

Comparison of amiodarone and propafenone for maintenance of stable sinus rhythm after bipolar radiofrequency ablation combined with a mitral valve procedure in patients with mitral valve disease and persistent atrial fibrillation

Mitral kapak hastalığı ve uzun süreli atriyal fibrilasyonu olan hastalarda mitral kapak işlemi ile kombine yapılan bipolar radyofrekans ablasyon sonrasında stabil sinüs ritminin devamlılığının sağlanmasında amiodaron ve propafenonun karşılaştırılması

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ABSTRACT

Background: This study aims to examine the effects of amiodarone versus propafenone for maintenance of stable sinus rhythm after left atrial bipolar radiofrequency ablation combined with a mitral valve procedure in patients with mitral valve disease and persistent atrial fibrillation.

Methods: The study included 75 patients (29 males, 46 females; mean age 66,8±7.4 years; range 54 to 82 years) who underwent left atrial bipolar radiofrequency ablation combined with mitral valve surgery between July 2008 and July 2010. Patients were divided into three groups of 25: propafenone group (group 1), amiodarone group (group 2), and control group (group 3). Atrial fibrillation patients with slow ventricular response were excluded from the study.

Results: Data was collected at preoperative period, during surgery, prior to discharge from hospital, and at 3, 6, and 18 months after discharge. Patients from all groups were followed for 18 months. In group 1, the number of patients in sinus rhythm was 22 at discharge, 20 at three months, and 21 at six and 18 months. In group 2, the number of patients in sinus rhythm was 18 at discharge, 13 at three months, 15 at six months, and 16 at 18 months. In group 3, the number of patients in sinus rhythm was 16 at discharge, 11 at three months, 12 at six months, and 14 at 18 months. Group 1 had a statistically significantly higher rate of stable sinus rhythm. No hospital mortality was observed in any group.

Conclusion: This study revealed that propafenone was more effective than amiodarone in maintenance of stable sinus rhythm at the postoperative period in patients who underwent bipolar radiofrequency ablation combined with a mitral valve procedure.

Keywords: Amiodarone; mitral valve surgery; propafenone; radiofrequency ablation.

ÖZ

Amaç: Bu çalışmada mitral kapak hastalığı ve uzun süreli atriyal fibrilasyonu olan hastalarda mitral kapak işlemi ile kombine bipolar radyofrekans ablasyon sonrasında stabil sinüs devamlılığının sağlanmasında amiodaron ve propafenonun etkileri karşılaştırıldı.

Çalışma planı: Temmuz 2008 - Temmuz 2010 tarihleri arasında mitral kapak cerrahisi ile kombine bipolar radyofrekans ablasyon yapılan 75 hasta (29 erkek, 46 kadın; ort. yaş 66,8±7.4; dağılım 54-82 yıl) çalışmaya dahil edildi. Hastalar 25'er kişilik üç gruba ayrıldı: propafenon grubu (grup 1), amiodaron grubu (grup 2) ve kontrol grubu (grup 3). Yavaş ventrikül yanıtı atriyal fibrilasyonu olan hastalar çalışma dışı bırakıldı.

Bulgular: Veriler ameliyat öncesi dönemde, ameliyat sırasında, taburculuk öncesinde ve taburculuk sonrası 3, 6. ve 18. aylarda toplandı. Tüm gruplardaki hastalar 18 ay izlendi. Grup 1'de sinüs ritminde kalan hasta sayıları taburculuk anında, üç, altı ve 18. aylarda sırasıyla 22, 20, 21 ve 21 idi. Grup 2'de sinüs ritminde kalan hasta sayısı taburculuk anında, üç, altı ve 18. aylarda sırasıyla 18, 13, 15 ve 16 idi. Grup 3'te sinüs ritminde kalan hasta sayısı taburculuk anında, üç, altı ve 18. aylarda sırasıyla 16, 11, 12 ve 14 idi. Grup 1 istatistiksel olarak anlamlı derecede daha yüksek oranda stabil sinüs ritmine sahipti. Hiçbir grupta hastane mortalitesi görülmüdü.

Sonuç: Bu çalışma mitral kapak işlemi ile kombine bipolar radyofrekans ablasyon yapılan hastalarda ameliyat sonrasındaki dönemde stabil sinüs ritim devamlılığının sağlanmasında propafenonun amiodarona göre daha etkili olduğunu gösterdi.

Anahtar sözcükler: Amiodaron; mitral kapak cerrahisi; propafenon; radyofrekans ablasyon.



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Atrial fibrillation (AF) is the most common heart rhythm disorder in adults and is responsible for significant cardiovascular morbidity and mortality, primarily due to thromboembolism.^[1] Pharmacological therapy, in particular the use of amiodarone, is still the most frequent choice for treating AF during the postoperative period, but according to Calò et al.,^[2] a medical regimen is unsuccessful in between 50 and 84% of patients with persistent AF. Thus, several surgical techniques, such as left atrial (LA) isolation, catheter ablation of the bundle of His, the corridor procedure, pulmonary button isolation, and the atrial compartment operation have been used to treat this condition. The maze III procedure was developed by Cox et al.,^[3] and because of its high success rate, it has become the gold standard for the surgical treatment of AF. In this method, various parts of both atria are cut and sewn to block the spread of chaotic electrical activity by forming areas of isolation in the atrial musculature. Unfortunately, since it is a complex and time-consuming procedure, experience is required, and there is a high rate of complications. Recently, alternative energy sources such as radiofrequency (RF), microwave, laser, bipolar cauterization, and cryoablation have been developed that allow for the creation of isolating lines without the need for cutting the tissue, thus making ablation easier.

The aim of this study was to examine the effects of amiodarone versus propafenone for the maintenance of stable sinus rhythm after undergoing LA bipolar RF ablation in conjunction with a mitral valve procedure in patients with mitral valve disease and persistent AF.

PATIENTS AND METHODS

The study was comprised of 75 patients who underwent a left atrial bipolar radiofrequency ablation procedure in conjunction with mitral valve surgery between July 2008 and July 2010. The patients were randomly divided into three groups. Group 1 (9 males and 16 females; mean age 66.7 ± 8.1 years) was given propafenone, group 2 was given amiodarone (10 males and 15 females; mean age 66.6 ± 8.02), and group 3 served as the control group (9 males, 16 females; mean age 66.9 ± 7.88 years). The local ethics committee approved the study protocol, and all patients gave their written consent to be included. Patients who required additional surgery, for example coronary bypass grafting or aortic valve surgery, were excluded from the study, but those who needed tricuspid intervention were not excluded.

The primary endpoint was a return to AF. Propafenone was one of the available anti-arrhythmic

drugs in our hospital, so it was selected to compare its efficacy against that of amiodarone. The ablation procedure was performed on the study participants in the three groups who had persistent AF plus mitral valve disease, but the AF cases with slow or normal ventricular response (heart rhythm <90 /minute) did not undergo this procedure. In addition, standard 12-lead electrocardiography (ECG), Holter ECG, transthoracic echocardiography (TTE), left and right heart catheterization, and coronary angiography were performed preoperatively on all of the patients and controls who were over the age of 40.

After the median sternotomy, the patients underwent aortic and bicaval venous cannulation. Antegrade blood cardioplegia was used for induction, and continuous retrograde blood cardioplegia via the coronary sinus was utilized to maintain myocardial protection. Mitral valve replacement was performed on all of the members of groups 1, 2, and 3. The surgical treatment for persistent AF was accomplished by means of a bipolar radiofrequency irrigated ablation system (Cardioblate®, Medtronic Inc., Minneapolis, MN), and pulmonary vein isolation, LA appendage isolation and plication were also carried out.

In group 1, the propafenone (Rytmonorm, Abbott Laboratuvarları İth. İhr. ve Tic. Ltd. Şti., İstanbul, Turkey) was administered nasogastrically via an infusion (560 mg/day) on the day of the surgery. After extubation, it was given orally (150 mg three times a day) for one month followed by the same dosage twice a day for three months and then once a day for 18 months. In addition, all of the patients were started on anticoagulation therapy (warfarin) for the life span of the mechanical mitral valve.

Group 2 was administered amiodarone (Cordarone) as an intravenous bolus (150 mg) before the completion of cardiopulmonary bypass (CPB) followed by an infusion of 900 mg/day for two days. It was then given orally (3×200 mg) for one month, but the dosage could be adjusted depending on body weight. This was followed by 2×200 mg/day for the next 18 months. In addition, all of the patients were also started on anticoagulation therapy (warfarin).

Warfarin was also given to group 3, and they received cardiac medication without any anti-arrhythmic drugs as well.

Data analysis

Statistical analysis was performed using the SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) software package with a confidence interval (CI) of 95%. Chi-square, Mann-Whitney U, and Wilcoxon

Table 1. Preoperative data

	Group 1			Group 2			Group 3			<i>p</i>
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age			66.7±8.1			66.6±8.0			66.9±7.9	>0.05
Gender										
Female	16			15			16			>0.05
Male	9			10			9			
NYHA class			3.1±0.6			3.2±0.6			3.2±0.6	>0.05
COPD	3	12		5	20		4	16		>0.05
Body mass index			24.1±2.6			24.3±2.4			24.3±2.6	>0.05
Ejection fraction			50.0±7.5			50.4±7.5			51.2±7.9	>0.05
Hypertension	10	40		12	48		9	36		>0.05

SD: Standard deviation; NYHA: NewYork Heart Association; COPD: Chronic obstructive pulmonary disease.

tests were used for all analyses, and a *p* value of <0.05 was considered to be statistically significant.

RESULTS

Our results showed no statistically significant differences between the three groups, and there were also no significant differences with regard to the preoperative data, which is shown in Tables 1 and 2.

In addition, no significant differences was detected between the mean cross-clamp and CPB times in groups 1 and 2. Furthermore, three patients in group 1, four in group 2, and three members of group 3 underwent tricuspid annuloplasty (Table 3).

No hospital mortality was observed in groups 1 and 2. Follow-up appointments were carried out for 18 months, and the number of patients in sinus rhythm in group 1 was 22 at discharge, 20 after three months, and 21 after six and 18 months. In group 2, 18 patients were in sinus rhythm at discharge while 13 achieved this state after three months, 15 after six months, and 16 after 18 months. In group 3, there were 16 patients in sinus rhythm at discharge while there were 11 after three months, 12 after six months, and 14 after 18 months. The rate of sinus rhythm was significantly higher in group 1 than in groups 2 and 3.

In addition, group 2 had better results than group 3, but the differences between the two groups did not reach statistical significance. (Table 4, Figure 1).

DISCUSSION

The increase in mortality associated with AF is related to the underlying cardiovascular condition. The main goal in patients with this condition is to restore and maintain a stable sinus rhythm. Atrial fibrillation has multiple clinical consequences. Patients can experience a rapid ventricular rate without AV synchronization as well as the loss of atrial contraction, resulting in reduced cardiac output and potential heart failure. Furthermore, AF increases the risk of stroke and doubles the rate of death.^[4] The risk of thromboembolic complications caused by blood stasis in the atria leads to systemic anticoagulation stemming from the associated risk of bleeding. Non-persistent AF usually culminates in persistent AF, the final form of this disease.^[5] In our series, the bipolar RF approach was used because it is less invasive and is associated with a shorter aortic cross-clamp time. In addition, all of the patients and controls were operated on by the same surgical team. In the literature, left atrial (LA) enlargement has been a strong independent risk factor for the failure of the pulmonary vein isolation

Table 2. Preoperative data

	Group 1	Group 2	Group 3	<i>p</i>
	Mean±SD	Mean±SD	Mean±SD	
Left atrial diameter	46.2±5.1	46.2±5.0	47.0±5.7	>0.05
Left ventricular enddiastolic diameter	51.1±5.5	51.1±5.1	52.1±6.0	>0.05
Left ventricular endsystolic diameter	42.4±4.8	42.3±4.9	43.0±5.1	>0.05
Pulmonary artery pressure	44.4±5.8	44.5±5.2	43.9±5.0	>0.05

SD: Standard deviation.

Table 3. Operative data

	Group 1			Group 2			Group 3			<i>p</i>
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Aortic clamp time			40.2±3.7			40.5±3.7			35.2±6.1	>0.05
Cardiopulmonary bypass time			55.9±5.5			56.2±5.7			50.2±5.0	>0.05
Number who had tricuspid annuloplasties	3	12		4	16		4	16		>0.05

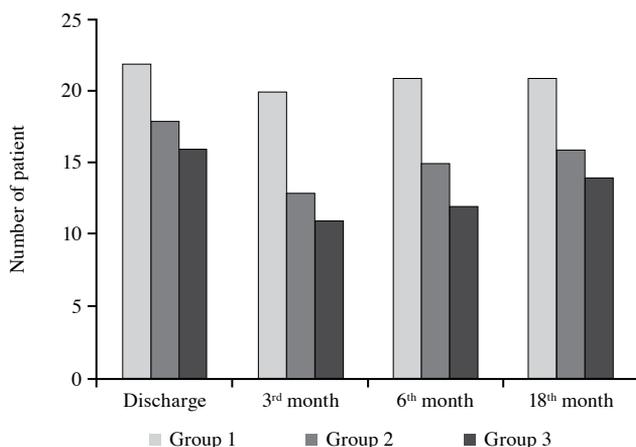
SD: Standard deviation.

Table 4. Postoperative data

	Group 1		Group 2		Group 3		<i>p</i>
	n	%	n	%	n	%	
At discharge	22	88	18	72	16	64	0.06
At the 3 rd month	20	80	13	52	11	44	0.03
At the 6 th month	21	84	15	60	12	48	0.034
At the 18 th month	21	84	16	64	14	56	0.041

procedure, which has led to a tendency toward it being performed selectively.^[6] Isobe and Kawashima^[6] reported that the risk of persistent AF after pulmonary vein isolation surgery is higher in patients with an LA diameter of greater than 80 mm. Conversely, Choo et al.^[7] recently reported that pulmonary vein isolation surgery was successful in 95% of mechanical ventilation (MV) patients with an LA diameter equal to or greater than 60 mm. Other authors have also joined Choo et al.^[7] in recommending a policy of aggressive LA size reduction in persistent AF patients with a dilated LA.^[8,9] However, in our series, we found no significant differences between the three groups with respect to LA diameter.

Nevertheless, it remains unclear whether the LA size itself is the only critical issue. It is reasonable to expect

**Figure 1.** Postoperative data.

that cellular, structural morphological, and parallel electrophysiological changes in the atrial tissue play a more prominent role in the progressive enlargement and hypertrophy of the atria.^[10,11] Restoration of sinus rhythm by ablation leads to a greater quality of life (QoL), especially when compared with patients who have persistent AF that experience a sustained abnormal heartbeat and undergo mitral valve surgery.^[12] Moreover, Pappone et al.^[13] reported reduced mortality and morbidity and an improved QoL in patients who underwent circumferential pulmonary vein ablation for AF versus those treated with medical therapy alone. In our study, no hospital mortality occurred.

Between 30 and 79% of patients who undergo mitral valve surgery have AF, and less than 10% of those will enjoy a spontaneous conversion to sinus rhythm after isolated mitral valve surgery.^[14] Patients who are cardioverted following mitral valve repair or replacement have a better survival rate as well as freedom from adverse events.^[15-17] Recently, new methods and devices have been available to facilitate the surgical treatment of AF during mitral valve interventions, and sinus rhythm can now be restored in the majority of patients with persistent AF. Our observations suggest that patients who receive treatment for AF during mitral valve surgery have a better QoL. Therefore, we strongly recommend this type of therapy for all patients with persistent AF who are also scheduled for mitral surgery.

Ablation is the gold standard treatment for AF; however, maintaining sinus rhythm in cardioverted patients is actually more important. The cardioversion

of AF to sinus rhythm via the pulmonary vein isolation procedure followed by maintenance therapy with amiodarone is the most commonly prescribe treatment.^[18] However, in this study, we investigated whether propafenone could serve as an alternative to amiodarone and found that it actually provided better patient outcomes.

Anti-arrhythmic drug selection is crucial because of the need to maintain a stable sinus rhythm. Camm^[19] determined that amiodarone was the most effective anti-arrhythmic drug but believed that its safety profile limited its usefulness. Freemantle et al.^[20] also found that amiodarone was the most effective drug for maintaining sinus rhythm. However, differences in outcomes between anti-arrhythmic drugs have been reported,^[21] with sotalol and possibly amiodarone increasing mortality. However, in their study, Feyrer et al.^[21] found no significant differences between the amiodarone and non-drug groups in their study on the restoration and maintenance of sinus rhythm in patients who underwent surgical ablation. Similarly, we also determined that there were no significant differences between the controls (group 3) and the patients taking amiodarone (group 2). Furthermore, Ventura et al.^[22] reported that patients who were previously medicated with amiodarone had a higher recurrence rate of arrhythmia compared with those who had not been previously medicated with anti-arrhythmic drugs or those who had been medicated with anti-arrhythmic that had short plasma half-lives, in particular propafenone. Additionally, in their series, Sestito and Molina^[23] found no differences regarding the side effects of propafenone and a placebo, and Larbuisson et al.^[24] suggested that propafenone produces a more prompt effect in converting patients from AF to normal sinus rhythm than amiodarone.

Conclusion

In this study, our findings indicated that propafenone was associated with better outcomes than amiodarone with respect to the restoration and maintenance of sinus rhythm during the postoperative period in patients who underwent valvular surgery in conjunction with ablation therapy for AF. Therefore, we recommend the use of propafenone because of its higher tolerability and effectiveness and its low incidence of side effects. However, more studies are needed to support our results.

Declaration of conflicting interests

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REFERENCES

1. Ezekowitz MD, Netrebko PI. Anticoagulation in management of atrial fibrillation. *Curr Opin Cardiol* 2003;18:26-31.
2. Calò L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol* 2005;45:1723-8.
3. Cox JL, Schuessler RB, Lappas DG, Boineau JP. An 8 1/2-year clinical experience with surgery for atrial fibrillation. *Ann Surg* 1996;224:267-73.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946-52.
5. Fuster V, Rydén LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. *Circulation* 2001;104:2118-50.
6. Isobe F, Kawashima Y. The outcome and indications of the Cox maze III procedure for chronic atrial fibrillation with mitral valve disease. *J Thorac Cardiovasc Surg* 1998;116:220-7.
7. Choo SJ, Park NH, Lee SK, Kim JW, Song JK, Song H, et al. Excellent results for atrial fibrillation surgery in the presence of giant left atrium and mitral valve disease. *Eur J Cardiothorac Surg* 2004;26:336-41.
8. Scherer M, Dzemali O, Aybek T, Wimmer-Greinecker G, Moritz A. Impact of left atrial size reduction on chronic atrial fibrillation in mitral valve surgery. *J Heart Valve Dis* 2003;12:469-74.
9. Bayrak S, Sahin A, Kestelli M, Yılık L, Gunes T, Gurbuz A. The effect of atrium diameter on the succesful treatment of atrial fibrillation through the radiofrequency ablation technique. *Turk Gogus Kalp Dama* 2012;20:503-9.
10. Kawara T, Derksen R, de Groot JR, Coronel R, Tasseron S, Linnenbank AC, et al. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. *Circulation* 2001;104:3069-75.
11. Biffi M, Boriani G. Atrial remodeling: evolving concepts. *Indian Pacing Electrophysiol J* 2003;3:81-7.
12. Forlani S, De Paulis R, Guerrieri Wolf L, Greco R, Polisca P, Moscarelli M, et al. Conversion to sinus rhythm by ablation improves quality of life in patients submitted to mitral valve surgery. *Ann Thorac Surg* 2006;81:863-7.
13. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G,

- Mazzone P, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *J Am Coll Cardiol* 2003;42:185-97.
14. Jessurun ER, van Hemel NM, Kelder JC, Elbers S, de la Rivière AB, Defauw JJ, et al. Mitral valve surgery and atrial fibrillation: is atrial fibrillation surgery also needed? *Eur J Cardiothorac Surg* 2000;17:530-7.
 15. Bando K, Kobayashi J, Kosakai Y, Hirata M, Sasako Y, Nakatani S, et al. Impact of Cox maze procedure on outcome in patients with atrial fibrillation and mitral valve disease. *J Thorac Cardiovasc Surg* 2002;124:575-83.
 16. Lakkireddy D, Nagarajan D, Di Biase L, Vanga SR, Mahapatra S, Jared Bunch T, et al. Radiofrequency ablation of atrial fibrillation in patients with mitral or aortic mechanical prosthetic valves: a feasibility, safety, and efficacy study. *Heart Rhythm* 2011;8:975-80.
 17. Hussein AA, Wazni OM, Harb S, Joseph L, Chamsi-Pasha M, Bhargava M, et al. Radiofrequency ablation of atrial fibrillation in patients with mechanical mitral valve prostheses safety, feasibility, electrophysiologic findings, and outcomes. *J Am Coll Cardiol* 2011;58:596-602.
 18. Yılık L, Bayatlı K, Lafcı B, Emreçan B, Kestelli M, Ozbek C, et al. Early and mid-term results of irrigated radiofrequency left atrial ablation in chronic atrial fibrillation with concomitant mitral valvular pathology. *Turk Gogus Kalp Dama* 2006;14:185-8.
 19. Camm J. Antiarrhythmic drugs for the maintenance of sinus rhythm: risks and benefits. *Int J Cardiol* 2012 ;155:362-71.
 20. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;13:329-45.
 21. Feyrer R, Ballazhi F, Seitz T, Weyand M, Harig F. Impact of medical treatment on long-term results after surgical ablation of atrial fibrillation in cardiac surgical patients. *Ann Thorac Cardiovasc Surg* 2014;20:207-12.
 22. Ventura M, Elvas L, Providência L. Previous therapy with amiodarone increases the recurrence rate in successfully ablated patients with isthmus-dependent atrial flutter. *Rev Port Cardiol* 2004;23:1303-11. [Abstract]
 23. Sestito A, Molina E. Atrial fibrillation and the pharmacological treatment: the role of propafenone. *Eur Rev Med Pharmacol Sci* 2012;16:242-53.
 24. Larbuisson R, Venneman I, Stiels B. The efficacy and safety of intravenous propafenone versus intravenous amiodarone in the conversion of atrial fibrillation or flutter after cardiac surgery. *J Cardiothorac Vasc Anesth* 1996;10:229-34.