【 ORIGINAL ARTICLE 】

Clinical Experience of Percutaneous Patent Foramen Ovale Closure Using the Amplatzer PFO Occluder in Japanese Patients to Prevent the Recurrence of Cryptogenic Stroke

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Abstract:
Objective Percutaneous patent foramen ovale (PFO) closure is a procedure widely used to prevent recurrence of cryptogenic stroke. Since December 2019, the Amplatzer PFO occluder device has been available in Japan through medical insurance. However, data on the clinical experience with this device are lacking, as it has been approved for use in only a limited number of institutions. This study assessed the clinical data of Japanese patients who underwent PFO closure using the Amplatzer PFO occluder.
Methods Between February and October 2020, 14 patients at our institution underwent percutaneous PFO closure using the Amplatzer PFO occluder. The procedural characteristics, safety, and adverse events were retrospectively analyzed.
Results The mean age of the patients was 52.4±13.3 years old, and 57.1% were women. Deep vein thrombosis was revealed in 2 patients, and the risk of paradoxical embolism score was 6.6±1.2 points. The PFO height and tunnel length were 2.3±1.4 mm and 11.5±4.1 mm. All patients had a PFO during the bubble study of grade >3 at the Valsalva maneuver on transthoracic echocardiography or transesophageal echocardiography. The average diameter of the PFO measured using a stiff guidewire and sizing balloon was 5.1±1.3 and 7.9±2.3 mm, respectively. Almost all cases (92.9%) were performed with a 25-mm device and without significant complications within approximately 1 hour.
Conclusion Percutaneous closure using Amplatzer PFO occluder is a safe procedure for Japanese patients. However, further investigations with a larger sample and longer follow-up are needed to confirm this result.

Key words: patent foramen ovale, percutaneous PFO closure, cryptogenic stroke, amplatzer PFO occluder

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Introduction

Percutaneous patent foramen ovale (PFO) closure is a common procedure for preventing recurrence of cryptogenic stroke (1-3). One of the standard devices used worldwide for PFO closure is the Amplatzer PFO occluder (Abbott, Chicago, USA), and more than 100,000 patients have undergone PFO closure with this device. In addition, the procedure using an Amplatzer PFO occluder is reported to have fewer complications in Europe than other occlude devices (4). However, in Japan, percutaneous PFO closure has been performed with the off-label use of atrial septal defect (ASD) occluder devices, such as the Amplatzer Cribriform (Abbott).

A few reports have shown that percutaneous PFO closure performed with off-label devices in Japanese patients is also safe and effective (5, 6). Since December 2019, the Amplatzer PFO occluder has been approved as a medical treatment covered by health insurance in Japan; however, it is approved for use only in a limited number of institutions. Therefore, data on the clinical experience with this device are insufficient.

Given the above, the present study evaluated the clinical data of patients who underwent PFO closure using the Amplatzer PFO occluder to prevent recurrence of crypto-

genic stroke and assessed the safety of the PFO closure procedure in Japanese patients.

Materials and Methods

Design

This was a single-center retrospective observational study. Between February 2020 and October 2020, 14 patients underwent percutaneous PFO closure using the Amplatzer PFO occluder to prevent recurrence of cryptogenic stroke at the Tokyo Bay Urayasu Ichikawa Medical Center, Japan. The procedural characteristics, safety, and adverse events over 30 days were retrospectively analyzed.

Inclusion criteria of percutaneous closure

Patients who experienced stroke of unknown etiology and had PFO confirmed by an echocardiographic examination were considered for inclusion. Of these patients, adaptation of PFO closure was performed in those who met the following criteria: 1) no causes of stroke aside from PFO; and 2) high-risk PFO morphology [e.g., large shunt, atrial septal aneurysm (ASA), long-tunnel type, etc.] (7, 8). Furthermore, the indication of PFO closure was determined by a brain-heart team consisting of neurologists and cardiologists. Patients who consented to receive closure underwent percutaneous PFO closure.

Procedure steps

Percutaneous closure was performed in the catheter laboratory. The procedure was performed under general anesthesia using transesophageal echocardiography (TEE) and/or intracardiac echocardiography (ICE) guidance. Almost all cases underwent the procedure with the right common femoral vein selected for inserting the 7-Fr sheath due to use of the exchange delivery sheath. For ICE-guided procedures, 2 puncture approaches were selected for inserting a 7-Fr sheath, 8-Fr long sheath, or 10-Fr long sheath due to use of the ICE catheter. A 0.035-inch guidewire inserted into a 5-Fr multipurpose catheter was used to pass through the PFO. After passing the 0.035-inch guidewire through the PFO, it was changed to a super-stiff guidewire while keeping the tip of the catheter positioned at the left superior pulmonary vein (LSPV). The multipurpose catheter and 7-Fr sheath were then removed, while the super-stiff guidewire remained fixed in the LSPV. Following the super-stiff guidewire, the sizing balloon was advanced, and the size of the PFO was measured. The PFO occluder delivery sheath was then passed through the PFO. After deployment of the PFO occluder, TEE and/or ICE were checked to ensure that the PFO occluder was in the appropriate position with no procedural complications, such as erosion or tamponade. After removing the delivery sheath, figure-eight sutures were placed at the puncture site to achieve hemostasis.

Device size selection

According to the intraprocedural TEE image, either a 25- or 35-mm occluder device was selected. In addition, we selected devices according to a previous report (7). When the PFO sizing balloon was dilated to less than 11 mm, we selected a 25-mm occluder. When the PFO sizing balloon was dilated to ≥11 mm, especially in cases of combined significantly hypermobile atrial septal aneurysm, we selected a 35-mm occluder. Our strategy was to exclude both 18- and 30-mm device sizes, as such disk sizes were not considered able to achieve a fully fitted PFO tunnel.

Adverse events from procedure to discharge

Procedure-related complications, defined as cardiac tamponade, erosion, and device dislodgement, were monitored during the procedure. An electrocardiogram (ECG) was performed until discharge to monitor atrioventricular block or arrhythmia. The puncture site was checked 4 hours after the procedure and 1 day after the procedure.

Follow-up

Examinations such as transthoracic echocardiography (TTE), chest radiography, and ECG were performed at discharge and one month later. In addition, changes in clinical symptoms were documented one month after the procedure in an outpatient setting.

Medications

Medications were generally selected by neurologists before closure. After closure, the decision to add antiplatelet (dual-antiplatelet therapy; DAPT) or/and anticoagulant drugs was made by interventional cardiologists.

Statistical analyses

Data are presented as the mean ± standard deviation, and statistical analyses were performed using the JMP software program, version 8 (SAS Institute, Cary, USA).

Results

Patient characteristics

The patients' characteristics are shown in Table 1. The mean age was 52.4±13.3 years old, and 57.1% of the patients were women. None of the patients were current smokers. About one-third of the patients had a history of hypertension and dyslipidemia. Deep-vein thrombosis was observed in two patients. The risk of paradoxical embolism (RoPE) score was 6.6±1.2 (the RoPE Score could not be calculated in 1 patient because the patient was under 18 years old) (9, 10).

Morphology of PFO

The morphology of PFO is shown in Table 2. The PFO height and tunnel length were 2.3±1.4 mm and 11.5±4.1

mm, respectively. The septum secundum thickness was 5.0± 1.3 mm. An ASA was present in five patients. All patients had a PFO observed during the bubble study as more than grade 3 at the Valsalva maneuver on TTE or TEE.

Procedural characteristics

The procedural characteristics are listed in Table 3. All procedures were performed under general anesthesia and TEE and/or ICE guidance (2 cases TEE only, 12 cases TEE and ICE). The diameter of PFO measured using a stiff guidewire and sizing balloon was 5.1±1.3 mm and 7.9±2.3 mm, respectively. A 35-mm device was selected for 1 case. PFO closure was successfully performed in all cases without complications. The procedural time was 55.1±13.7 minutes, and the time from entering the catheter room to leaving the room was 96.6±19.2 minutes.

Medications

The medications are listed in Table 4. Anticoagulant ther-

apy alone was selected for more than half of the patients before closure, from the day of closure to one month later, and from one month later onward. DAPT was selected in four patients from the day after closure to one month later, and three patients were prescribed single-antiplatelet therapy (SAPT) from one month onward. SAPT plus direct oral anticoagulant (DOAC) was selected for only one patient before closure, from the day of closure to one month later, and from one month later onward.

Outcomes

The outcomes are shown in Table 5. There were no procedural complications, such as cardiac tamponade, erosion, or device dislodgement. No significant arrhythmia occurred after closure. Minor re-bleeding occurred in three patients. None of the patients had experienced changes in clinical symptoms or examination findings after one month in an outpatient setting.

Discussion

To our knowledge, this is the first clinical report on the use of the Amplatzer PFO occluder in Japanese patients since the device was made available in Japan.

Recently, a clinical expert opinion and consensus statement for the Asian-Pacific region were published (11). The statement suggests that Asians should comply with international guidelines on the indication for PFO closure, similar to European guidelines. However, data on PFO closure in Japanese patients are limited. In addition, the characteristics of patients undergoing PFO closure and procedural data have not been documented in Japanese patients. In this study, patients with a mean age of 52.4 years old and no significant atherosclerotic risk factors had PFO-associated stroke. In addition, regarding PFO morphology in this study, the PFO height, tunnel length, ASA, Chiari network, and bubble test grade were categorized as high-risk. The mean RoPE score was 6.6 points; however, we considered the risk

Table 1. Baseline Patients' Characteristics.

Characteristics	Overall (n=14)
Age, years (range)	52.4±13.3 (16-71)
Female gender (%)	8 (57.1)
BMI, kg/m^2	22.5±3.1
Current smoker (%)	0 (0)
Hypertension (%)	5 (35.7)
Diabetes mellitus (%)	0 (0)
Dyslipidemia (%)	5 (35.7)
Chronic kidney disease (%)	2 (14.3)
Previous PCI (%)	0 (0)
Deep vein thrombus (%)	2 (14.3)
Rope Score[*]	6.6±1.2

[*]The RoPE Score could not be calculated in one patient because the patient was less than 18 years old.

Values represent the mean±SD or n (%).

BMI: body mass index, PCI: percutaneous coronary intervention

Table 2. Morphology of Patent Foramen Ovale.

Characteristics	Overall (n=14)
PFO height, mm	2.3±1.4
PFO tunnel length, mm	11.5±4.1
Defect to aorta, mm	7.5±2.9
Defect to superior vena cava, mm	13.2±5.1
Septal length	
Short axis, mm	24.8±3.7
Long axis, mm	36.6±7.2
Septum secundum thickness, mm	5.0±1.3
ASA (%)	5 (35.7)
Chiari network (%)	2 (14.3)
Bubble test grade ≥3 at Valsalva maneuver by TTE or TEE (%)	14 (100)

Values represent the mean±SD or n (%).

PFO: patent foramen ovale, ASA: atrial septal aneurysm, TTE: transthoracic echocardiogram, TEE: transesophageal echocardiogram

Table 3. Procedural Characteristics.

Characteristics	Overall (n=14)
Procedural time, min	55.1±13.7
Fluoroscopic time, min	14.8±4.2
Anesthesia	
General anesthesia (%)	14 (100)
Time from enter the catheter room to leave, min	96.6±19.2
Imaging guidance	
TEE and/or ICE (%)	14 (100)
TEE (%)	2 (14.3)
TEE and ICE (%)	12 (85.7)
TEE measurement	
Diameter of PFO by stiff guide wire dilatation, mm	5.5±1.3
Diameter of PFO by sizing balloon, mm	7.9±2.3
Device size	
18 mm (%)	0 (0)
25 mm (%)	13 (92.9)
30 mm (%)	0 (0)
35 mm (%)	1 (7.1)
Procedural success (%)	14 (100)

Values represent the mean±SD or n (%).

TEE: transesophageal echocardiography, ICE: intracardiac echocardiography, PFO: patent foramen ovale

Table 4. Medications.

Variable	Overall (n=14)
Medications before closure	
Warfarin (%)	4 (28.6)
DOAC (%)	5 (35.7)
SAPT (%)	3 (21.4)
DAPT (%)	1 (7.1)
SAPT plus DOAC (%)	1 (7.1)
Medications from day of closure to 1 month	
Warfarin (%)	3 (21.4)
DOAC (%)	6 (42.9)
SAPT (%)	0 (0)
DAPT (%)	4 (28.6)
SAPT plus DOAC (%)	1 (7.1)
Medications from 1 month onward	
Warfarin (%)	3 (21.4)
DOAC (%)	6 (42.9)
SAPT (%)	3 (21.4)
DAPT (%)	1 (7.1)
SAPT plus DOAC (%)	1(7.1)

Values represent the mean±SD or n (%).

DOAC: direct oral anticoagulant, DAPT: dual antiplatelet therapy, SAPT: single antiplatelet therapy

Table 5. Outcomes.

Events	Overall (n=14)
Total hospitalization days	3
Hospitalization days after the closure	1
Procedural complications	
Cardiac tamponade (%)	0 (0)
Erosion (%)	0 (0)
Device dislodgement (%)	0 (0)
Arrhythmia after closure	
Atrioventricular block (%)	0 (0)
Atrial fibrillation (%)	0 (0)
Puncture site complications until discharge	
Minor re-bleeding (%)	3 (21.4)
Hematoma (%)	1 (7.1)
Pseudoaneurysm (%)	0 (0)
Arteriovenous fistula (%)	0 (0)
Change in clinical symptoms at 1 month (%)	0 (0)
Change in examinations findings at 1 month (%)	0 (0)

Values represent the n (%).

of recurrent stroke to be high, so closure was performed. The PFO was gradually dilated in this study. The mean PFO height was 2.3 mm, but the diameter of PFO measured using stiff guidewire dilatation and a sizing balloon was 5.5 and 7.9 mm, respectively. However, in almost all cases (92.9%) complete percutaneous closure was performed using a 25-mm Amplatzer PFO device. One case had a PFO of 12.9 mm measured by a sizing balloon (PFO height: 3.9 mm, diameter of PFO by stiff guidewire dilatation: 6.2 mm) with a significantly hypermobile ASA; therefore, a 35-mm device was used. PFO closure guided by echo imaging was able to be performed without significant complications within approximately 1 hour.

The average procedural time of approximately 1 hour seems a bit long; however, we performed closure guided by both TEE and ICE in almost all cases (85.7% cases). Therefore, the procedural time was deemed acceptable with both TEE and ICE guidance.

In addition, we did not experience any cases with significant complications, arrhythmia, worsening symptoms, or changes in examination findings at one month. Regarding medications administered before and after closure, anticoagulation therapy was selected in more than half of cases. Though DVT was seen in just two patients, nine also received anticoagulation after the procedure; this was because medications in all cases were administered based on the decision of the neurologists in the acute phase of stroke. Therefore, we continued administering medications after the procedure in most cases. Further investigations concerning the most appropriate medical therapy for PFO closure patients are required.

The procedural steps performed by experienced PFO closure operators are gradually changing worldwide. A previous report showed that fluoroscopic guidance alone could be used safely during percutaneous closure, without any other echocardiographic guidance (TEE or ICE) (12). However, there have been a few complications reported, such as aortic erosion or atrioventricular block, similar to with other interatrial septum devices (13, 14). In Japan, the Amplatzer PFO occluder has been approved by medical insurance institutions only for the secondary prevention of cryptogenic stroke in younger patients. Therefore, this procedure should be performed as safely and carefully as possible to avoid complications. In particular, in Japan, most interventional cardiologists are not accustomed to performing interatrial septum structural heart intervention (approximately 100 limited certified interventionalists of ASD closure in Japan in 2019). We performed PFO closure TEE and/or ICE guidance under general anesthesia. As a result, there were no procedural complications, as the most appropriate device size was selected for each case and performed according to the step-by-step procedure. In general, this procedure can be performed under local anesthesia using ICE guidance alone. In Japan, however, it is recommended to perform PFO closure with both TEE and ICE guidance in the first few cases. Therefore, we used both imaging for PFO closure in 12 of the 14 cases.

The SCAI Operator and Institutional Requirement document recommends experienced PFO procedural operators perform device closure; this includes a minimum of 50 lifetime structural/congenital catheter interventions with at least 25 involving septal interventions or 12 interventions specific to PFO device placement (15). Interventionalists in Japan without sufficient experience performing closure through the interatrial septum should thus perform PFO closure alongside an experienced proctor who can monitor the implants.

Minor re-bleeding requiring additional compression after four hours' bed rest occurred in three patients (two with DOAC, one with DAPT). However, additional manual compression and/or pressure bandages achieved complete hemostasis without extended hospitalization. It is well known that Japanese patients are at risk of bleeding when receiving antithrombotic agents; therefore, we recommend carefully checking the puncture site for associated complications.

Study limitations

Several limitations associated with the present study warrant mention. First, the sample size was very small because this was a single-center observational study. However, this percutaneous closure device has been available since December 2019 at a limited number of institutions in Japan. In addition, in the era of COVID-19, we were unable to examine the cause of stroke by a TEE or TTE bubble study due to the potential for aerosol or contact transmission. Therefore, the number of patients reviewed was quite small. However, post-marketing surveillance is progressing and may be able to support our clinical data. Second, interventionalists of PFO closure at our institution were experienced in performing percutaneous secundum ASD closure with similar procedural steps. Therefore, further investigations will be needed to confirm the safety in Japanese patients when interatrial septum is performed by less-experienced interventionalists.

Conclusion

Percutaneous closure using the Amplatzer PFO occluder is a safe procedure when performed in Japanese patients. However, further investigations with a larger sample size and longer follow-up are needed to confirm this result.

The authors state that they have no Conflict of Interest (COI).

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