period was markedly smaller in Group 2. The comparisons of groups for operational data and postoperative complications are summarized in Table 2. Patients were closely followed-up during the postoperative period for blood gases and liver function tests; the data obtained from patients in Group 2 were not significantly different compared to patients in Group 1 (Table 3). AF occurred at a mean of 21±6 hours after surgery in the Group 1 and 64±8 hours after surgery in the Group 2 ($p=0.001$).

In Group 1, none of the patients returned to the sinus rhythm spontaneously. Two hundred and one patients (33.7%) returned to sinus rhythm with amiodarone, after 16.7 (±22.4) hours. When sinus rhythm could not be achieved despite amiodarone therapy after approximately 24 hours in Group 1, beta blockers, digoxin, calcium channel blockers and/or electrical cardioversion were initiated alone or in combination in addition to amiodarone therapy the day after, and sinus rhythm was achieved in 382 patients (64.2%). Remaining 12 (2.01%) patients were considered to have refractory AF, their heart rates were controlled and they were discharged with oral warfarin.

In Group 2, AF development rate after CABG was 5.4% (27/500 patients who received prophylactic amiodaron), and AF developed after an average of 26.2 (±17.4) hours. There were statistically significant differences between the groups in terms of AF development rates ($p=0.0001$). Thirteen of 27 patients (48.1%) who developed AF despite prophylactic amiodarone therapy returned to sinus rhythm spontaneously without any additional therapy. In Group 2, beta blockers were initiated

TABLE 2: Complications and mortality after coronary artery bypass grafting.

	Group 1, n=595 (amiodarone after AF)	Group 2, n=500 (amiodarone as a prophylactic agent)	p value
Number of distal anastomosis (Mean±SD)	3.39±5.6 (1-4)	3.37±6.2 (1-4)	0.615
Time of cross clamp (min) (Mean±SD)	39.6 ±12.3	41.1±4.3	0.058
Time of perfusion (min) (Mean±SD)	69.7±26.2	67.3±14.6	0.068
Positive inotropic support, n (%)	169 (28.4)	130 (25.9)	0.294
IABP, n (%)	8 (1.34)	4 (0.8)	0.006
Using Grafts			
-LITA, n (%)	535 (89.91)	482 (96.4)	0.001
Blood Transfusion	2.8±2.7	2.7±1.4	0.455
Days in ICU (Mean±SD)	1.3±4.3	1.2±2.1	0.635
Total Days in hospital (Mean±SD)	6.2±5.8	4.9±3.6	0.001
Intubation time (hour) (Mean±SD)	9.67±4.8	7.86±9.2	0.036
Reoperation for bleeding, n (%)	2 (0.4)	3 (0.6)	0.166
Postoperative bleeding (mL)	450±25	510±45	0.001
Heart rate (beat/minute)	105.16±19.4	98.23±15.12	0.001
AF refractory to amiodarone, n (%)	12 (2.01)	-- (0.0)	0.001
CVE, n (%)	2 (0.4)	3 (0.5)	0.515
Cumulative mortality in hospital, n (%)	9 (1.51)	6 (1.2)	0.176

AF: Atrial fibrillation; SD: Standard deviation; IABP: Intra-aortic balloon counter pulsation; LITA: Left internal thoracic artery; ICU: Intensive care unit; CVE: Cerebrovascular event; Postop: Postoperative.

in 4 (0.8%) of 14 (2.8%) patients who developed AF and failed to return sinus rhythm, and 10 (2%) patients returned to sinus rhythm with a combination of digoxin and electrical cardioversion.

Liver enzyme levels were followed up closely in patients using amiodarone. Amiodarone was discontinued in a total of 31 patients due to high liver enzyme levels. Among them, 17 (2.85%) patients were from Group 1 and 14 (2.80%) were from Group 2 (p=0.97). All patients who discontinued amoidarone were over 70 years of age, and they were thin. Amiodarone had to be withdrawn because cardiac rhythm dropped below 44 beats/min in 107 (17.98%) patients in Group 1 and in 92 (18.4%) patients in Group 2. It was reinitiated when heart beat increased above 70 beats per minute.

A total of 15 patients, 9 in Group 1 (1.5%) and 6 in Group 2 (1.2%), died in the postoperative period due to multiorgan insufficiency caused by low cardiac flow rate. The difference between groups was not statistically significant (p=0.176). An intra-aortic balloon pump (IABP) was used in 8 (1.34%) patients in Group 1, as compared to only 4 (0.8%) patients in Group 2 (p=0.006). The mean hospital stay was 6.2 (±5.8) days in Group 1 and 4.9 (±3.6) days in Group 2, and the difference between groups was significant (p=0.001).

Patients' ECG records, obtained 3 weeks and 6 weeks after surgery, were scrutinized. One hundred and fifteen (19.3%) patients in Group 1 and 102 (20.4%) patients in Group 2 could not be get in touch with for various reasons. In patients who could get in touch with, the AF development rate during the first and second controls was 3% and 1.8% in Group 1 and 0.5% and 0.3% in Group 2, and the differences between the groups were statistically significant (p=0.002 and p=0.001, respectively). The LVEF values by through trans-thoracic echocardiography during controls were compared with the preoperative values. A significant improvement was observed when compared to intragroup postoperative values. Intergroup comparisons of postoperative LVEF values did not show statistically significant differences between Groups 1 and 2 in terms of 3 and 6-week LVEF values (p=0.067 and p=0.135, respectively). There was no difference between the groups for late cardiac problems (appearing after 30 days), such as congestive heart failure and ongoing angina pectoris (p=0.124). Data obtained from patients during postoperative period are summarized in Table 3.

DISCUSSION

Atrial fibrillation is the most frequently seen arrhythmia in patients who undergo CABG surgery

TABLE 3: Liver function tests and blood gases in the postoperative period.

	Group 1, n=595 (amiodarone after AF)	Group 2, n=500 (amiodarone as a prophylactic agent)	p value
pH (Mean±SD)	7.46±0.7	7.47±0.2	0.757
pO2 (Mean±SD)	87.4±6.8	88.6±5.7	0.651
pCO2 (Mean±SD)	38.4±0.7	39.2±0.4	0.082
AST* (Mean±SD)	44.1±2.3	43.6±0.8	0.621
ALT* (Mean±SD)	47.1±1.6	46.2±0.3	0.074
Preop EF (Mean±SD)	39.6±6.7	37.9±7.8	0.001
Postop 3th week EF (Mean±SD)	40.3±8.6	41.4±6.2	0.067
Postop 6th week EF (Mean±SD)	49.2±7.4	48.6±4.3	0.135
Postop first week AF rhythm, n (%)	12 (2.01)	14 (2.8)	0.002
Postop 3th week AF rhythm, n (%)	18 (3)	3 (0.5)	0.001
Postop 6th week AF rhythm n (%)	11 (1.8)	2 (0.3)	0.001
Refractory AF time of externation, n (%)	12 (2.01)	-- (0.0)	0.001

*: IU/L.

EF: Ejection fraction; SD: Standard deviation; AST: Aspartate amino transaminase; ALT: Alanine amino transaminase; Preop: Preoperative; Postop: Postoperative; AF: Atrial fibrillation.

due to ischemic cardiac disease. AF incidence increases with age.[6] Although great advances have been made in both cardiac surgery and intensive care follow ups in terms of personal skills and technique, there are publications reporting an increase in AF incidence rather than a significant decrease.[6,7] Elderly patient profile, presence of those with cardiac insufficiency, increased need for inotropic drugs, presence of hypertensive patients, presence of right coronary lesion, and male gender can be shown as reasons for this.[8,9] It is well known that AF development increases the risk of mortality, morbidity and stroke as well as the cost of therapy by prolonging the hospital stay.[8,10] Although a number of therapy methods were tried during the perioperative period to prevent development of postoperative AF, a therapy protocol accepted by all centers has not been established yet. Although some authors suggest use of magnesium, beta blockers, statins, and amiodarone in prophylaxis, other authors state that these are ineffective.[6,8,11] It has been shown that amiodarone, one of the most frequently used antiarrythmic agents worldwide, is effective in prevention and treatment of AF.[1,9,12,13] If AF develops in the postoperative period, the preferred first-line drug is amiodarone.[4,5] Amiodarone is a lipofilic, iodinized benzofuran compound, and it is a grade III antiarrythmic agent with widespread use in treatment of refractory and symptomatic ventricular and supraventricular tachyarrythmias.

It is well known that amiodarone, because of its negative inotropic effect, may cause heart failure, especially in patients with left ventricular dysfunction.[14] Its ability to be used both intravenously and orally is an advantage. Amiodarone has many side effects on a number of organs, including liver; however, the prevalence of serious side effects that could limit the use of drug is about 10-15%. In about 40% of patients using amiodarone as antiarrythmic, temporary liver enzyme elevations are seen. However, in 1-2% of patients, serious hepatic damage has been reported.[15] Unwanted effects disappear in the vast majority of patients by withdrawal of the drug. However, it may rarely result in more serious side effects, such as fatal toxic hepatitis. There are publications suggesting smaller daily doses instead of bigger doses, to prevent occurrence of side effects.[9,16] In our study, liver enzyme elevation was not significantly different between two groups. Amiodarone's half-life is 2-3 months and it may stay in the body for months, even after the drug is withdrawn.[17,18]

In a study by Yağdı et al., postoperative AF incidence in patients using prophylactic amiodarone post-CABG was 10.4% while this rate was 25% in patients who did not receive prophylactic amiodarone.[12] In our study, postoperative AF incidence in patients receiving prophylactic amiodarone post-CABG was 5.4% and this rate was 17% in patients who did not receive prophylactic amiodarone. These results are consistent with the literature.

One of the largest randomized amiodarone studies was PAPABEAR study. In this study, oral amiodarone prophylaxis of atrial tachyarrhythmia after cardiac surgery was found effective and safe. After this study, it was postulated that aggressive and routine arrhythmia prophylaxis with amiodarone was safer and more effective in the care of cardiac surgical patients. This approach could significantly reduce postoperative arrhythmias, which have occurred in as many as a third of cardiac patients in recent series.[19]

Selimoglu et al. reported that arrhythmia prophylaxis with amiodarone could significantly reduce postoperative arrhythmias after cardiac surgery.[20]

In our patients who received prophylactic amiodarone, the atrial and/or ventricular arrhythmia rates were lower and hospital stays were shorter. In this group, the rate of AF which returned to sinus rhythm spontaneously was also higher, and none of the patients was discharged with refractory AF. In patient groups using prophylactic amiodarone, AF development rates (late postoperative AF) during three and six week follow ups after operation were significantly lower. In addition, any impairment was not encountered in LVEF values of the patients using amiodarone. The most important factor affecting the results of our study was the considerable number of patients

who could not be get in touch with during the 6-week follow up (19.3% in Group 1 and 20.4% in Group 2).

Postoperative amiodarone therapy is well tolerated by patients who have undergone CABG surgery, and decreases the incidence of postoperative supraventricular arrhythmias considerably while not causing impairment in the left ventricular functions. However, liver enzymes must be closely monitored in the elderly and in thin patients. In the light of the data obtained from this study, we believe that prophylactic amiodarone is more effective, requires smaller doses, does not appear to cause any serious side effects, and reduces surgical costs by shortening hospital stay.

This study is retrospective and short-term results are reported. This is the major limitation of our study. Otherwise, the patients who had ventricular arrhythmias in the preoperative or postoperative period were not evaluated in the study.

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