Prevention of recurrent cryptogenic stroke with percutaneous closure of patent foramen ovale; one year follow-up study with magnetic resonance imaging and Holter monitoring

Foramen ovale açıklığının perkütan kapatılmasıyla tekrarlayan kriptojenik inmenin önlenmesi; manyetik rezonans görüntüleme ve Holter monitörizasyonu ile bir yıllık izlem çalışması

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ABSTRACT

Objectives: In this study, we aimed to evaluate the effect of percutaneous closure of patent foramen ovale (PFO) on the recurrence of stroke and new cardiac arrhythmia using magnetic resonance imaging (MRI) and Holter monitoring.

Study design: Patients with PFO had >1 previous stroke or transient ischemic attack documented with MRI in the first event. PFO with right to left shunt was detected by transesophageal echocardiography (TEE) and transcranial Doppler ultrasound. MRI examinations were performed on patients before and one year after PFO closure was applied. A twenty-four hour Holter monitoring was performed in all patients within 1 month before and 6 months after the procedure.

Results: Percutaneous PFO closure was performed on 47 patients (25 female, mean age: 38.7 years) who had cerebral ischemic events detected by MRI. A year after the procedure, TEE showed that there was no residual interatrial right-to-left shunting. After a 14 month follow-up, no new cerebrovascular event and no new lesion on MRI were recorded. The incidence of arrhythmia did not increase significantly after the procedure on Holter monitoring (p=0.917).

Conclusion: One-year clinical and MRI follow-up study of patients with cerebral ischemic events and percutaneous closure of PFO showed no recurrent event and no significant complication associated with the procedure. In addition, Holter monitorization demonstrated that the procedure did not increase the incidence of arrhythmias compared with pre-procedural monitoring.

ÖZET

Amaç: Bu çalışmada, foramen ovale açıklığının (FOA) perkütan yolla kapatılmasının tekrarlayan inmeleri önlemesi ve yeni aritmi oluşumuna etkisi manyetik rezonans görüntüleme (MRG) ve Holter monitörizasyonu ile değerlendirildi.

Çalışma planı: Tüm hastalar birden fazla kez MRG ile tanısı doğrulanmış inme veya geçici iskemik atak geçirmişlerdi. Sağdan sola geçişin olduğu FOA tanısı, transözofajiyal ekokardiyografi (TÖE) ve transkraniyal Doppler ile gösterildi. Manyetik rezonans görüntüleme ile değerlendirme, FOA kapatılmadan önce ve bir yıl sonra yapıldı. Yirmi dört saatlik Holter monitörizasyonu işlemden önceki bir ay içinde ve işlemden sonra altıncı ayda yapıldı.

Bulgular: Daha önce MRG ile tespit edilmiş serebral iskemik olayı olan 47 hastada (25 kadın, ortalama yaş: 38.7 yıl) FOA, perkütan yolla kapatıldı. Bir yıl sonra yapılan TÖE ile hiçbir hastada kalıcı sağdan sola geçiş izlenmedi. On dört aylık izleme sonucunda yeni serebrovasküler olay veya MRG'de yeni lezyonlar görülmedi. Holter monitörizasyonu ile aritmi insidansı işlem sonrasında anlamlı derecede artış göstermedi (p=0.917).

Sonuç: Klinik ve MRG ile yapılan bir yıllık izleme sonucunda, perkütan yolla FOA kapatılan hastalarda tekrarlayan iskemik olay ve işleme bağlı ciddi bir komplikasyon görülmemiştir. Ayrıca Holter monitörizasyonu, işleme bağlı aritmi insidansında işlem öncesine göre artış olmadığını göstermiştir.

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The etiology of ischemic stroke remains unknown in up to 40% of patients despite extensive diagnostic evaluation, and it is defined as cryptogenic stroke.[1] Patent foramen ovale (PFO) is an anatomical interatrial communication having the potential for right-to-left shunt and paradoxical embolization. Several studies suggested a link between cryptogenic stroke and PFO as a possible etiological mechanism.[2,3] The prevalence of PFO in patients with cryptogenic stroke is significantly higher, with estimates ranging from 30% to as much as 70%.[4] Different findings about the association between PFO and cryptogenic cerebral ischemic events necessitated new studies aimed at determining the risk of PFO for ischemic events or whether percutaneous PFO closure decreased recurrent cerebral ischemic events.

Although percutaneous closure of PFO has emerged as an alternative treatment strategy for lifelong anticoagulation, the data relevant to the efficacy of this approach has been evaluated mainly in non-randomized studies, single center experiences and a limited number of randomized studies.[5-10] Recently, certain meta-analysis and reviews didn't demonstrate any benefit of percutaneous closure in prevention of stroke.[11,12] Additionally, the presence of PFO was found to be associated with cerebral ischemic events which might be clinically silent, and percutaneous closure of PFO resulted in few clinical or silent cranial events.[13,14] In addition, percutaneous closure contains several peri-procedural complications such as arrhythmia, arterio-venous fistula formation, device embolization or thrombosis.[15]

Despite extensive interventional and clinical experience in percutaneous closure of PFO, there is limited data regarding follow-up of these patients beyond clinical data. In this study, we aimed to evaluate whether percutaneous PFO closure prevents recurrent cerebral ischemic events detected by cranial magnetic resonance imaging (MRI) examination, and to evaluate the efficacy and safety of the procedure, including for arrhythmic events.

PATIENTS AND METHODS

Patients with cryptogenic stroke who were admitted or referred to our cardiology department were prospectively enrolled for this study. Cryptogenic stroke is defined as the unknown cause of stroke despite extensive investigation to exclude other causes, such as aortic and carotid atheroma, carotid dissection, cardioembolic causes as well as intracerebral hemorrhage and space-occupying lesions.[16] A complete blood count, blood biochemistry, electrocardiography and chest x-ray were performed at the initial clinical visit. Neurological examination, transcranial Doppler ultrasonography and hypercoagulability screening were also added. In all patients with cryptogenic stroke, the decision for PFO closure was made in collaboration with the neurology clinic in our center. Exclusion criteria were cardioembolic causes including valvular heart diseases, atrial fibrillation, cardiac thrombus or mass and infective endocarditis, significant stenosis of the carotid arteries, known thrombophilic disorders, pregnancy, acute infection, allergic reaction to clopidogrel, acetyl salicylic acid, and nickel, age <18 years, and patients with emboli due to any causes other than PFO. The study protocol was approved by the local ethics committee and informed consent was received from each patient.

Abbreviations:

ASA	*Atrial septal aneurysm*
DWI	*Diffusion weighted imaging*
FLAIR	*Fluid-attenuated inversion recovery*
MRI	*Magnetic resonance imaging*
PFO	*Patent foramen ovale*
SVPB	*Supraventricular premature beats*
TCD	*Transcranial Doppler ultrasound*
TEE	*Transesophageal echocardiography*
TIA	*Transient ischemic attacks*
TTE	*Transthoracic echocardiography*
VPB	*Ventricular premature beat*

In all patients, transthoracic echocardiography (TTE) was performed initially and transesophageal echocardiography (TEE) was used subsequently to diagnose right-to-left shunt. All echocardiographic examinations were performed by an experienced cardiologist by using cardiac ultrasound machine Vivid Five (GE Vingmed Ultrasound AS, Horten, Norway). The diagnosis of PFO was made after an agitated saline contrast study which showed a spontaneous or Valsalva maneuver-induced interatrial right-to-left shunt.[17] A positive bubble study was defined as the passage of at least 3 bubbles through the interatrial septum within three beats of right atrial filling with agitated saline.[18,19] The diagnosis of atrial septal aneurysm (ASA) was made in the presence of several components including: (I) the atrial septum protruding at least 1.5 cm beyond the plane of the interatrial septum or phasic excursion exceeding 1.5 cm, (II) the base of the aneurysm being greater than 1.5 cm in diameter.[20]

A twenty-four hour Holter monitorization was performed on all patients before the procedure and 6 months after the intervention (ELA Medical Corp, Montrouge, France). Early monitorization was performed in case of suspected new arrhythmias. If supraventricular premature beats (SVPB) were >2000 beat/day, it was considered as frequent. Ventricular premature beat (VPB) stage was assessed as occasional if its frequency was <30 beats/hour, and as frequent if it was >30 beats/hour according to previous definitions.[21]

In addition to TEE, right-to-left shunt was also confirmed by neurologists in transcranial Doppler ultrasound (TCD) studies. A contrast agent with a mixture of isotonic saline solution 9 ml and air 1 ml was prepared. A pulse-wave Doppler of the middle cerebral artery was recorded at rest and, if negative, after a Valsalva maneuver. Passage of the microbubbles was evaluated for 25 s after the end of the Valsalva maneuver. Quantification of shunt was defined as class 0 in the absence of microbubbles passage, class 1 in the passage of 1-10 microbubbles passage, class 2 in the passage of 10-25 microbubbles passage, class3 for the passage of more than 25 microbubbles passage (without curtain effect), and class 4 for massive microbubbles passage with curtain effect, making it impossible to count the number of spikes. The examination was considered positive for a shunt level of ≥1.

Magnetic resonance imaging (MRI) was performed on a 1.5 T scanner (Symphony; Siemens Medical Systems, Erlangen, Germany). The area of stroke was identified on the diffusion weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR), and T2-weighted sequences. Acute strokes were identified initially on the DWI sequence, and older lesions appeared on T2 and FLAIR sequences (Figure 1). The vascular territories (anterior, middle, and posterior cerebral artery; infratentorial arteries) of all ischemic lesions were noted according to previous studies.[22] Based on the vascular territories, the lesion patterns were divided into three groups: (1) single lesion; (2) multiple lesions within one vascular territory; and (3) multiple lesions involving more than one vascular territory. MRI studies (i.e. pre-procedural, and follow-up) were analyzed by two independent expert observers (one stroke neurologist and one neuroradiologist); in case of disagreement final consensus was achieved.

Before the intervention, all patients having cryptogenic stroke underwent TEE examination for the confirmation of right-to-left shunt, as well as for assessment of remaining cardiac structures and left atrial thrombus. The procedure was guided and monitored for placement of the device by TTE and fluoroscopy. Length of the PFO tunnel, mobility of interatrial septum, presence or absence of ASA or multiple fenestrations are the main factors determining the appropriate device size. The passage of a 0.035-inch exchange wire was controlled best with TTE from apical four chamber or subcostal views. After documenting the correct position under fluoroscopic guidance, location of the device and its relationship to neighboring structures was also controlled with TTE. Special attention was given to detect possible impingement on the atrioventricular valves or any obstruction of the caval or pulmonary veins.[23] The Amplatzer PFO occluder (AGA Medical Corporation, Golden Valley, MN, USA®) and Occlutech Figulla PFO Occluder (International Occlutech AB, Helsingborg, Sweden®) were used to close the defect. 300 mg aspirin and 75 mg clopidogrel was given to all patients for six months and they were informed about the prophylaxis for infective endocarditis for the first 6 months. Clinical evaluation, TTE with saline contrast study, and TCD were performed in the 1st, 6th and 12th months, and annually thereafter.

Statistical analysis

Continuous variables were expressed as mean±SD and categorical variables were expressed as percentages. Comparisons of categorical and continuous variables between the two groups were performed

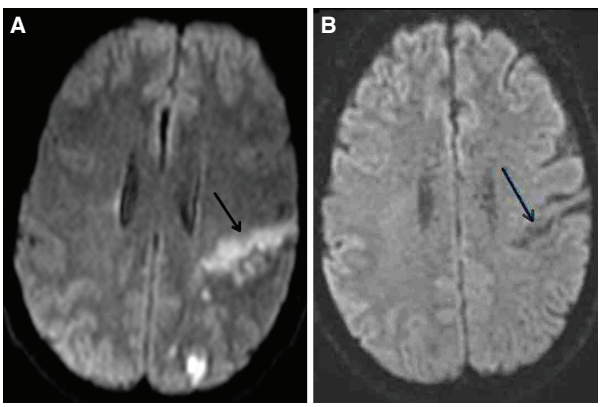

Figure 1. (A) Diffusion weighted imaging shows acute ischemic lesion (arrow) before the PFO closure. **(B)** On the post-procedural examination, chronic ischemic lesion (arrow) is seen in the left posterior central gyrus.

using the chi-square test and independent samples t-test respectively. Statistical analyses were performed using SPSS statistical software (version 15.0; SPSS Inc., Chicago, IL, USA). A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

In 47 patients (25 [53.2%] female, mean age: 38.7 years), percutaneous PFO closure was successfully performed under TTE guidance. The baseline demographic characteristics of the study population are illustrated in Table 1. TTE examination showed that all patients had normal chamber size, normal ejection fraction, and no moderate or severe valvular disease. ASA was detected in addition to PFO in 6 (12.7%) patients. TCD examination showed that six (12.7%) patients had large right-to-left shunt (class 4); fourteen (29.8%) patients had class 3, thirteen (27.6%) patients had class 2, and fourteen patients (29.7%) had class 1 right-to-left shunt (Table 2).

A twenty-four hour Holter monitorization was performed on all study patients. Before the procedure, occasional SVPB in 4 (8.5%), and occasional VPB in 3 (6.3%) patients was recorded. Two (4.2%) patients

Table 1. Baseline demographic characteristics of the study population

Parameters	n=47		
	n	%	Mean±SD
Age			39±11.1
Male gender	22	46.8	
Diabetes mellitus	1	2.1	
Hyperlipidemia	2	8.5	
Smoking	2	6.4	
Migraine	1	2.1	
Stroke	33	70.2	
Transient ischemic attack	14	29.8	
Peripheral embolism	None	None	
>1 clinical event	47	100	

Table 2. Baseline ultrasonography characteristics

	n	%	Mean±SD
Left ventricle ejection fraction (%)			67.2±5.2
Left ventricle end-diastolic diameter (mm)			46.6±4.9
Left ventricle end-systolic diameter (mm)			28.9±4.6
Left atrium (mm)			31±4.2
Right atrium (mm)			22.3±3.1
Pulmonary artery pressure (mmHg)			25.8±6.6
Patent foramen ovale only	41	72.3	
Patent foramen ovale+Atrial septal aneurysm	6	12.7	
Right-to-left shunt on transcranial doppler			
Class 1	14	29.8	
Class 2	13	27.6	
Class 3	14	29.8	
Class 4	6	12.7	

Table 3. Procedural and follow-up data

	n	%	Mean±SD
Procedural success	47	100	
18 mm	6	12.8	
25 mm	41	87.2	
Amplatzer device	34	72.3	
Figulla device	13	27.7	
Mean procedure time, minutes			28.7±5.5
Mean fluoroscopy time, minutes			3.6±1.2
Migration device	None	None	
Perforation	None	None	
Residual shunt (transcranial doppler)	3	6.4	
Residual shunt (transesophageal echocardiography)	None	None	
New cerebrovascular event	None	None	
Death	None	None	
Thrombus on the device	None	None	
Arrhythmia during the procedure	2	4.2	

had occasional SVPBs, 2 (4.2%) had frequent SVPBs, 1 (2.1%) had occasional VPB, 2 (4.2%) had frequent VPB, and 1 (2.1%) had mobitz type 1 AV block after the procedure. Atrial fibrillation, atrial flutter or atrial tachycardia was not detected after the procedure. Eventually, the incidence of arrhythmia did not statistically increase after the procedure (p=0.917).

For closure, we used an Amplatzer PFO occluder device in 34 (72.3%) patients, and an Occlutech Figulla PFO occluder devices in 13 (27.7%) patients. The device was successfully implanted in all patients. The mean fluoroscopy time and the mean procedure time were 3.6 ±1.2 and 28.7±5.5 minutes respectively. We observed atrial fibrillation episodes in 2 (4.2%) patients during the left atrial instrumentation, which converted to sinus rhythm during the procedure without any treatment. Major complications like device embolization, thrombus formation, fracture or migration was not observed in any patient. Two patients experienced mild inguinal hematomas, which resolved without any treatment. TCD showed persistent shunt in 3 patients (6%) at six months after the procedure, while TEE examination did not reveal any residual defect on the device. Special attention was given to the detection of any increase in gradient or insufficiency in the aortic or mitral valves, as well as the position of device in the interatrial septum during the echocardiographic evaluation, neither of which revealed any change during the follow-up. None of the patients had clinically significant complaints like chest pain, dyspnea, palpitations or syncope (Table 3).

All patients had experienced two or more previous stroke or transient ischemic attacks previously (TIA). The indications for PFO closure were ischemic stroke in 33 (70.2%), transient ischemic attacks in 14 (29.8%) of the patients. When MRI findings were evaluated, patients were more likely to have left-sided lesions (58.1% for left side vs. 41.9% for right side, p=0.040). Anterior circulation was more often involved than posterior circulation (63.7% vs. 36.3%, p=0.042, respectively). Two patients (4.3%) had single ischemic lesions, fifteen patients (31.9%) had multiple lesions within one vascular territory, and thirty patients (63.8%) had multiple lesions involving more than one vascular territory. During the follow-up period (mean 14±6.4 months) there was no death, stroke, or TIA. Cranial MRI study demonstrated previous ischemic lesions at the same location and there was no new infarct on MRI examination.

DISCUSSION

Our study demonstrated that percutaneous closure of PFO might offer a favorable clinical outcome evalu-

ated by both clinical and MRI examination. Follow-up MRI examination demonstrated no new cranial lesion after 1 year. The present study also showed that percutaneous closure of PFO was associated with a high success rate, low incidence of procedural and in-hospital complications, and an excellent short-term outcome. In addition, Holter monitorization detected only inconsiderable arrhythmic events after the procedure.

In a previous study, Ruchat et al.[24] reported that in 118 patients surgical closure of a PFO reduced the risk of both clinical events and silent new brain lesions detected by cranial MRI efficiently. Likewise, in another study including 71 patients, only one clinical event was reported and only one patient showed new clinically silent lesions at cranial MRI during a 13.6-month follow-up period.[13] Our study showed no clinical or silent new cerebral ischemic events after 14 months of follow-up.

Despite the favorable results after percutaneous closure of PFO reported in single center experiences, CLOSURE 1 trial failed to show a benefit of PFO closure for patients with cryptogenic stroke. However, the results of that study did not rule out the possibility that some patients might benefit from PFO closure. Furthermore, CLOSURE 1 outcomes might be influenced by several factors, including device-type, thrombus formation and tendency for atrial fibrillation affecting both procedural success and long term outcomes. Thrombus formation after device implantation has been extensively investigated and its prevalence has been reported to be around 2%.[25] The majority of these clots were seen on devices with uncoated metal arms (like the StarFLEX devices®), but very rarely on PFO occluder devices with nitinol wire frame filled with polyester fabric (like the Amplatzer or Figulla occluder devices).[26] In the RESPECT trial, interventional and medical therapy yielded similar outcomes in patients with previous cryptogenic stroke and a patent foramen ovale. However, a subgroup analysis revealed better outcomes with percutaneous closure than medical therapy in patients with an atrial septal aneurysm or a moderate or severe right-to-left shunt.[10] More recently, Meier et al.[8] conducted a randomized trial of 414 cryptogenic embolism patients with PFO. In this trial, closure of a patent foramen ovale did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy, and there was no evidence of device-associated thrombi in any patient. The meta-analysis of three randomized trials (CLOSURE I, RESPECT and PC Trial) showed that individual randomized trials have failed to demonstrate the benefit of percutaneous closure of PFOs in patients with cryptogenic strokes; however, when the three randomized trials data are pooled, it appears that successful transcatheter closure of PFO might be more effective than medical therapy alone for the prevention of recurrent thromboembolic events.[27] Another important point of the procedure for clinical outcome is device type. Recently published meta-analysis without the CLOSURE trial found that the Amplatzer PFO occluder device was associated with significant reduction in recurrent strokes compared with medical therapy.[11]

In addition to the presence of PFO, the anatomical characteristics of the interatrial septum also affect the clinical course in patients with cryptogenic stroke.[28] In accordance with this data, atrial septal aneurysm (ASA) has been identified as an indicator of a particularly high stroke risk in patients with PFO.[29,30] In addition, recurrent thromboembolic events after percutaneous closure of the PFO have been linked to the persistence of a communication between the atria. Although six patients (12.8%) in our study had ASA, none of these patients had a clinical or silent ischemic event after PFO closure, and TCD showed a small residual shunt in three patients evaluated three months after the closure. However, TEE evaluation was carried out in these patients, and residual shunt was not detected. Although TCD appears to be the desirable technique to identify subjects with residual shunts after percutaneous closure of a PFO, its specificity and positive predictive value was low compared with TEE.[31]

In the present study, we found that cerebral ischemic lesions are frequently located at the left side of brain. Previous studies tried to explain the differing right–left propensity of cerebral infarct. A proposed mechanism is that the brachiocephalic artery supplying blood to the right side of the brain has a larger caliber than the left carotid artery. Furthermore, the direction of brachiocephalic trunk is upwards and parallel to the direction of the ascending aorta, whereas the left carotid artery arises perpendicular to the aortic arch. Therefore, it was shown that cardiac embolism was frequently associated with brain lesions on the

right side.[32] However our results are contrary to previous findings and may be explained by a low patient number. In addition, it was previously reported that cognitive deficits associated with right-hemisphere lesions might be less clinically obvious compared to left-hemisphere lesions. Therefore, patients with left-sided lesions would more frequently consult physicians.[33]

In our study, there was no significant difference between the frequency of rhythm disorders (i.e., supraventricular and ventricular premature beats, atrial fibrillation and other atrial arrhythmias) before and after the procedure and during the follow-up period of Holter monitorization assessment. Although PFO closure in patients with a cryptogenic stroke was reported to be safe and effective, a new concern emerged regarding the occurrence of arrhythmic complications like atrial tachyarrhythmias or heart block after the procedure.[34] Fibrosis or compression of atrial conduction bundles in particular may be expected to result in prolongation of interatrial conduction time and changes in P-wave morphology. These changes could provide the substrate for re-entry and subsequent tachyarrhythmias.[35] Another aspect of increased arrhythmia risk is that the closure procedure itself may increase the risk of atrial fibrillation. Furthermore, it was shown that atrial and pulmonary vein instrumentations with guide-wires and other necessary items may often unmask some underlying and misdiagnosed pre-existing atrial arrhythmias. Meta-analysis of three recent publications has shown that closure of the PFO may be associated with higher incidence of AF. However, the high rate of new arrhythmias noted in the CLOSURE 1 trial in that study most of the observed cases of AF were periprocedural in the closure group with STARFlex devices.[27] Additionally, Staubach et al.[36] reported the incidence of AF increased substantially with age and the use of STARFlex devices compared with the other utilized devices (e.g., Amplatzer PFO occluder).

Although our study had a prospective follow-up for one year, it was a non-randomized and single-arm study. Another limitation was that arrhythmic evaluation of patients before and after the procedure was performed with 24 hours of Holter monitoring. It has been demonstrated by many studies that the detection of atrial arrhythmias increases on prolonging the monitoring time.[37] Repetitive, long-term, Holter monitoring is necessary to analyze rhythm outcome after the procedure to ensure that asymptomatic arrhythmia recurrences are detected. Additionally, each observer was not blinded to the clinical information, which could bias their interpretation of the clinical significance of the lesion, but is not likely to influence his perception. Finally, long term follow-up with a larger study population might give more accurate data in that patient group.

Our short-term follow-up study revealed that percutaneous closure of PFO was an effective and safe method to avoid not only symptomatic but also asymptomatic recurrent ischemic events in patients with previous neurological events. Long-term MRI follow-up trials are needed to confirm the effectiveness of this technique in the secondary prevention of cerebrovascular events and strict ECG monitoring is fundamental for the detection of possible asymptomatic arrhythmic events.

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