

Carvedilol Is More Effective Than Metoprolol In Preventing The Atrial Fibrillation Seen After Coronary Artery Bypass Surgery

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ABSTRACT

Atrial fibrillation (AF) which is a common complication seen after open heart surgery may be a cause of postoperative heart failure and embolic events as well as it increases the hospitalization costs due to increased hospitalization duration. AF incidence is decreased by prophylactic beta blocker medication. In this study we retrospectively evaluated the prophylactic carvedilol and metoprolol medications in prevention of AF after coronary bypass surgery.

Materials and methods: The preoperative, perioperative and postoperative data of 146 patients who were operated for isolated coronary artery disease and who were under beta-blocker treatment were evaluated. Preoperatively 76 patients were under carvedilol medication whereas 70 patients were under metoprolol medication. Beta-blocker treatment was continued before and after the operation. Patients who had AF after the operation (group 1, n=27) and who don't have AF (group 2, n=119) were evaluated as separate groups.

Results: Univariate analysis showed that advanced age, left atrial dimensions, carvedilol medication and statin medication were related with postoperative AF. On the other hand multivariate analysis revealed that advanced age and left atrial dimensions were independent risk factors for postoperative AF occurrence whereas carvedilol medication was found to be an independent factor for prevention of AF. Postoperative hospitalization was significantly increased in patients with AF.

Conclusion: The incidence of postoperative AF is decreased by prophylactic beta-blocker medication. Carvedilol has a more prominent effect on prevention of AF when compared with metoprolol.

ÖZET

Koroner Arter Baypas Cerrahisi Sonrasında Görülen Atriyal Fibrilasyonun Önlenmesinde Karvedilol Metoprololden Daha Etkilidir

Açık kalp cerrahisinden sonar yaygın olaarak görülen bir komplikasyon olan Atriyal fibrilasyon (AF), post-operative dönemde kalp yetmezliğine, embolik olaylara neden olabilir ve hastanede kalış süresini de uzatarak hastane maliyetlerini artırabilir. Beta blokör tedavi uygulanması ile bu hastalarda AF görülme sıklığı azaltılabilmektedir. Bu araştırmada koroner arter baypas cerrahisi sonrasında AF gelişmesini önlemede karvedilol ve metoprolol kullanımını karşılaştırdık.

Gereç Yöntem: İzolekoroner arter baypas cerrahisi uygulanan, betabloker tedavisi alan 146 hastanın operasyon öncesinde, operasyon esnasında ve sonrasında kayıt edilen verileri değerlendirildi. Ameliyata alınmadan önceki dönemde 76 hasta karvedilol, 70 hasta metoprolol kullanmaktaydı. Beta blokör tedavisine ameliyat sabahına kadar devam edilerek ameliyattan sonar tekrar başlandı. Ameliyat sonrası AF ritmi görülen (grup 1, n=27) ve görülmeyen hastalar (grup 2, n=117) iki ayrı grup olarak değerlendirildi.

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Bulgular: İleri yaş, sol atriyum çapı, karvedilol tedavisi, statin tedavisi univaryans analiz ile değerlendirme sonucunda postoperative AF ritminin gelişiminde rol oynayan faktörler olarak tespit edildi. Multivaryans analiz ile bu faktörler değerlendirildiğinde ise ileri yaş ve sol atriyum çapları AF gelişiminde bağımsız risk faktörleri olarak tespit edilirken, karvedilol kullanımı AF gelişimi üzerine önleyici etkisi olan bağımsız bir faktör olarak belirlendi. Postoperatif dönemde hastanede kalış süresi AF ritmi görülen hastalarda belirgin olarak uzundu.

Sonuç: Atriyal fibrilasyon ritminin görülme sıklığı profilaktik betablokör kullanımı ile azaltılmaktadır. Karvedilol, koroner arter baypas cerrahisi sonrasında AF ritmi gelişmesini metoprolole göre belirgin oranda azaltmaktadır.

INTRODUCTION

The most commonly encountered complication in patients who have open heart surgery is new onset of atrial fibrillation (AF). Its incidence is 10-40% and is mostly seen in the 2nd and 4th postoperative day. Disappearance of atrial contractions may cause hemodynamic disorders (1-3). This arrhythmia which is mostly transient and responds to antiarrhythmic treatment has been found to be related with postoperative stroke, congestive heart failure, renal insufficiency, embolization, low cardiac output syndrome and increased intensive care unit and hospitalization length (4-5). It has also been shown to increase the hospitalization expenses. AF which has been described as benign up to the recent times is now proven to increase the early and late postoperative mortality (6).

Many factors are related with postoperative AF development such as advanced age, left heart failure, chronic obstructive pulmonary disease, ischemia-reperfusion injury, multi organ failure, electrolyte imbalances, left atrial dimensions, prolonged ventilator support, acidosis, inotropic support and discontinuation of beta-blockers (7-9).

Many agents have been studied in prevention of postoperative AF (10-11). The most common conclusion of these studies is that postoperative AF incidence is significantly decreased by beta-blocker treatment which is started before the operation and continued after the operation (12). American College of Cardiology and American Heart Association guidelines suggest beta-blocker treatment after coronary artery bypass grafting (CABG) for prevention of postoperative AF (13).

Recent clinical reports have shown that carvedilol has a role in prevention of postoperative AF occurrence (14-15). Carvedilol which is a nonselective adrenergic blocker has anti-inflammatory, antioxidant and multiple cationic channel blocker properties (15). Therefore carvedilol may decrease the reperfusion injury and inflammatory response which are related with AF development. Therefore, carvedilol may be more effective than the selective beta-1 blocker metoprolol in prevention of postoperative AF.

In this study evaluated the prophylactic carvedilol and metoprolol medications in prevention of AF after coronary bypass surgery.

METHODS

Patients and Study Groups

The study included 146 patients who were medicated with carvedilol or metoprolol before isolated CABG operation between November 2005 and December 2006. preoperative, perioperative and postoperative patient data were gathered. Exclusion criteria were patients who did not use beta-blocker before the operation, concomitant valvular pathology necessitating intervention, sick sinus syndrome, off-pump surgery and preoperative AF. The patients were divided into two groups according to development of AF in the postoperative period. Patients who had AF after the operation (group 1, n=27) and who don't have AF (group 2, n=119) were evaluated as separate groups. Patients continued betablocker medication up to the operation date.

Surgical Technique

The patients were operated under cardiopulmonary bypass (CPB). Standard median sternotomy incision was done. After preparation of the conduit grafts and intravenous anticoagulation with heparin, the pericardium was opened. Moderate degree hypothermia (32°C) and hemodilution (Htc ~ %22) was maintained under 2.2-2.4 L/m² CPB flow. Perfusion pressure was between 50- 85 mmHg during the CPB. Distal anastomosis was done in cross clamped aorta after hyperpotassemic cold blood cardioplegic arrest. The proximal anastomoses were done on side clamped aorta. Heparin was neutralized after the discontinuation of CPB.

Postoperative Follow-Up

Extubation criteria were hemodynamic stability, consciousness with normal muscular activity and normal mediastinal drainage. The chest drainage tubes were taken out when the drainage decreased below 10 ml/hr. Beta-blocker medication was continued if the oral intake of the patients was possible. The patients were monitored for the cardiac rhythm during their intensive care unit stay and up to their 5th postoperative day. Early after the operation and every day in the morning routine ECG evaluation was done. AF criteria were disappearance of p waves, irregular QRS intervals and

continuation of these more than 30 seconds. Patients who had the diagnosis of AF were continuously monitored during their hospitalization. The patients who had AF were anticoagulated and medicated with amiodarone.

Statistical Analysis

Statistical analysis was done with SPSS 12.0 statistical software program (Statistical Package for the Social Sciences, version 12.0, SPSS Inc., Chicago, Ill, USA). Continuous variables were expressed as mean \pm 1 SD.

In the Univariate analysis the difference between the groups according to categorical variables were analyzed by chi-square test whereas continuous variables were compared by the Mann-Whitney U-test. Multivariate analysis was done by multiple logistic regression (enter method) analysis; and odds ratio (ORs) and 95% confidence interval (%95 CI) were calculated. P values less than 0.05 were considered to be statistically significant.

RESULTS

Most of the patients were male (81.5%). Mean age was 62.05 ± 9.54 years. Age of the patients who developed AF were significantly higher ($p < 0.001$). Preoperative demographics and medication except carvedilol and metoprolol medications were similar in the groups (Table 1). Furthermore echocardiographic data were evaluated and left atrial dimensions were significantly higher in the AF group (Table 1). The groups were similar according to their operative data. The lowest body temperature measured during CPB was lower in the AF group without statistical significance ($p = 0.066$) (Table 2).

Factors causing AF were analyzed with Univariate analysis and advanced age, dilated left atrial dimensions, statin medication, and beta-blocker medication were found to be statistically related with AF development (Table 1). Logistic regression analysis revealed that carvedilol medication ($p < 0.001$, ORs: 1.102, 95%CI: 1.045-1.161), age ($p < 0.001$, ORs: 9.091, 95%CI: 2.832-29.178) and LA dimension ($p < 0.05$, ORs: 1.090, 95%CI: 1.017-1.168) were independent factors for postoperative AF.

AF was developed after a mean 2.14 ± 0.90 days in the postoperative period. It continued to mean 24.66 ± 30.08 hours. No mortality was seen in this patient population. One patient was in normal sinus rhythm after 15th postoperative date. Intensive care unit follow-up and hospitalization durations were significantly higher in the patients with AF ($p < 0.05$). One patient with AF and metoprolol treatment had cerebral embolization in the postoperative period.

DISCUSSION

Postoperative AF is still an important problem for the surgeons in spite of the increased number of

series, technologic developments, improvements in myocardial protection methods, and increased surgical experience. There are a lot of studies in the literature concerning this subject. Especially the prophylactic effects of beta-blockers are common conclusion of most of these studies. The meta-analysis of 27 randomized prospective studies including 3840 patients has shown that prophylactic beta-blocker treatment decreases the postoperative AF incidence from 33% to 19% (8). Although beta-blockers are known to prevent postoperative AF, there is limited number of comparative studies (16). These studies reveal that nearly all newly developed AF disappears in six weeks; however embolic events and hemodynamic deterioration are seen more during this period (17).

Although the mechanism of AF after cardiac surgery has not been clarified yet, mechanical injuries to the atrial structures, hypertension, volume overload, atrial ischemia induced by the operation, electrolyte imbalances and pericardial lesions were blamed for AF development (7,18). However the effects of these factors on AF development are still on debate. In addition to these, it has been proven that inflammation and oxidative injury are more on atrial tissue during the operation (3,6,7,19). Besides, C-reactive protein levels have been high in the patients who had postoperative AF (20,21). Prophylactic ascorbic acid and statins have been shown to prevent the postoperative AF development after the relation between postoperative AF and oxidative injury has been exposed (22,23). These studies all show the importance of inflammation and oxidative injury in development of postoperative AF.

Age, beta-blocker medication and congestive heart failure have been found to be related with but independent factors for AF development (24,25,26). In addition to these, DM, pericardial effusion, arrhythmias before the operation, redo cardiac operations and off-pump coronary artery bypass surgery have been found to be independent risk factors (27,28). This can be explained by the diagnostic criteria of AF, inclusion and exclusion criteria of the study and different surgical techniques. In the present study, advanced age and left atrial dimension were risk factors whereas preoperative carvedilol medication was a prophylactic factor for postoperative AF development.

Carvedilol has anti-inflammatory and antioxidant properties besides its being a commonly used agent for congestive heart failure and after myocardial infarction (15,28,29,30). Different from the other beta-blockers, it antagonizes the rapid depolarized sodium channels and L-type calcium channels (29,30). Therefore, carvedilol has similar pharmacologic properties with the amiodarone which is used for treatment of postoperative AF (31). Carvedilol antagonizes the α_1 receptors as well as beta 1 and beta 2 receptors; therefore it decreases

Table 1: Characteristics of the patients

	Group 1 (n=27)	Group2 (n=119)	Univariate p value
Age (year)	68.59 ± 8.14	60.57 ± 9.23	P < 0.001
Female:Male	2/25	24/95	NS
Angina			
No	2	7	
Stable	15	78	NS
Unstable	10	32	
MI	11	29	NS
HT	15	87	NS
COPD	3	3	NS
DM	12	35	NS
LMCA	12	43	NS
Carvedilol /metoprolol	5/22	71/48	P < 0.05
Statin	11	77	P < 0.05
ACE inhibitor	17	76	NS
Ca channel blocker	5	39	NS
Nitrate	18	68	NS
Digoxin	7	22	NS
EF (%)	46.14 ± 8.89	49.51 ± 8.91	NS
LA (mm)	39.51 ± 8.33	35.58 ± 6.41	P < 0.05
LVEDD (mm)	46.51 ± 6.73	45.38 ± 5.92	NS
LVESD (mm)	37.19 ± 7.93	34.47 ± 7.42	NS

(MI: Myocardial infarction, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, LMCA: Left main coronary artery lesion, ACE: Angiotensin converting enzyme, EF: Ejection fraction, LA; Left atrium, LVEDD; Left ventricular enddiastolic diameter, LVESD; Left ventricular endsystolic diameter, NS: Non significant)

Table 2: Perioperative data of the patients

	Group 1 (n=27)	Group2 (n=119)	Univariate p value
Cross clamp time (min)	77.00±29.18	78.97±23.54	NS
Cardiopulmonary bypass time (min)	117.11 ± 39.22	125.03 ± 39.65	NS
Minimal rectal temperature (?C)	31.11 ± 3.10	32.15 ± 2.51	NS
Number of Distal anastomosis	2.66 ± 0.55	2.82 ± 0.54	NS
Defibrillation (%)	7.4	14.3	NS
Inotropic support	4	13	NS
Intra Aortic Balloon Counterpulsation	3	7	NS
Intensive care unit follow-up (hour)	62.22 ± 20.32	44.08 ± 18.58	P < 0.001
Ventilator support (hour)	10.48 ± 4.18	8.39 ± 3.26	P < 0.05
Mobilization time (hour)	25.22 ± 7.58	22.22 ± 8.35	NS
Blood transfusion (450 ml pack)	1.37 ± 1.00	1.34 ± 1.11	NS
Mediastinal drainage (ml)	763.88 ± 281.29	715.79 ± 245.46	NS
Hemoglobin (gr/dL) Postoperative 1st hour	11.65 ± 1.26	11.52 ± 1.44	NS
Hematocrit (%) Postoperative 1st hour	33.00 ± 4.16	33.24 ± 4.16	NS
WBC (K/ μ L) Postoperative 1st hour	14.32 ± 4.40	12.52 ± 4.97	NS
Creatinine (mg/dL) Postoperative 1st hour	1.19 ± 0.25	1.21 ± 0.38	NS

WBC: White blood cell

Table 3: Multivariate analysis results of the factors which have a role on postoperative AF development

Factors	Ba	p value	Exp(B)b	95% CI Exp(B)
Age	0.093	0.000	1.098	1.043-1.156
LA dimension	0.079	0.033	1.082	1.006-1.163
Carvedilol medication	2.268	0.000	9.656	2.904-32.110

the cardiac norepinephrine levels and increases the parasympathetic tonus. In this situation, arrhythmia incidence including AF decreases (29,30). Carvedilol show antioxidant properties by increasing the superoxide dismutase and glutathione synthetase enzyme levels. However metoprolol does not have anti-inflammatory or antioxidant property (32).

In the present study the incidence of AF was found to be lower in the patients who were on statin treatment. However statin treatment was not found to be a independent factor in multivariate analysis. Independent from their lipid lowering properties, statins have anti-inflammatory effects. This anti-inflammatory effect is related with their CRP lowering effect on hyperlipidemic patients (33). Statins have prevented postoperative AF development with their anti-inflammatory affects in experimental studies (34). Although the present study proved on univariate analysis that statins prevented AF development, it may be useful in these patients.

Besides the drugs, different techniques have also been studied for prevention of AF. Some of these are cardiopulmonary bypass techniques, cardioplegia methods, hypothermia, bypass conduit grafts, left ventricular venting and different pericardiotomy techniques (35). In the present study only the coronary artery bypass operations done under cardiopulmonary bypass were studied. Moderate degree hypothermia and antegrade cold blood cardioplegia techniques were used in all of the patients. The groups were similar according to surgical techniques used, graft selections, cross clamp times, cardiopulmonary bypass times. Body temperature of the patient during cardiopulmonary bypass was lower in the patients in whom AF developed but this difference was not statistically significant ($p=0.06$). Sun and coworkers reported that sympathetic activity increased during the warming period after hypothermic CPB and this might be responsible for postoperative AF (35).

Advanced age like beta-blocker and congestive heart failure is closely related independent factor. The present study revealed that the age of the patients in the AF group was significantly higher when compared with the other group ($p<0.001$). Structural changes like dilatation, focal fibrosis and muscular atrophy occur in the atrial tissue with increased age (36). The effects of these changes become evident with the mechanical injury during the surgery and volume overload during CPB. As a result changes in the local atrial refractory period which lead to AF occur (37).

There are many studies which report that AF increases the hospitalization duration and costs. In the present study, the hospitalization length was higher in the AF group. This also reflects to the hospitalization costs. However no cost analysis was done in the present study. Tamis et al (3) re-

ported that hospitalization duration did not increase in all but in the patients with long lasting or recurrent AF. It has been emphasized that AF should not have been accepted as a single pattern arrhythmia and it should have been followed up and treated with different strategies for different patterns.

There are studies which report that the post operation ventilator support is higher in patients with AF. On the other hand AF is frequently seen on the 2nd-4th postoperative days. Extubation is mostly before this period. So it is contradictory whether prolonged intubation is caused by AF or AF is caused by prolonged intubation. The present study did not reveal any statistical significance between the ventilator support and AF. As a summary; AF is a common but unwanted complication after CABG. Studies concerning preventive measures are still going on. Advanced age and left atrial dimensions were independent risk factors for postoperative AF development. AF risk may be decreased by preoperative carvedilol medication. Preventive effect of carvedilol which is an anti-inflammatory and antioxidant agent on AF is superior to metoprolol. Prophylactic carvedilol medication which is started before the operation especially in the patients with advanced age and increased left atrial dimensions may decrease the postoperative AF incidence.

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