

Prophylactic Amiodarone Administration Before Intraoperative Radiofrequency Ablation

Intraoperatif Radyofrekans Ablasyon Öncesi Profilaktik Amiodaron Uygulaması

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Giriş: Bu çalışma, profilaktik amiodaron tedavisinin intraoperatif radyofrekans ablasyonunun sonuçları üzerine etkisini değerlendirmek amacıyla planlandı.

Hastalar ve Yöntem: İntraoperatif radyofrekans ablasyonu uygulanmak üzere seçilen 80 hasta bu çalışmaya katıldı ve bu hastalar 2 gruba randomize edildi: ilk grup operasyondan önce 24 saat süreyle 30mg/saat amiodaron alırken, 2. gruba plasebo verildi. Klinik çıktılara ek olarak kalp hızları ve kalp ritmi hastanede kalım süresince ve 1. ayın sonunda kaydedildi.

Bulgular: Demografik ve kardiyak bulgular her iki grupta da benzerdi. Her ne kadar hastaneye yatırılma sırasındaki kalp hızları benzerse de (102,07±16,04 amiodaron grubu için ve 99,17±17,23 kontrol grubu için, p=0,477), anestezi indüksiyonu (83,17±11,77, p<0,001) ve taburculuk sırasında (79,83±10,08, p=0,012) kalp hızları amiodaron grubunda anlamlı olarak düşük bulundu. Hastaneye yatırılma sırasında ve anestezi indüksiyonunda bütün hastalar atriyal fibrilasyondaydı. Radyofrekans ablasyonu sonrası amiodaron grubundaki 31 (77,5%) hasta ve kontrol grubundaki 29 (72,5%) hasta sinus ritmindeydi, aradaki fark anlamlı değildi (p=0,770). Birinci ayın sonunda kalp hızları (83,91±9,11 amiodaron grubu için ve 86,41±9,31 kontrol grubu için, p=0,671) ve sinus ritmindeki hasta sayısı (amiodaron grubunda 29, kontrol grubunda 28 hasta, p=1) gruplar arasında benzerdi.

Tartışma: Preoperatif amiodaron kullanımı kalp hızında operasyondan önce ve sonra anlamlı düşüş kaydetmekle beraber, radyofrekans ablasyonunun başarı oranını değiştirmemektedir.

Anahtar Sözcükler: *Atriyal Fibrilasyon, Mitral Kapak, Aritmiler*

Objectives: This study was designed to evaluate the effects of prophylactic amiodarone infusion on the outcomes of intraoperative radiofrequency ablation.

Design: Eighty patients who were scheduled for intraoperative radiofrequency ablation were enrolled in this study and randomized into two groups: first group received 30mg/h amiodarone 24 hours before the operation, and the second group received placebo. Heart rates and cardiac rhythms in addition to clinical outcomes were measured during hospitalization and at the end of the 1st month.

Results: The demographic and cardiac data were similar in both groups. Although the heart rates at the time of admission were similar between groups (102,07±16,04 for amiodarone group and 99,17±17,23 for control group, p=0,477), they were significantly lower in the amiodarone group at the time of anesthesia induction (83,17±11,77, p<0,001) and discharge (79,83±10,08, p=0,012). All the patients in both groups were in AF at the time of admission and anesthesia induction. Following RFA 31 (77,5%) of the patients in the amiodarone group and 29 (72,5%) of the patients in the control group were in NSR, and the difference was insignificant (p=0,770). At the end of the first month the mean heart rates (83,91±9,11 for amiodarone group and 86,41±9,31 for control group, p=0,671) and the number of patients in NSR (29 patients in amiodarone group and 28 patients in control group, p=1) were similar between groups.

Conclusion: Preoperative use of amiodarone makes a significant decrease in heart rate before and after the operation but doesn't change the success rate of radiofrequency ablation.

Key Words: *Atrial Fibrillation, Mitral Valve, Arrhythmias*

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Atrial fibrillation (AF) is a common arrhythmia, seen in 0,4% of the general population, and 1% of the older patients (>60 years) (1,2). It is present in 60-84% of the patients who are

scheduled for mitral valve operation, but only 15-21% of these patients remain in normal sinus rhythm (NSR) following the operation (3,4). The risk factors for persistent postoperative AF

are believed to be older age, prolonged duration of AF, larger left atrium diameter, and rheumatoid heart disease in etiology (5).

The main hemodynamic disturbances and the incidence of thromboembolic events are higher in patients with AF which make permanent treatment of AF more important and life saving. The presence of AF is an independent risk factor for stroke. When compared with AF-free patients, there is a 5 fold increase in the incidence of stroke (6).

In the past a few number of surgical methods were defined aiming to treat AF, but the most effective one has been the Maze procedure, which was first performed by Cox et al (7). It is a set of atrial incisions aimed at interrupting the atrial macro re-entrant circuits which were believed to be the cause of AF. The success of the procedure in reported series is about 80-95% (7-15). But this procedure significantly lengthens both the cross-clamp and operation times, and increases the postoperative bleeding risk (16). As a result Maze procedure can only be performed at definite cardiac centers by experienced surgeons.

The complexity of the Maze procedure forced the surgeons to investigate less complex techniques which were as successful as the Cox-Maze III.

Percutaneous radiofrequency ablation has been performed by cardiologist for many years (17). However it was first used intraoperatively by Melo et al. (21), and today it has been performed widely in many centers. Early and midterm results were found as successful as Maze procedure (14-21). After the definition of the technique, many modifications of the procedure and new ablation catheters were studied and many studies are still continuing in many centers.

The goal of this study is to evaluate the effects of prophylactic infusion of preoperative amiodarone on the outcomes of intraoperative radiofrequency ablation.

Material and Methods

Patient Selection

Eighty patients who were scheduled for intraoperative radiofrequency ablation (RFA) for the treatment of long-lasting permanent atrial fibrillation were enrolled in this study. RFA was performed in addition to a mitral valve procedure.

All the patients were informed about the study and informed consents were taken from all, which was approved by the Ethics Committee.

Patients who had preoperative thyroid disease, diffuse coronary artery disease, EF less than 40%, acute mitral valve endocarditis were excluded from the study.

Patients were randomly assigned in a double-blind fashion either to an amiodarone group receiving intravenous amiodarone or to a control group receiving intravenous placebo. Patients received 30mg/h amiodarone infusion following 150mg of rapid infusion (in 15 minutes). The infusion dose was lowered to half in case of bradycardia or hypotension, and increased to 30mg/h after hemodynamic recovery.

Operative Data

Following anesthesia induction and systemic heparinization cardiopulmonary bypass was started with routine bicaval cannulation. Cardiac arrest was achieved with systemic cooling and antegrade cardioplegia. The ablation procedure was always performed before other surgical procedures. A monopolar surgical catheter (Cardioblate TM, Medtronic) at a reference temperature of 80C with an impedance of 25Watt was used to perform the lesions in Figure-1.

After systemic warming if adequate cardiac rhythm couldn't be maintained patients were paced before weaning of CPB. Administration of amiodarone was started with an intravenous

bolus of 150mg before the end of CPB and followed by an infusion of 900mg/24h for a day. Oral administration of 600mg/24h in 3 divided doses was begun for a week following first postoperative day and maintained with 1x200mg/24h for 3 months. Operative and postoperative amiodarone were administered in both groups.

Patients were kept in the intensive care unit for a day and carried to the ward if the early postoperative period was eventful. Monitorized telemetric ECG follow up was performed in the first 2 postoperative days additional to 12 lead ECG obtained in every 6 hours, and daily ECG follow up was continued until discharge. Transthoracic echocardiography was performed by a specialized cardiologist on the first postoperative day and discharge. The blood potassium levels were kept between 4,5 and 5,5 mEq/L during hospitalization.

At the end of the 1st month all the patients were also examined with echocardiography and Holter ECG was obtained.

Statistical Analysis

All data were expressed as mean \pm standard deviation and p value <0,05 were found to be statistically significant. Continuous variables were analyzed by Student's t and Mann-Whitney U-test, where appropriate. Chi-square and Fisher's Exact test were used to test categorical variables between two groups. Statistical analysis of data was conducted for statistics (SPSS 11.0 for Windows, SPSS Inc).

Results

There were no hospital mortality and all the patients in both groups completed the study. There were 28 male and 12 female patients with a mean age of 53,20 \pm 9,44 in the amiodarone group, whereas 25 of the patients were male and 15 were female in the control group, and the mean age in this group was 49,47 \pm 11,71. The other demographic data listed in Table-1.

Table 1: Demographic and cardiac data.

VARIABLE	AMIODARONE GROUP	CONTROL GROUP	P
Number of patients	40	40	
Mean Age (y)	53,20±9,44	49,47±11,71	0,179
Sex Ratio (M/F)	28/12	25/15	0,478
EF	49,80±5,25	47,70±5,56	0,137
Diabetes Mellitus	5	7	0,531
Hypertension	9	7	0,576
NYHA CLASS			
I	10	9	0,792
II	15	13	0,639
III	10	10	1
IV	5	8	0,363
LA diameter	5,53±0,49	5,57±0,57	0,888
AF duration	3,07±1,44	2,67±1,40	0,266
HEART RATE admission	102,07±16,04	99,17±17,23	0,477
HEART RATE anesthesia induction	83,17±11,77	102,90±24,57	<0,001
HEART RATE discharge	79,83±10,08	85,43±9,94	0,012
HEART RATE 1st month	83,91±9,11	86,41±9,31	0,671

Table 2: Operative and postoperative data.

VARIABLE	AMIODARONE GROUP	CONTROL GROUP	P
Number of patients	40	40	
Hospital Mortality	-	-	
Cross clamp time (min)	49,53±13,84	54,50±13,54	0,088
CPB time (min)	74,53±18,15	80,17±20,03	0,230
RFA duration (min)	11,26±1,55	11,08±1,43	0,744
Reexploration	1	0	1,000
Postoperative drainage	452,50±122,89	394,17±94,16	0,068
Use of blood products (units)			
Erythrocyte	1,27±0,5	1,23±0,5	0,765
Thrombocytes	2,47±1,0	2,43±0,9	0,806
Fresh frozen plasma	2,20±0,6	2,13±0,5	0,750
Inotropic requirement	5	4	0,723
ICU stay (h)	38,27±9,3	34,27±7,2	0,099
Hospital stay (days)	8,53±1,7	7,87±1,5	0,103

The mean ejection fraction was 49,80±5,25 for the amiodarone group and 47,70±5,56 for the control group, and the mean left atrial diameter in the amiodarone and control group were 5,53±0,49 cm and 5,57±0,57 cm respectively. The cardiac data also listed in Table-1.

In none of the patients severe adverse effects of amiodarone were observed and all of them received amiodarone as indicated above.

Radiofrequency ablation with a monopolar

catheter (Cardioblate TM, Medtronic) was performed additional to mitral valve procedures with/without a concomitant heart procedure. The left sided RFA lesions were performed as shown in the Figure-1. The mean RFA durations in both groups weren't significantly different (11,26±1,55 and 11,08±1,43, p=0,744). Also other operative data were similar between groups (Table-2).

In the postoperative period only one patient was re-explored for bleeding. The mean amount of postoperative

bleeding and the number of blood products were similar in both groups and listed in Table-2. The procedures additional to RFA were listed in Table-3.

The mean heart rates at the time of admission were similar between groups (102,07±16,04 for amiodarone group and 99,17±17,23 for control group, p=0,477), after amiodarone infusion there was a decrease in heart rates measured at the time of anesthesia induction compared to admission (83,17±11,77 rates/min), but the heart rates at the time of anesthesia induction were similar to the admission values in the control group (102,90±24,57) and the p value was <0,001, which was significant between groups.

After RFA there was a decrease in the mean heart rate of the control group (85,43 ± 9,94), however the mean heart rate of the amiodarone group was significantly lower (79,83 ± 10,08) than the control group (p=0,012) at the time of discharge.

There were significant differences in mean heart rates between the groups, but the rhythms of the patients in the both groups were similar at the time of admission, anesthesia induction and discharge. All the patients (n=80) were in AF at the time of admission and at the time of anesthesia induction. Following RFA 31 (77,5%) of the patients in the amiodarone group and 29 (72,5%) of the patients in the control group were in NSR and the difference was insignificant with a p value of 0,770. Nine patients were in junctional rhythm following RFA, 4 of these were in amiodarone group and 5 were in the control group. And 2 patients in each group required temporary pacing.

We didn't observe any complication due to RFA procedure in any of the patients involved in the study.

The durations of ICU and hospitalization were 38,27±9,26 hours and 8,53±1,65 days respectively in the amiodarone group and 34,27±7,2 hours and

Table 3: Cardiac procedures performed additional to RFA.

OPERATIONS	AMIODARONE GROUP	CONTROL GROUP
Total number of patients	40	40
MVR	13	11
MVRe	9	10
MVR+TRA	6	4
MVRe+TRA	2	3
AVR+MVR	2	-
MVR+CABG+TRA	1	1
MVRe+CABG+TRA	-	2
MVR+CABG	3	3
MVRe+CABG	4	6

*MVR; mitral valve replacement, MVRe; mitral valve repair, TRA; tricuspid ring annuloplasti, AVR;aortic valve replacement, CABG;coronary artery bypass grafting

7,87±1,48 days in the control group, which were insignificant between groups.

At the end of the first month all of the patients were examined with TTE and 12 lead ECG was obtained. The mean heart rates (83,91±9,11 for amiodarone group and 86,41±9,31 for control group, p=0,671) and the number of patients in NSR (29 patients in amiodarone group and 28 patients in control group, p=1) were similar between groups.

Discussion

Cox-maze procedure has been the most commonly performed surgical treatment for long lasting permanent atrial fibrillation (7, 14-16). Despite its impressive results in treating AF; this procedure significantly lengthens both the cross-clamp and operation times, it increases the postoperative bleeding risk, and can be performed only by experienced surgeons (14-16). For these reasons Cox-Maze-III procedure can only be performed in definite cardiac centers.

The requirement of a less invasive technique for the surgical treatment of AF forced surgeons to perform studies on alternative procedures. The aim of these studies was to find a technique which was as successful as Maze procedure and less complex.

After the use of RF energy intraoperatively for the treatment of AF by Melo et al. in 1998 (18)studies with intraoperative ablation using different energy sources were carried in many cardiovascular departments all over the world (22-24). Though various energy sources were used since 1998 radiofrequency has been the most widely used technique. Many studies carried out to increase the success of the intraoperative RFA, which includes the first use of cooled-tip RF catheters, use of different energy levels, especially the invention of bipolar catheter has been another milestone in surgical treatment of AF, with proven transmuralit (25).

In the GAP study performed by Kerstein et al. it's been reported that the administration of IV amiodarone in conjunction with oral amiodarone preoperatively appears to be a hemodynamically well-tolerated, safe, and

effective treatment in decreasing the incidence of postoperative atrial fibrillation, shortening length of stay, and a trend toward lowering hospital costs, even in patients with significantly reduced left ventricular functions (26). Also amiodarone has been the commonly used drug following RFA in the postoperative period. Nowadays many centers are practicing the postoperative amiodarone administration as a part of intraoperative RFA procedure (14, 21).

Studies were performed concerning postoperative drug treatment in addition to surgical technique; however there are no reports studying the effects of preoperative medications in the literature. In our study amiodarone was infused a day before the surgery and continued after the surgery for 24h intravenously and maintained orally. We didn't experience any side effects due to the medication. Only 4 of the patients experienced temporary hypotension attacks which didn't require cessation of the medication.

At time of admission the hearts rates were similar in both groups however at the time of anesthesia induction, after amiodarone infusion, the heart rates were significantly lower in the amiodarone group than the control group. Following RFA heart rates of the control

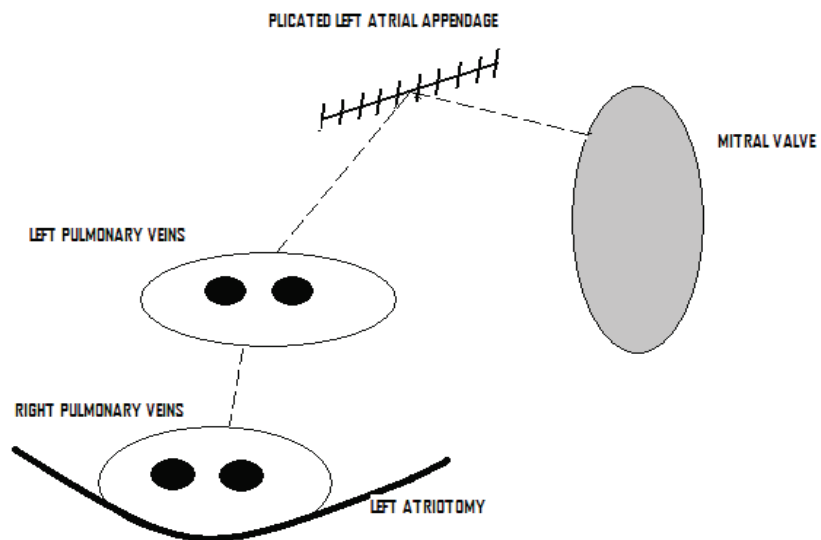


Figure 1: Left Sided Radiofrequency Ablation Lesions.

group also decreased, but the discharge heart rates were still significantly lower in the amiodarone group. Although the patients in amiodarone group have lower heart rates this doesn't make any clinical significance during the study period.

The main decrease in heart rate was at the time of anesthesia induction in the amiodarone group just after the infusion of amiodarone and didn't change after RFA ablation. But the patients were in AF before the RFA and were in NSR after the procedure. The heart rates of the patients in control group didn't change after the infusion of placebo but significantly decreased after surgical ablation. There were more patients in NSR in amiodarone group compared to the control group but the difference wasn't significant. Also the clinical courses of the patients in both groups were similar.

We assume that the safe and effective use

of amiodarone requires a firm understanding of its unusual pharmacokinetics. During the analyzes of the both groups, we surprised with the results, however, one of the properties of highly lipophilic amiodarone compound which results in a delayed onset of action (an interval of 2 to 3 days) and a long elimination half-life (up to 6 months) may be responsible from these outcomes (27). We predict this effect of amiodarone action is due to a substantial lag between the initiation, modification, or discontinuation of treatment with amiodarone, and a change in drug activity. As Hauser et al point out, given the delay in the onset of antiarrhythmic action with amiodarone, it is common for atrial fibrillation to persist or recur during the loading phase of drug administration; however, this does not predict rates of sinus rhythm at 1 month (28). We believe that the further studies including the blood level of amiodarone taken after the procedure may enlighten this

latent activity of amiodarone.

As a conclusion preoperative use of amiodarone makes a significant decrease in heart rate before and after the operation, which doesn't lead a clinical significance. Also it doesn't change the success rate of radiofrequency ablation in the early and late postoperative period.

The limitations of this study included the relatively small number of patients involved in each group. However this is the first study, even with 80 patients, evaluating the effects of preoperative prophylactic administration of amiodarone on the outcomes of intraoperative radiofrequency ablation in treating long lasting permanent AF. The strengths of this study are that it is a prospective study of a consecutive group of patients with 100% follow-up. Further studies with larger group of patients with longer follow up periods must be performed.

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