Congenital Heart Disease

Tech Science Press

DOI: 10.32604/chd.2023.028979

ARTICLE

Safety and Efficacy of Biodegradable Patent Foramen Ovale Occluder in Patients with Migraine: A Clinical Trial

Xingbang Li[1,#], Xuan Zheng[2,#], Bowen Jin[1], Yunyan Li[1], Yongyu Shao[1], Xiaoxian Deng[1], Dingyang Li[1], Shanshan Li[1], Hongmei Zhou[1], Jie Zhang[3], Xianya Zhang[4], Qunshan Shen[1,*] and Gangcheng Zhang[2,*]

[1]Congenital Heart Disease Center, Wuhan Asia Heart Hospital, Wuhan University of Science and Technology, Wuhan, 430022, China

[2]Structural Heart Disease Center, Zhongnan Hospital, Wuhan University, Wuhan, 430071, China

[3]Department of Cardiothoracic and Vascular Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China

[4]Department of Medical Ultrasound, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China

[*]Corresponding Authors: Qunshan Shen. Email: 18963980686@163.com; Gangcheng Zhang. Email: zgcsir@163.com

[#]The first two authors contributed equally to this work

Received: 21 January 2023 Accepted: 21 March 2023 Published: 12 June 2023

ABSTRACT

Background: Transcatheter closure of patent foramen ovale (PFO) has been widely accepted as a highly effective way to treat high-risk PFO-related diseases. However, traditional non-degradable occluders made of metal alloys will permanently exist in the body, resulting in thrombosis, valve damage, hemolysis, arrhythmia, or other complications. The biodegradable PFO occluder developed by Shanghai Mallow Medical Instrument Co., Ltd., China can be fully absorbed and degrade into nontoxic ingredients, reducing postoperative complications. **Objectives:** To study the safety and efficacy of biodegradable PFO occluders in treating PFO. **Methods:** This single-center clinical trial collected 30 patients treated with a biodegradable PFO occluder. The follow-up period lasted 12 months to analyze the echocardiographic characteristics and headache relief through HIT-6 scores. **Results:** The immediate success rate was 100%, with no intraoperative severe occlusion-related complications. The contrast transcranial Doppler (cTCD) at 12 months showed that all patients' right-to-left shunts (RLS) were grade I or 0 with no serious postoperative complications, indicating the overall success rate was 100%. The biodegradable PFO occluder mostly degraded six months after the occlusion. **Conclusion:** PFO closure with a Mallow biodegradable occluder is safe and effective and has no severe complications.

KEYWORDS

Patent foramen ovale; biodegradable occluder; transcatheter closure; migraine; complications

1 Introduction

Patent foramen ovale (PFO) is a physiological channel in the heart that does not close the way it should after birth. It is an anatomical anomaly in up to a quarter of the general population and is usually asymptomatic [1]. However, there are still potential shunts in the left and right atria that may cause

stroke, recurrent transient ischemic attack (TIA), migraine, etc., seriously affecting the quality of life and human health [2]. Percutaneous PFO closure has become the preferred option and has been increasingly used for PFOs with high-risk conditions [3–6].

Currently, the special Amplatzer occluders used for PFO closure are mostly metal alloys that are non-degradable. Once implanted in the body, it will accompany the patient for a lifetime, resulting in thrombosis, valve damage, hemolysis, arrhythmia, or other complications [7,8]. Previous animal experiments confirmed the biodegradable PFO occluder possessed excellent biocompatibility and can be degraded at 6 months after occlusion. This study aimed to analyze the perioperative clinical data to study the safety and efficacy of biodegradable PFO occluders in treating PFO.

2 Materials and Methods

2.1 Study Population

We collected 30 patients diagnosed with PFO and admitted to the Department of Congenital Heart Disease Center of the Wuhan Asia Heart Hospital of Wuhan University of Science and Technology from August 2019 to December 2020. The enrollment criteria were as follows: (1) PFO diagnosed with a medium-large right-to-left shunt (RLS) by clinical imaging; (2) age ≥ 16 years; (3) voluntarily participate in human clinical trials with signed informed consent. (4) occult ischemic stroke, migraine, dizziness, or other recurrent neurological and psychiatric symptoms. The exclusion criteria were as follows: (1) cerebral embolism of any cause can be found; (2) contraindications to antiplatelet or anticoagulant therapy; (3) inferior vena cava or pelvic vein thrombosis, systemic or local infection, sepsis, intracardiac thrombosis; (4) pregnancy; (5) combined pulmonary hypertension or PFO as a survival channel; (6) massive cerebral infarction within four weeks; (7) migraine of other known causes.

Ethical approval was granted by the local ethics committee of Wuhan Asia Heart Hospital of Wuhan University of Science and Technology (2019-YXGCP-012), and all study participants provided informed consent. This study was registered in the Chinese Clinical Trial Registry (Registration date: 23/06/2019; Number: ChiCTR1900024036).

2.2 PFO Biodegradable Occluder Device

The biodegradable occluder, made from a polydioxanone (PDO) single filament of 0.298 mm diameter and a polyethylene terephthalate matrix membrane, consists of a blocking umbrella disc, interlayer membrane, and suture (Fig. 1). This device exhibited great structural stability owning to many cross points to resist external force [9] and can be fully compressed and collected into the catheter owning to good shape memory ability. By minimally invasive interventional technology, the biodegradable occluder is transferred to the PFO through the delivery device under the guidance of ultrasound and digital subtraction angiography imaging equipment. Once planted, the occluder will close the PFO tunnel and provide a temporary scaffold for the tissue around to cover the device and the defect underneath, which eventually degrade into nontoxic ingredients (water and carbon dioxide) and be fully absorbed, leaving "native" tissue behind [10].

2.3 Preoperative Diagnostic Criteria for PFO Imaging

The diagnosis of PFO was mainly through transthoracic echocardiography (TTE)/contrast-transthoracic echocardiography (cTTE), transesophageal echocardiography (TEE)/contrast-transesophageal echocardiography (cTEE) and contrast transcranial Doppler (cTCD). To achieve maximal accuracy in PFO diagnosis, combining different techniques is warranted [11]. TTE is usually used for an initial evaluation of patients for a possible PFO. We used two-dimensional (2D) echocardiography to scan the anatomical structure of the atrial septum and color Doppler to observe the left-to-right shunt on the parasternal aortic short-axis view, the apical 4-chamber view, or the apical 5-chamber view. As adults are usually affected by various factors such as

obesity, excessive lung gas, etc., the detection rate of PFO by TTE is not very high, and it is difficult to measure the size of PFO accurately. TEE provides a clear visualization of the atrial septal anatomy and is the "gold standard" and preferred method for the diagnosis of PFO [12]. Given that TEE is a semi-invasive test, it is not suitable for screening purposes but is used for accurate reassessment before the release of the occluder during the operation. In our study, RLS was mainly assessed using cTCD, and the number of micro-embolic signals determined its classification observed within 10–20 s: grade 0, no microbubbles, no RLS; grade I, 1–10 microbubbles, a small RLS; grade II, 11–25 microbubbles, a moderate RLS; grade III, >25 microbubbles, a large RLS, and the signals could be in the shape of a rain curtain or shower [13].

Figure 1: Biodegradable occluder

2.4 Patients with Cerebral Infarction Received a Risk of Paradoxical Embolism Score

The risk of paradoxical embolism (RoPE) score, which can evaluate the role of PFO in the etiology of ischemic stroke, was used to predict the probability of PFO-related stroke [14] and the assessment of PFO occlusion before the operation. The RoPE score was calculated as follows: no history of diabetes (1 point); no history of hypertension (1 point); non-smoking (1 point); no history of stroke or transient ischemic attack (TIA) (1 point); cortical infarct on imaging (1 point); an age of 18–29 (5 points), 30–39 (4 points), 40–49 (3 points), 50–59 (2 points), 60–69 (1 point), and ≥70 years (0 points). Given a higher RoPE score indicating a stronger association between PFO and stroke, the score obtained over 6 (population attributable fraction: 62%, 95% CI: 54%–68%) is more likely to reflect a PFO-related stroke [15], indicating possible benefit from PFO closure. The original questionnaire is provided in Supplementary Table 1.

2.5 Patients with Migraine Received Headache Impact Test (HIT-6 Score)

The Headache Impact Test-6 (HIT-6), consisting of six items: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress [16], measures the intensity and frequency of headaches within the previous four weeks to assess the impact of headaches especially migraine on the patients' life [17]. The patients answered each of the six related questions using one of the following five responses: "never", "rarely", "sometimes", "very often", or "always". The HIT-6 score (ranged from 36 to 78 points) was divided into four grades: (1) little-to-no impact (HIT-6 score: 36–49), moderate impact (HIT-6 score: 50–55), substantial impact (HIT-6 score: 56–59), and severe impact (HIT-6 score: 60–78), where a higher score indicates a more significant impact of headache on the daily life of the respondent. The headache impact test scale is provided in Supplementary Table 2.

2.6 Procedure

The implantation of the biodegradable PFO occluders referred to the European Society of Cardiology Guidelines for managing adult congenital heart disease [18]. Prophylactic antibiotics can be given 1 h before the operation. Occluders implantation was guided under local anesthesia for X-ray and TTE monitoring or general anesthesia for TEE monitoring alone. For the blocking process, we routinely punctured the femoral vein as the occluder implantation pathway. After an intravenous injection of heparin (100 u/kg) was given, a right cardiac catheter was passed through the PFO, and an exchange guidewire were advanced and placed in left superior pulmonary vein. After immersing in heparinized saline, the occluder was delivered to the left atrium through a delivery sheath and released under the guidance of X-ray and TTE monitoring or simple TEE. First, we released distal umbrella in the left atrium, then we withdraw the occluder device and sheath until the distal umbrella was opposed to the left atrial septum. The right umbrella disc was then released by further withdrawal of the sheath. A descending traction test was conducted to ascertain the steadiness and location under color doppler ultrasonography to observe the morphology and location of the occluder, after which the delivery system was activated to release the implant.

After the operation, patients received routine heparin anticoagulation for 48 h, oral aspirin 100 mg/d for six months, and clopidogrel 75 mg/d for one month.

2.7 Research Process

Patients diagnosed with PFO received intraoperative delivery and release of biodegradable occluder under the guidance of X-ray and TTE or TEE alone. An immediate efficacy evaluation was conducted after occlusion to secure the occluder localization. We evaluated the morphology and location of the occluder and the presence of a residual shunt by TTE at 48 h, 1, 3, 6, and 12 months after the procedure. Residual shunts were detected postoperatively using cTCD 1, 3, 6, and 12 months.

2.8 Study Endpoints

The endpoint of this study was Clinical follow-up at 12 months after occlusion. The incidence of complications during follow-up at 48 h, 1, 3, 6, and 12 months after occlusion was used as the safety evaluation index. The success rate of device release in the immediate postoperative period, the success rate of blocking at each of the times above points, the frequency of migraine and RLS decreased or not at each of the times above points, and the overall success rate at 12 months after occlusion was used as the evaluation indices for efficacy.

2.9 Statistical Analysis

All analyses were performed by using R software (The R Foundation, http://www.r-project.org, version 4.2.0) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA).

Continuous variables conforming to the non-normal distribution were expressed as Median (IQR) for representation, and pairwise comparisons were made using the Mann–Whitney U test. Categorical data were expressed as frequencies and percentages, and comparisons between groups were performed using the $\chi 2$ test. Two-sided $p < 0.05$ indicated that the difference was statistically significant.

3 Results

3.1 Patients Baseline Characteristics

The 30 patients (10 males and 20 females) received biodegradable PFO occluder, aged 41.5 (28.0–49.8) years. Twenty-five patients (83.3%) had an ischemic stroke; among these, 7 patients (23.3%) had both cortical infarcts on imaging. The RoPE scores of the 7 patients were 6.0 (6.0–7.0) points. Eighteen patients (60.0%) had migraine, and 9 (30.0%) patients had dizziness. Under the guidance of TEE during the operation, the PFO size was 1.4 (1.0–2.0) mm, the PFO length was 11.0 (8.0–15.0) mm, the secondary septal thickness of the patients was 4.0 (3.0–4.0) mm, and 3 patients (10.0%) got atrial septal aneurysm (ASA). The maximum basal diameter of ASA in the 3 patients was 22 mm. All patients had no secondary atrial septal defect, long inferior vena cava valve, or secondary hypertrophic septum. Other medical conditions included hypertension (n = 7, 23.3%), diabetes mellitus (n = 8, 26.7%), and smoking history (n = 11, 36.7%). The procedure had a 100% success rate, and null of the patients developed perioperative complications (Table 1).

Table 1: Baseline characteristics

Variable	
Age (years, mean ± SD)	41.5 (28.0–49.8)
Male	10/30 (33.3%)
Ischemic stroke	25 (83.3%)
Cerebral infarction	7 (23.3%)
Migraine	18 (60.0%)
Dizziness	9 (30.0%)
Hypertension	7 (23.3%)
Diabetes	8 (26.7%)
Smoking	11 (36.7%)
RoPE scores of patients with cerebral infarction	6.0 (6.0–7.0)
ASA	3 (10.0%)
PFO size by TEE/mm	1.4 (1.0–2.0)
PFO length by TEE/mm	11.0 (8.0–15.0)
Secondary septal thickness/mm	4.0 (3.0–4.0)
Intraoperative complication	none

Note: ASA: atrial septal aneurysm; PFO: patent foramen ovale; TEE: transthoracic echocardiography.

3.2 Treatments and Follow-Up

All those 30 patients took oral aspirin 100 mg/d for six months and clopidogrel 75 mg/d for one month after the operation without any bleeding complications. During follow-up for one year, according to the trial procedures, none of the patients got lost to follow-up. In clinical follow-ups at 1, 3, 6, and 12 months after the operation, there was no occluder displacement or loss, thrombosis of the occluder, new arrhythmias, or

recurrent stroke. Compared to pre-occlusion levels, no clinically obvious abnormalities were found in routine blood and urine chemistry panels, hematology, liver and kidney function tests, coagulation function, or Electrocardiograms (ECG).

3.3 Efficacy Results

HIT-6 scores of patients with migraine were 57.0 (54.5–61.5), 57.0 (54.0–60.0), 55.0 (50.0–56.0), 50.0 (50.0–55.0), 46.0 (46.0–50.0) before the operation, 1, 3, 6, and 12 months after the operation separately. The scores measured at 1, 3, 6 and 12 months all indicated significant differences compared to the scores measured before the operation ($p < 0.05$) (Fig. 2). Headache symptoms in all patients were significantly relieved compared with those before the procedure.

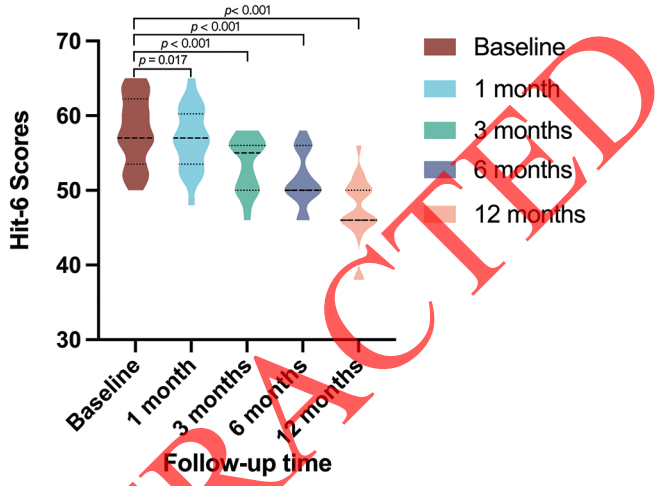

Figure 2: HIT-6 score comparison in patients with migraine

Furthermore, all patients underwent cTCD to screen for RLS at 1, 3, 6, and 12 months postoperatively, both at a resting state and a Valsalva maneuver. The proportion of the follow-up cTCD grading III results at the Valsalva maneuver were 96.7%, 40.0%, 16.7%, 26.7%, and 0% separately as follow-up progressed (Fig. 3), indicating the overall success rate of occlusion 12 months after the operation was 100%. Looking at Fig. 3, it is apparent that the proportion of grade 2 and grade 3 measured at a Valsalva maneuver at 6 months accounted for more than one-third of the cohort. In this subgroup, stratified by the cTCD grading results at six months ≥2 or not, the data of patients' baseline characteristics were analyzed, and no statistical differences were found (Table 2).

The results of follow-up imaging were as follows. We could easily detect the morphology in the former 3 months. About three months after occlusion, the umbrella disc framework degraded slowly from the edge. The evenness and clarity of the occluders showed in TTE images were obviously less than those at 1 day. The architecture of the occluders were mostly degraded at about six months with the outline of the occluders barely visible. Twelve months after occlusion, the hyperechoic area became significantly smaller in the middle of the atrial septum and an echocardiogram demonstrated an intact atrial septum without residual shunts (Fig. 4).

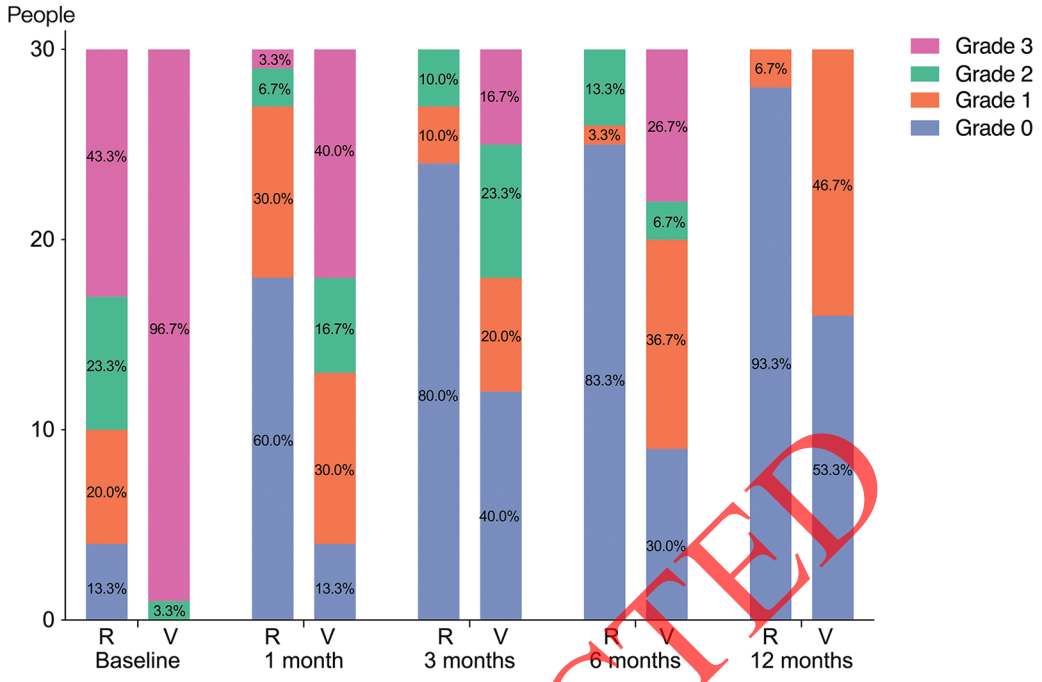

Figure 3: Proportion of RLS grading results preoperatively and postoperatively

Note: R refers to the state at rest, and V refers to the state at a Valsalva maneuver.

Table 2: Stratified analysis by the cTCD grading results at six months

cTCD grading results	0&1	2&3	*p* value
N	20	10	
Age	37.0 (27.8–49.2)	42.0 (35.2–48.2)	0.628
Male	6 (30.0%)	4 (40.0%)	0.891
Ischemic stroke	18 (90.0%)	7 (70.0%)	0.300
Cerebral infarction	6 (30.0%)	1 (10.0%)	0.372
Migraine	10 (50.0%)	8 (80.0%)	0.235
Dizziness	8 (40.0%)	1 (10.0%)	0.204
Hypertension	4 (20.0%)	3 (30.0%)	0.657
Diabetes	5 (25.0%)	3 (30.0%)	>0.990
Smoking	7 (35.0%)	4 (40.0%)	0.893
ASA	2 (10.0%)	1 (10.0%)	>0.990
PFO size by TEE/mm	1.4 (1.2–2.0)	1.2 (1.0–1.4)	0.179
PFO length by TEE/mm	11.0 (8.0–13.5)	12.0 (9.5–15.8)	0.674
Secondary septal thickness/mm	3.8 (3.0–4.0)	4.0 (3.5–4.0)	0.752

Note: cTCD: contrast transcranial Doppler; ASA: atrial septal aneurysm; PFO: patent foramen ovale; TEE: transthoracic echocardiography.

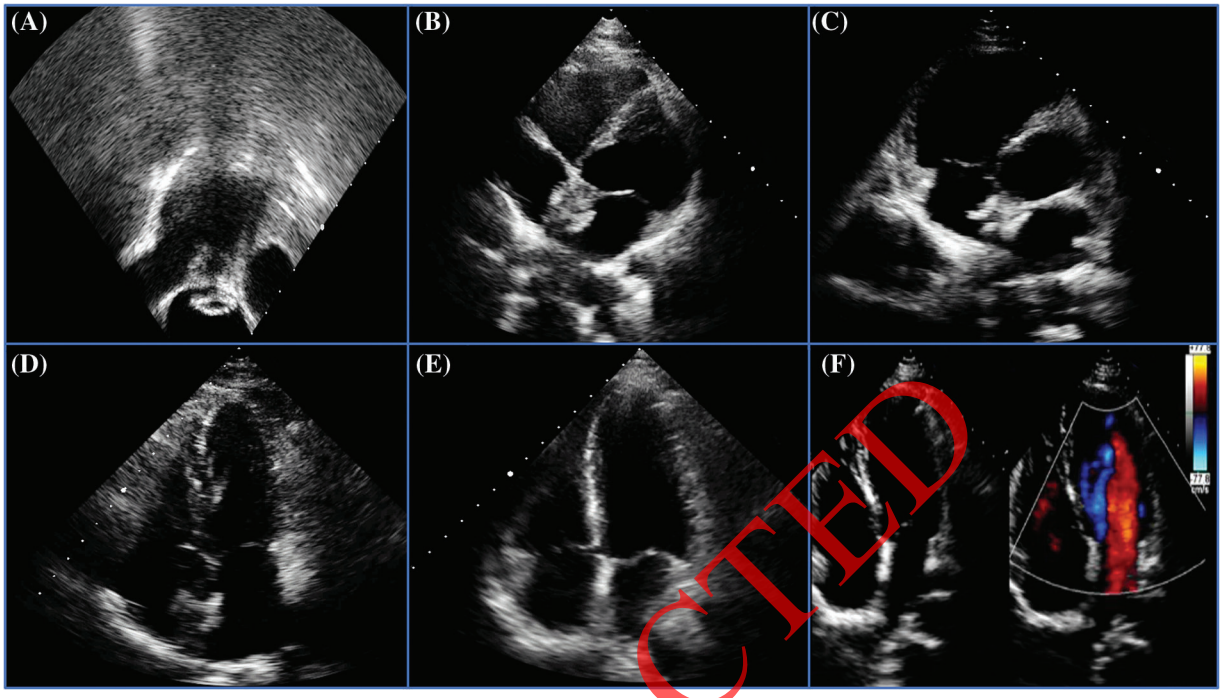

Figure 4: The degradation process of the biodegradable occluder at different time points after occlusion. (A) TEE displaying the morphology of the occluder during the operation; (B) TTE displaying the morphology of the occluder at 1 day; (C) TTE displaying the morphology of the occluder at 1 month; (D) TTE displaying the morphology of the occluder at 3 months; (E) TTE displaying the morphology of the occluder at 6 months; (F) TTE displaying the morphology of the occluder at 12 months and Color doppler TTE showing no residual shunt at the atrial level

4 Discussion

In our study, all 30 cases of biodegradable occluders were successfully implanted via catheter occlusion, and the immediate success rate was 100%, with no serious intraoperative or postoperative occlusion-related complications. TTE imaging showed that the devices were both stable and in satisfactory position during follow-up, and cTTE showed no residual shunts at 12 months. The success rate of complete occlusion based on cTCD findings 12 months after the operation was 100%. The migraine grade 12 months after the procedure of patients with migraine all decreased in different degrees compared to preoperative status.

The recommendation of PFO closure has gradually increased in the revision of the guidelines for three consecutive years: (1) in 2020 American Academy of Neurology recommended that in patients being considered for PFO closure, clinicians should ensure that an appropriately thorough evaluation had been performed to rule out alternative mechanisms of stroke [6]. (2) In 2021, a guideline from the American Heart Association/American Stroke Association recommended percutaneously close PFO in patients who were diagnosed with non-lacunar stroke with no other identified cause, and high-risk patent foramen ovale features at the age of 18–60 years [19]. (3) In 2022, the Society for Cardiovascular Angiography and Interventions strongly recommended PFO closure rather than antiplatelet therapy alone, high-risk PFO anatomical conditions were removed, and the RoPE score was emphasized [2]. By the current guidelines, all our patients had surgical indications for PFO closure, and no recurrence of stroke occurred in 12 months follow-up after the occlusion. Besides, in our study, the dose of oral aspirin 100 mg/d for

six months based on the 2013 consensus of Chinese experts on antiplatelet therapy did not follow the standard method of 3–5 mg/(kg·d) for 6 months recommended by current guidelines. With dose adjusted as clinically indicated during follow-up and no occurrence of intracardiac thrombus, thrombosis of the occluder, or other thromboembolic complications, it suggests a limited influence on this study.

The PFO occluders used in the previous large randomized controlled trials (RCTs) mainly included Amplatzer, STARFlex, HELEX, and Cardioform, which were made of nondegradable materials. A meta-analysis compromising five RCTs with 3,440 patients (CLOSURE 1, PC, RESPECT, REDUCE, CLOSE) at a mean follow-up of 4.02 ± 1.57 years reported PFO closure was associated with increased new-onset atrial fibrillation/flutter (RR = 4.66; 95% CI 2.15–10.1; $p < .001$; $I^2 = 29\%$), pulmonary embolism (RR = 3.07; 95% CI 1.08–8.75; $p < .04$; $I^2 = 0\%$), and device-related complications (RR = 22.8; 95% CI 6.42–81.2; $p < .001$; $I^2 = 0\%$) compared with medical therapy alone [20]. The main device-related complications were erosion of cardiac structures, cardiac thrombus, device dislocation, device-related thrombosis, and cardiac tamponade. None of the above complications occurred in our study. Because the endothelialization process finished at around 6 months, leaving "native" tissue behind, the incidence of those complications that occurred after our one-year follow-up is rare. However, this result should be treated with caution due to the small sample size.

Over the last few years, a great deal of studies has reported a significant association between migraine headaches and the presence of a PFO. As a potential embolic source, RLS is commonly associated with cryptogenic strokes and migraine headaches [21]. Although the previous three RCTs (MIST, PREMIUM, and PRIMA) have not met their primary efficacy endpoints [22–24], many observational studies have found that the migraine symptoms got relieved from PFO closure. In 2021 a pooled analysis of individual participant data from the two randomized trials using the Amplatzer PFO Occluder demonstrated that 87% of patients had a migraine load reduction by >50%, and PFO closure resulted in even complete migraine cessation [25]. Consistent with the previous literature, our study also found that the proportion of the 12-month follow-up cTCD grading I and II accounted for 100%. The HIT-6 scores consistently decreased from baseline to follow-up, with patients' migraine symptoms relieved.

The current common PFO occluder technology has significant disadvantages and limitations. Most of the available occluders are made of a metal frame with synthetic fabrics (especially nitinol), which may cause allergy and long-term complication risks for the permanent presence of foreign nondegradable materials *in vivo* [26,27]. By contrast, in our study, the complete encapsulation of the polymer membrane for the fibrous granulation tissue of the biodegradable occluder took 1–3 months, and endothelialization took approximately 3–6 months, by the previous studies [28].

However, the cTCD grading results at 6 months showed 10 (33.3%) patients graded ≥2 at Valsalva maneuver. Possible reasons might include the following: (1) patients might get mild mitral or tricuspid valve insufficiency, so the process of endothelialization is slowed down by the regurgitant blood flow. (2) Endothelialization process varied according to different individual adaptability to the material of the biodegradable occluders [29]. The degradation speed is too fast or uneven in various directions. (3) Extracardiac shunts, like functional pulmonary arteriovenous shunts, occurred in some patients.

Limitations

The small sample size of the study, 12 months of short follow-up, and the small number of events represent a source of bias. Besides, we used TEE only during the operation but not at follow-up for the need for general anesthesia. The disadvantages of TTE cannot be ignored for patient statuses like adiposity, digestive gas, and abdominal compartment syndrome can strongly impact the image quality of ultrasound examination [30,31]. Furthermore, a randomized controlled study between degradable and non-degradable occluders is needed to determine which patient subgroups may benefit more from each type.

5 Conclusions

Biodegradable PFO occluders are safe and effective in the treatment of PFO closure. A multi-center, long-term, and large sample-size randomized clinical trial is still needed to enable accurate and individualized prediction-based therapy.

Acknowledgement: We would like to thank the patients who participated in the study and data collection at Wuhan Asia Heart Hospital.

Funding Statement: This study was supported by the Health and Family Planning Commission of Wuhan Municipality, Grant WX21Z26.

Author Contributions: The authors confirm contribution to the paper as follows: XL designed the study, analyzed the data, and wrote the manuscript. XZ and BJ helped to write and revise the manuscript. BJ, YL, YS, XD, DL, SL, HZ, JZ, and XZ supervised the research project. GZ and QS helped with project administration and funding acquisition. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: The data and materials are available from the corresponding author on reasonable request.

Ethics Approval: Ethical approval was granted by the local ethics committee of Wuhan Asia Heart Hospital (2019-YXGCP-012). All experiments were performed in accordance with *Declaration of Helsinki* and *Clinical Trials of Medical Devices Quality Management Standard*. Informed consent was obtained from all individual participants included in the study. This study was registered in the Chinese Clinical Trial Registry (Registration date: 23/06/2019; Number: ChiCTR1900024036).

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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Supplementary Materials

Supplementary Table 1: RoPE[a] score

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, y		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

Note: [a]RoPE = Risk of Paradoxical Embolism.

Supplementary Table 2

HIT-6™ **HEADACHE IMPACT TEST**

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please check one box for each question.

1. When you have headaches, how often is the pain severe?

□ **Never** □ **Rarely** □ **Sometimes** □ **Very Often** □ **Always**

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

□ **Never** □ **Rarely** □ **Sometimes** □ **Very Often** □ **Always**

3. When you have a headache, how often do you wish you could lie down?

□ **Never** □ **Rarely** □ **Sometimes** □ **Very Often** □ **Always**

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

□ **Never** □ **Rarely** □ **Sometimes** □ **Very Often** □ **Always**

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

□ **Never** □ **Rarely** □ **Sometimes** □ **Very Often** □ **Always**

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

□ **Never** □ **Rarely** □ **Sometimes** □ **Very Often** □ **Always**

COLUMN 1	COLUMN2	COLUMN3	COLUMN4	COLUMN5
(6 points each)	(8 points each)	(10 points each)	(11 points each)	(13 points each)

To score, add points for answers in each column

Please share your HIT-6 results with your doctor.

Total Score: _____