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Article

Clinical Efficacy of Transcatheter Closure of Patent Foramen Ovale with Positive Foaming Test

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Abstract

Background and Aims: To explore and evaluate the clinical therapeutic effect of interventional occlusion in the treatment of patent foramen ovale (PFO) with positive foaming test in the prevention and treatment of cryptogenic stroke (CS) and to provide clinical basis for individualized treatment of CS patients with PFO. **Methods**: A total of 151 patients who was admitted to Beijing Anzhen Nanchong Hospital Hospital from January 2019 to June 2021 were divided into two groups: drug therapy group (n = 63) and interventional occlusion + drug therapy group (n = 88). The general clinical data of the patients were collected by retrospective study, including sex, age, body weight, right to left shunt (RLS) magnitude, the degree of migraine before treatment, and telephone follow-up of all patients after treatment. **Results**: There was no significant difference in general clinical data ($p > 0.05$). In the interventional occlusion + drug therapy group, the stroke recurrence rate within 6th month after operation was significantly lower than that in the drug therapy group, and the difference was statistically significant ($p < 0.05$); The degree of migraine was lower than that in the drugs treatment group at the 3rd month after operation and the difference was statistically significant ($p < 0.01$); The degree of migraine at the 6th month was lower than that in the drug therapy group but the difference was not statistically significant ($p > 0.05$). The results of comprehensive generalized analysis showed that the risk of moderate or severe headache in the interventional occlusion + drug therapy group decreased by 40% (odds ratio [OR] = 0.60, $p < 0.05$). The degree of migraine in female patients was statistically lower after three and six months postoperatively ($p < 0.05$ and $p = 0.01$, respectively). Combined with generalized analysis, the risk of moderate or severe migraine in female patients was reduced by 55%. There were significant differences in the migraine before operation, migraine at the 3rd month and migraine at the 6th month in patients with three different kinds RLS grades ($p < 0.01$, $p < 0.01$, $p < 0.05$). Compared with the preoperative migraine and the migraine at the 3rd month, patients with RLS grade 3 had the most obvious migraine relief at the 6th month after operation than those with RLS grade 2. **Conclusion**: Compared with the drug therapy, interventional occlusion + drug therapy can reduce the risk of CS recurrence, improve the prognosis and significantly reduce the degree of migraine. Patients of different genders had different degrees of migraine, women had a lighter degree of migraine and a reduced risk of moderate or severe migraine, women benefited more after treatment. Patients with different RLS grades have different postoperative migraine relief. Patients with preoperative RLS grade 3 have the most obvious postoperative migraine relief and patients with preoperative RLS grade 3 benefit more after treatment.

Keywords

congenital heart disease; patent foramen ovale; atrial septal defect; cryptogenic stroke

Introduction

The foramen ovale is a physiological channel on the atrial septum of the heart during the fetal stage, and the functional closure gradually forms after birth, if the channel is still not closed after 3 years of birth, it is called patent foramen ovale (PFO) [1]. PFO is the most common congenital structural cardiac abnormality, with an incidence of approximately 20–34% [2]. PFO can be divided into simple PFO and complex PFO according to its structural characteristics. The criteria for determining complex PFO were as follows: long tunnel length (≥8 mm), atrial septal aneurysm (ASA), septal thickness (≥10 mm), very short septal valve (i.e., short or absent aortic margin), and eustachian valve of inferior vena cava [3–5]. The width of adult PFO is 1~19 mm (average 4.9 mm) [6]. In diameter, PFO can be divided into three types: large PFO (≥4.0 mm), medium PFO (2.0–3.9 mm) and small PFO ≤1.9 mm [7].

There are many clinical methods for the diagnosis of PFO, including contrast-enhanced transthoracic echocardiography (c-TTE), contrast-transesophageal echocardiography (c-TEE), intracardiac echocardiography (ICE) and the contrast-enhanced transcranial Doppler (c-TCD). c-TEE is used as the gold standard for the diagnosis of PFO, with a diagnostic specificity and sensitivity of 100% [8].

Studies indicate that c-TCD or c-TTE is preferred for PFO diagnosis, and c-TEE is used as a follow-up examination method to provide a clinical diagnosis or grading information (1A) [9,10]. A large number of studies have shown that the sensitivity of c-TCD in the diagnosis of PFO is significantly higher than that of c-TTE and c-TEE, and the detection rate of PFO is 27% higher than that of c-TEE [11,12]. It can be seen that c-TCD has high clinical application value in the diagnosis of PFO.

The treatment of PFO is mainly divided into two categories: drug and surgical treatment. Traditional drug therapy includes anticoagulant therapy and antiplatelet therapy. So far, studies have not clearly indicated which class of drugs has better therapeutic effect. In a study comparing the efficacy of warfarin and aspirin in patients with cryptogenic stroke (CS) and PFO, the Patent foramen ovale in Cryptogenic Stroke Study (PICSS) trial indicted there had no statistically significant difference in the risk of subsequent death or stroke between warfarin and aspirin [13]. In a study of PFO occlusion or anticoagulant therapy versus antiplatelet therapy in preventing stroke recurrence—CLOSE study, the probability of stroke recurrence and final mortality of patients in the antiplatelet therapy group was higher than those in the anticoagulant therapy group, but the difference was not statistically significant [14]. A meta-analysis in 2018 showed that anticoagulant therapy have a lower recurrence rate than antiplatelet therapy in preventing stroke recurrence, but the related bleeding risk may be higher [15].

The surgical treatment mainly includes PFO thoracotomy and PFO interventional occlusion. A study have shown that there are more residual shunt after PFO thoracotomy, and the recurrence rate of cerebral ischemic events such as Transient ischemic attack (TIA) is also high [16]. The development of ultrasound equipment, especially the emergence of TEE, has greatly promoted the implementation of modern PFO interventional occlusion surgery [17]. PFO occlusion of esophageal echocardiography is gradually recommended by many scholars at home and abroad [18,19]. This procedure has become the first choice for the treatment of PFO [20]. A prospective study in 2006 showed that the recurrence rate of neurological events in stroke patients after PFO occlusion was reduced [21]. At present, there is no clear study on which type of occluder is the most suitable for PFO closure, but early and recent studies do not recommend the use of STARFlex occluder [22]. Only the Amplatzer PFO (Abbott) and Cardioform occluders has been approved by the US Food and drugs Administration (FDA) [23]. In recent years, a large number of studies have also shown that PFO interventional occlusion has less damage and faster postoperative recovery compared with traditional heart surgery [21]. The latest guidelines from the American Society of Cardiovascular angiography and Interventions (SCAI) recommend that PFO interventional occlusion is better to antiplatelet therapy alone aged between 18 and 60 years with a previous PFO-related stroke [24].

The incidence of patent foramen ovale (PFO) in the general population is about 1/4, and most PFO patients usually have no obvious clinical symptoms [25]. However, most results show that PFO is significantly correlated with cryptogenic stroke (CS), and relevant epidemiological studies also show that the probability of PFO detected in CS patients is much higher than that in healthy people or stroke patients with clear etiology [26].

Cryptogenic stroke (CS) refers to ischemic stroke with unknown etiology, accounting for 10%–40% of ischemic stroke patients [27,28]. A number of clinical studies have explored PFO-related stroke, and the results show that there is a clear correlation between PFO and CS [29]. In patients with CS and PFO, score on the abnormal Embolization Risk Scale (the Risk of Paradoxical Embolism, RoPE) was highly correlated with the relative risk reduction (RRR) value of interventional occlusion or medication, and it can identify cryptogenic stroke patients who may be pathogenic rather than incidental PFO [30]. The detection rate of PFO in CS patients was 40%~56%, which was significantly higher than that of stroke patients with clear etiology [26,31]. The recurrence rate of stroke is high, and the recurrence rate of stroke is 50% in people who live to be over 50 years old [32]. Studies have shown that the incidence of PFO in adults ranges from 17% to 35%, and the incidence of ischemic stroke in these patients is 20% to 40%, but the detection rate of CS in healthy people is only 4% to 18% [29,33].

Migraine places a greater burden on both the patients and the society, The World Health Organization defines it as one of the most disabling chronic diseases [34]. In migraine patients, the detection rate of PFO is higher than that in the general population, and many clinical studies have found that PFO is closely related to migraine [35,36]. The incidence of migraine in the PFO population ranges from 9.13–51.7% [35]. The relationship between PFO and migraine was first demonstrated in 1998 by Del Sette *et al*. [37]. Research, among which PFO accompanied by right to left shunt (RLS) accounted for 41% in patients with migraine, while the control group (group without migraine) accounted for 16%, and the difference between the two groups was statistically significant [37]. A 2008 systematic analysis indicating that PFO and migraine are positively correlated and each other is a risk factor [38]. A 2020 study also further validates the relationship between migraine and PFO [39].

In order to further study the effectiveness of interventional therapy for patients with PFO complicated with CS, this paper, by collecting preoperative data of patients with cryptogenic stroke and combined with postoperative follow-up, adopts a retrospective study to discuss and evaluate the clinical effectiveness of interventional occlusion therapy for PFO with positive foam test, aiming at provide clinical basis for individualized therapy for patients with CS complicated with PFO.

Materials and Methods

Clinical Data

CS patients admitted to Beijing Anzhen Nanchong Hospital from January 2019 to June 2021 and diagnosed with PFO were collected and divided into drug therapy group alone and interventional occlusion + drug therapy group according to treatment methods. Patients were selected by inclusion and exclusion criteria, and all relevant data were collected, including: General clinical data (gender, age, weight), preoperative RLS magnitude, and patients' migraine before and after treatment. In all patients, PFO-related migraine was diagnosed by the neurologist of our hospital or by the neurologist who assessed the condition and supplemented the diagnosis of migraine through in-hospital consultation.

Patient Inclusion Criteria

(1) Patients age $\geq$16 years old, $\leq$60 years old; (2) CS was diagnosed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of cerebral infarction, and the diagnosis met the criteria formulated by the Academic Conference on Cerebrovascular Diseases in 2005 [40]. Patients with migraine symptoms must be evaluated by a neurologist and diagnosed with PFO-related migraine; (3) Patients diagnosed with PFO by examination (patients with or without migraine) and c-TCD foam test positive; (4) Patients receiving long-term drug therapy or drug combined with interventional closure therapy; (5) The patients received interventional occlusion successfully, and no right-to-left shunt was found in postoperative follow-up; (6) The patients had good compliance, and was admitted to hospital for regular review after discharge and insisted on telephone follow-up.

Patient Exclusion Criteria

(1) Stroke patients with other causes, such as atherosclerosis, vascular dissection, vascular stenosis, *etc*.; (2) Clearly have non-PFO-related migraine patients, such as hereditary migraine, vascular migraine, cervical headache, *etc*.; (3) Patients with other serious complex heart disease; (4) Patients with a history of a long-term severe depression and other mental illnesses; (5) Patients with poor compliance, who did not take drugs on time or stop drug treatment midway due to drug side effects; (6) Patients who failed to complete the full follow-up.

Study Methods

According to the treatment plan, they were divided into interventional occlusion + drug therapy group and drug therapy group alone. Patients in the interventional occlusion + drug therapy group received drug therapy before and after surgery, and the way of drug therapy before surgery was the same as that in the drug therapy group. All patients received anticoagulant, nutritional neurotherapy, antiplatelet and other conventional treatments in the department of neurology at the early stage of stroke. According to the patients' vascular conditions and relevant examinations after admission, they were selected to receive single antiplatelet therapy (SAPT) (Bayer Healthcare Manufacturing S.r.l., Via Delle Groane, Garbagnate Milanese MI, Italy) or aspirin enteric coated tablets (100 mg, Bayer Healthcare Manufacturing S.r.l., Via Delle Groane, Garbagnate Milanese MI, Italy) combined with Clopidogrel hydrogen sulfate tablets (75 mg, Sanofi Hangzhou, Pharmaceutical Co., Ltd., Hangzhou, Zhejiang, China) dual antiplatelet therapy. Patients in the interventional occlusion + drug treatment group continued to take aspirin enteric-coated tablets (100 mg) for 3 months after surgery. All patients were regularly re-examined in the outpatient department of our hospital after discharge. Neurologists were able to determine whether there was any recurrence of stroke by means of head computed tomography, head nuclear magnetic resonance imaging and clinical tests. All patients were followed up by telephone after treatment, including migraine at 3rd and 6th month after treatment.

This study was under ethical review and conducted in a retrospective manner after obtaining the consent of the study subjects. All patients included in this study underwent c-TCD foam test after exclusion of intracranial hemorrhage by head computed tomography (CT) or head nuclear magnetic resonance imaging (MRI). Before the telephone follow-up, all follow-up personnel were trained uniformly to avoid errors caused by the Follow-up method. All patients keep their treatment plans confidential and then randomized to different follow-up personnel. All follow-up personnel are strictly required not to ask patients about their treatment method or to make inductive questions. Telephone follow-up target is guaranteed to be the patient himself or life nursing staff of the patient.

Classification Standard for Right-to-Left Shunt Volume

The grading criteria for right-to-left shunt volume are according to the relevant literature [22]. RLS is divided into 4 grades according to the number of microbubbles present in the left heart on the single-frame image. (1) Grade 0, there was no microvesicles in the left atrium; (2) Grade 1, 1–10 microvesicles/frames can be seen in the left atrium; (3) Grade 2, 11–30 microvesicles/frames were seen in the left atrium; (4) Grade 3, microvesicles in the left atrium were more than 30 microvesicles/frame.

Follow-Up of Patients

The method of telephone follow-up was adopted, and the discharged patients or the family members who usually took care of the patients were contacted by telephone to ask

Table 1. The Hit-6 headache scale.

Question	Never	Little	Once in a while	Often	Always
1. When you have a headache, is the headache degree often severe?	6	7	8	9	10
2. Do headaches often limit your daily activities?	6	7	8	9	10
3. Do you often want to lie down and rest when you have a headache?	6	7	8	9	10
4. Do you feel a headache and unable to work or do daily activities?	6	7	8	9	10
5. Do you often get bored or annoyed with a headache?	6	7	8	9	10
6. Does the headache affect your attention at work or during your daily activities?	6	7	8	9	10

Table 2. Comparison of baseline characteristics of subjects.*

Influence factors	Simple drug therapy group (n = 63)	Interventional occlusion + drug therapy group (n = 88)	χ^2/T	*p*
Gender, n (%)			1.30	0.25
Female	36 (57.14%)	42 (47.73%)		
Male	27 (42.86%)	46 (52.27%)		
Age, mean (SD)	49.48 (3.86)	49.52 (7.91)	–0.04	0.97
Weight, mean (SD)	55.62 (4.77)	56.88 (5.45)	–1.47	0.14
Preoperative headache grading, n (%)			3.10	0.38
No headache	7 (11.11%)	4 (4.55%)		
Mild	15 (23.81%)	27 (30.68%)		
Moderate	36 (57.14%)	52 (59.09%)		
Severe	5 (7.94%)	5 (5.68%)		

*The two independent sample *T*-test or Chi-square test is used, and the statistic is either T-value or χ^2 value. SD, standard deviation.

the patients and their family members according to the set score scale. Follow-up for migraine was performed using the Hit-6 headache scale (Table 1), with a total score of 36–60.

Statistical Method

The mean ± standard deviation ($\bar{x} \pm s$) was used to describe the measurement data conforming to the normal distribution, and the percentile [P25, P75] was used to describe the distribution of the measurement data not conforming to the normal distribution, and the frequency and composition ratio of the measurement data was calculated. *T*-test (normal distribution), one-way analysis of variance (normal distribution) and rank sum test (non-normal distribution) was used to compare the distribution differences of measurement data. Chi-square test or fisher exact probability method was used to compare the counting data. The longitudinal repeated measurement data were analyzed by generalized estimation equation. All calculations were performed using STATA/IC (Version 14.1), StataCorp LLC, 4905 Lakeway Drive, College Station, Texas, USA.

This study mainly discusses the situation of recurrent stroke and headache relief after treatment in different treatment groups and the improvement of headache in different gender subgroups after pharmacological and interventional treatment. Among them, "recurrent stroke" and "no stroke" belongs to categorical variables, so chi-square test was used for statistical analysis. Use fisher exact probability method for data with one case the number of theory less than 5. Headaches after treatment in different gender subgroups were classified as no headache, mild headache, moderate headache and severe headache according to the Hit-6 headache scale score, which was also a categorical variable, the chi-square test rather than the rank-sum test was used. In the part of "Comparison of preoperative RLS and preoperative migraine, migraine at 3rd month and migraine at 6th month after surgery in interventional occlusion + drug therapy group" of the study, the study data were multiple repeated measures, which was paired design, so repeated measures analysis of variance was used.

Results

General Information

This section performed the statistical analysis of the basic information of clinical study subjects. A flow-chart of the study is provided, see Fig. 1 for details. A total of 151 eligible patients was collected including 78 female cases (51.66%) and 73 male cases (48.34%), aged 33–60 years (49.50 ± 5.89). There were 88 patients in the interventional occlusion + drug therapy group and 63 patients in the simple drug therapy group. The interventional occlusion + drug therapy group included 42 females (47.73%) and 46 males (52.27%), aged 33–60 years (49.52 ± 7.91). In the drug therapy group, there were 36 females (57.14%) and 27 males (42.86%), aged 35–57 years (49.48 ± 3.86). The difference analysis of baseline data showed that there were no significant differences in gender, age, body weight and

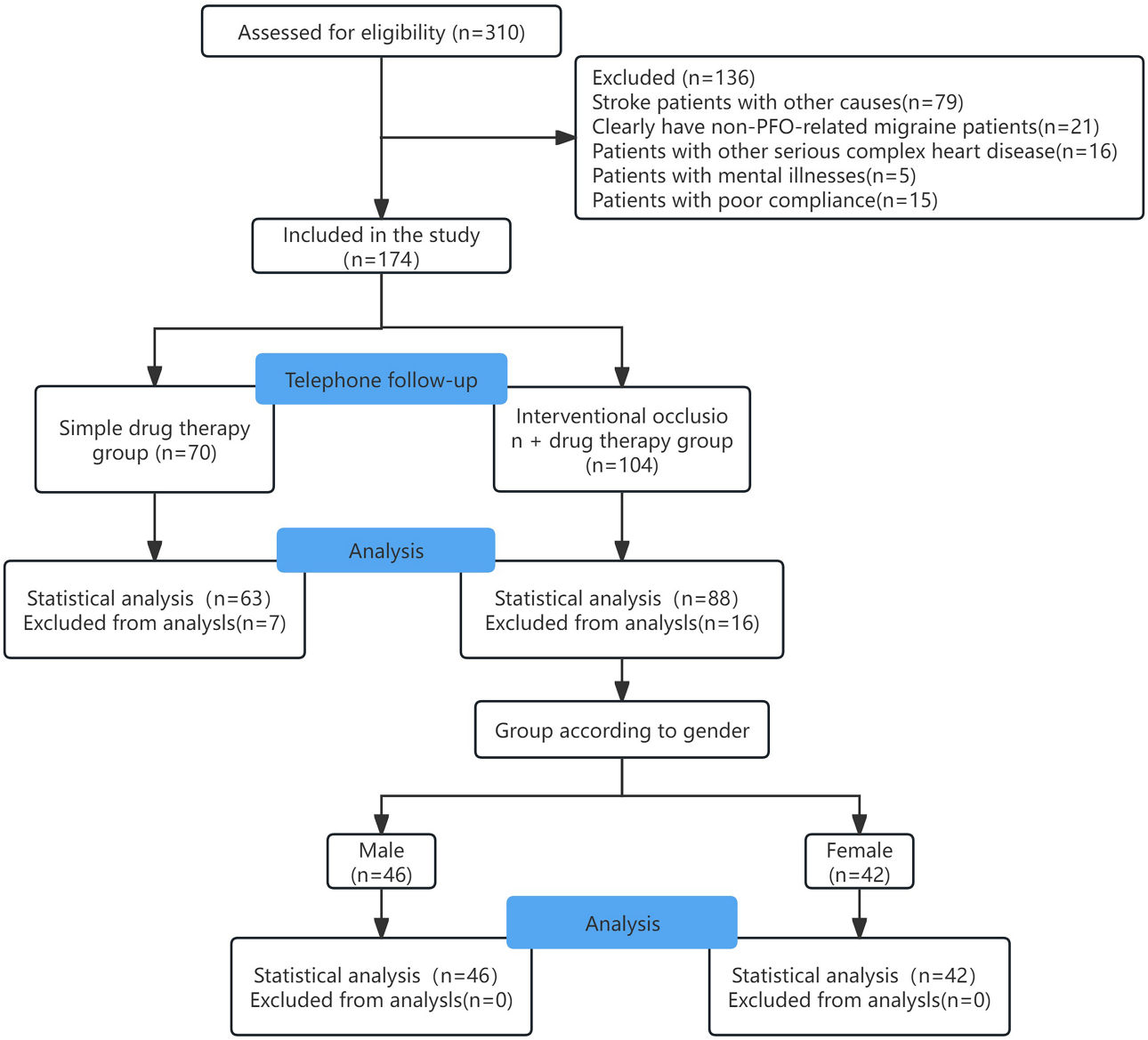

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) patients flow diagram.

preoperative migraine among different groups ($p > 0.05$), see Table 2 for details.

Recurrence of Stroke in 2 Groups within 6 Months after Treatment

In the interventional occlusion + drug therapy group, there were no cases of recurrent stroke within 6 months after operation. Fisher exact probability method was used for statistical analysis and bar graph description of stroke recurrence in patients with different therapy groups, see Table 3 and Fig. 2 for details. The statistical results showed that the incidence of stroke recurrence within 6 months after treatment in the interventional occlusion + drug therapy group was lower than that in the simple drug group, and the difference between the two groups was statistically significant ($p < 0.05$).

Comparison of Migraine between the Two Groups at the 3rd and 6th Month after Treatment

Statistical analysis was conducted on the migraine evaluation results of patients in different therapy groups at the 3rd and 6th month after treatment, see Table 4 for details, and corresponding composition bar charts were made, see Figs. 3,4 for details. The statistical results showed that the distribution of migraine in patients with different therapy groups was different and had statistical significance ($p < 0.01$) at the 3rd month after treatment. The proportion of patients with no or mild migraine in the interventional occlusion + drug therapy group was higher (73.86%), while the proportion of patients with no or mild migraine in the simple drug treatment group was lower (47.62%). It can be seen that patients in the interventional occlusion + drug therapy group had less migraine at the 3rd month after treatment. At the 6th month after treatment, migraine in differ-

Table 3. Comparison of recurrent stroke in different therapy groups.*

Recurrence rate of stroke, n (%)	Simple drug therapy group (n = 63)	Interventional occlusion + drug therapy group (n = 88)	*p* value
No	59 (93.65%)	88 (100.00%)	<0.05
Yes	4 (6.35%)	0 (0.00%)	

*Using fisher exact probability method, no statistics.

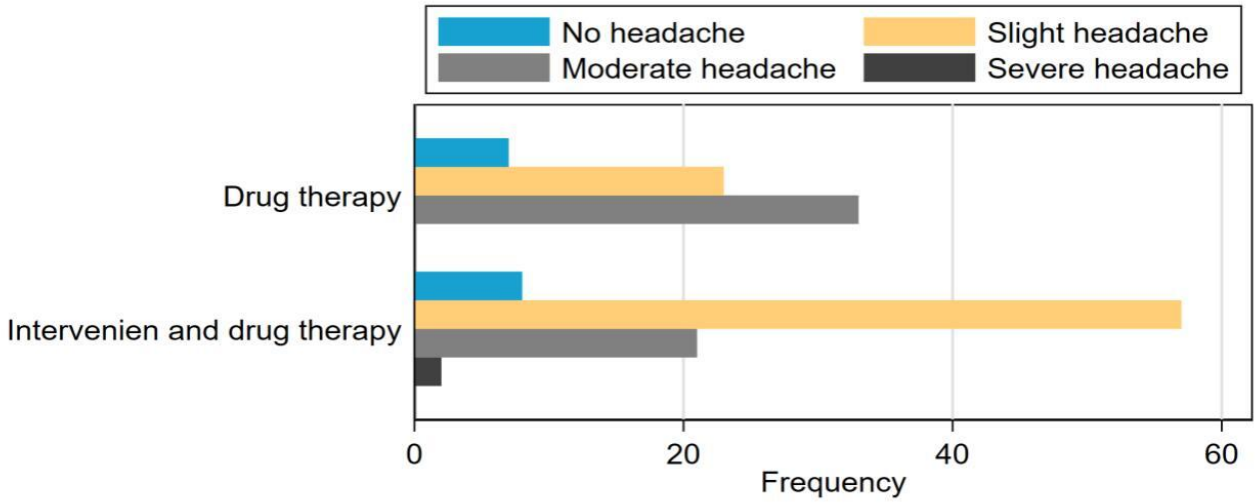

Fig. 2. Bar chart of recurrent stroke composition in different therapy groups.

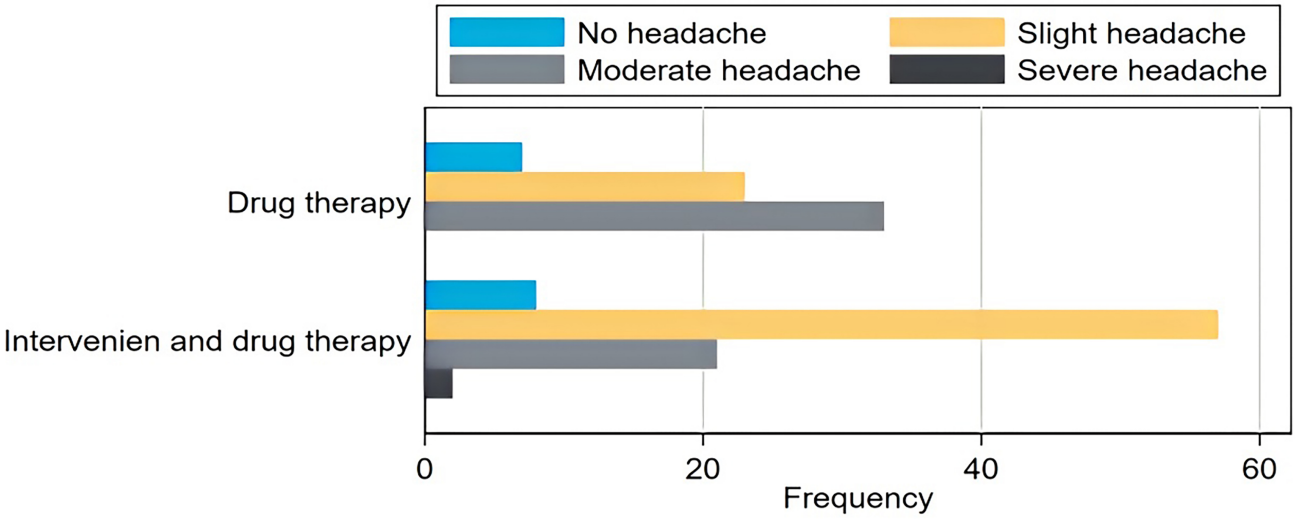

Fig. 3. Bar chart of difference composition ratio of migraine in patients of different treatment groups at 3rd month after treatment.

ent treatment groups had a decreasing trend compared with the 3rd month, and the migraine in the interventional occlusion + drug therapy group was less severe than that in the simple drug group, but there was no statistical difference between the two groups ($p > 0.05$).

Comparison of Migraine Improvement before and after Treatment between the Two Groups

A comprehensive statistical analysis was conducted on headache conditions before treatment, headache conditions at the 3rd month after treatment and headache conditions at the 6th month after treatment of the two groups of patients. As the collected data were longitudinal repeated measurement data, generalized estimating equations (GEE) were introduced in statistical analysis, and the results showed that when the value of moderate or severe was 1, the OR (odds ratio) value of the interventional occlusion + drug therapy group was 0.6 compared with the drug therapy group alone. The risk of moderate or severe headache in the interventional occlusion + drug therapy group was 0.6 times that of the drug therapy group alone (see Table 5 for details). The generalized analysis results were statistically

Table 4. Difference comparison of migraine between the two different groups at the 3rd and 6th month after treatment.*

Headache grading	Simple drug therapy group (n = 63)	Interventional occlusion + drug therapy group (n = 88)	χ^2	*p* value
Classification of headache at 3rd month after treatment, n (%)			-	<0.01
No headache	7 (11.11%)	8 (9.09%)		
Mild	23 (36.51%)	57 (64.77%)		
Moderate	33 (52.38%)	21 (23.86%)		
Severe	0 (0.00%)	2 (2.27%)		
Classification of headache at 6th month after treatment, n (%)			3.26	0.20
No headache	8 (12.70%)	11 (12.50%)		
Mild	43 (68.25%)	69 (78.41%)		
Moderate	12 (19.05%)	8 (9.09%)		
Severe	0 (0.00%)	0 (0.00%)		

* "at 3rd month" uses fisher's exact probability method with no statistics, and "at 6th month" uses chi-square tests.

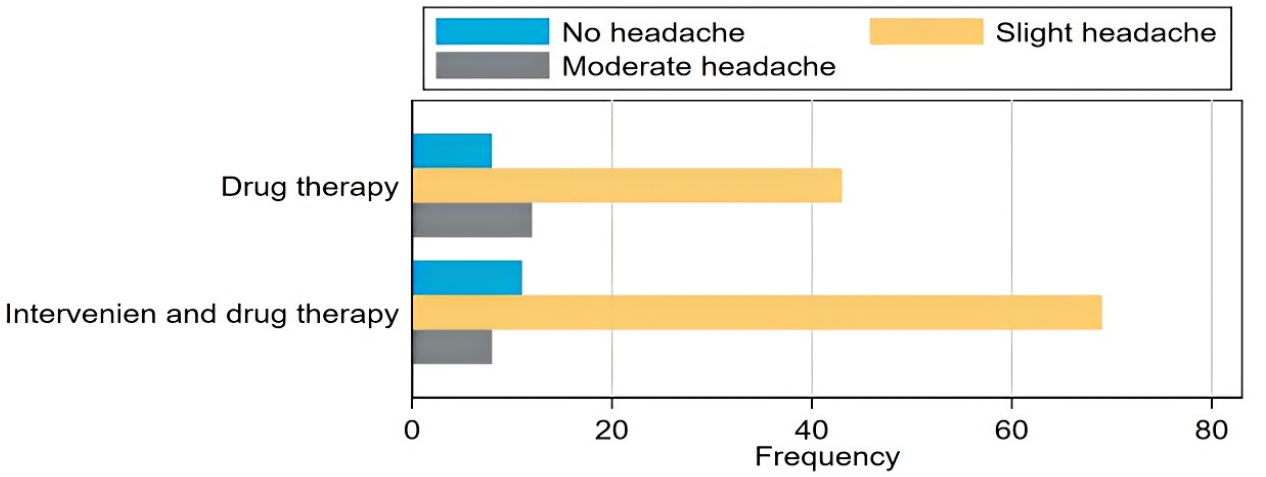

Fig. 4. Bar chart of composition ratio of migraine difference among patients in different treatment groups at 6th month after treatment.

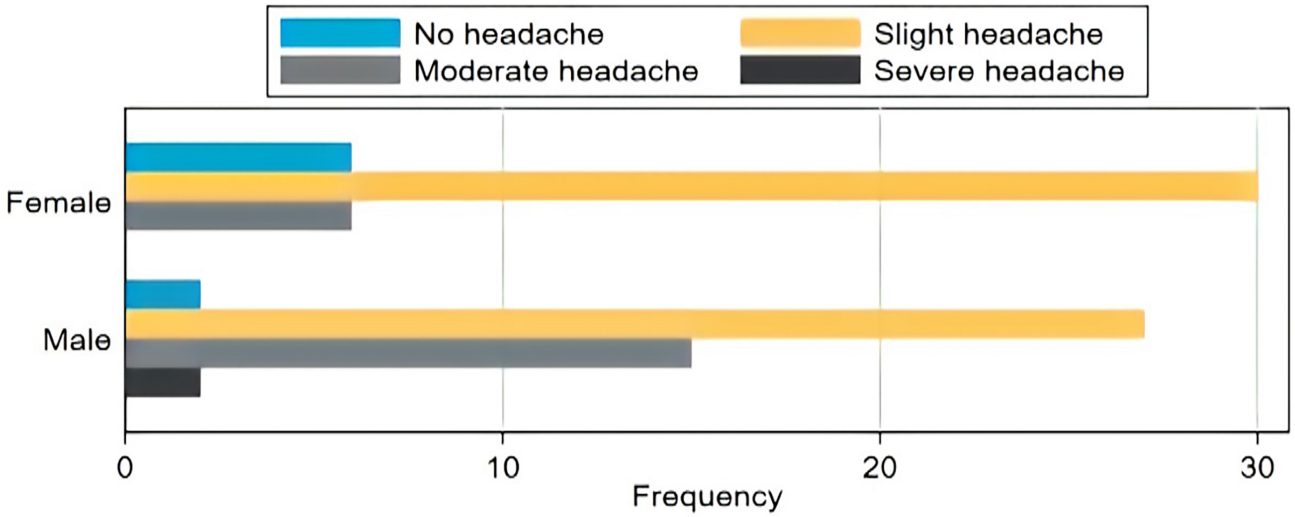

Fig. 5. Bar chart of migraine grading composition ratio in the interventional occlusion + drug therapy group at the 3rd month after treatment.

Table 5. Generalized estimation analysis of headache before and after surgery in two groups.*

Factors	OR	Standard error	95% CI	95% CI	*p* value
			Lower limit	Upper limit	
Group (Interventional occlusion + drug therapy group)	0.60	0.14	0.38	0.95	<0.05

*95% CI, 95% Confidence Interval; OR, odds ratio.

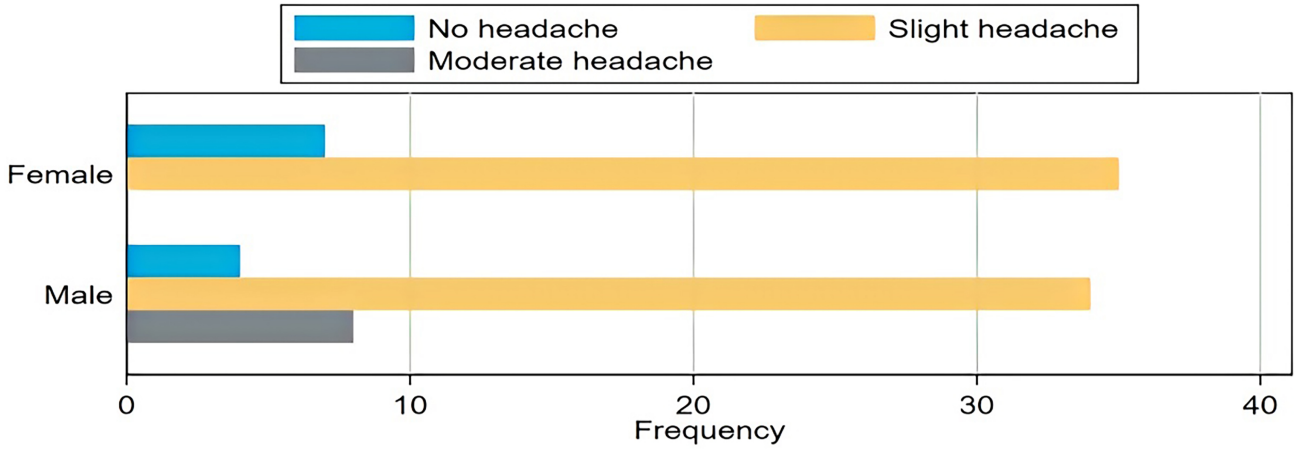

Fig. 6. Bar chart of migraine grading composition ratio in the interventional occlusion + drug therapy group at the 6th month after treatment.

significant ($p < 0.05$). The results show that interventional occlusion and the drug therapy can significantly improve the headache status of patients.

Comparison of Migraines at the 3rd and 6th Month after Surgery in Different Gender Subgroups of Interventional Occlusion + Drug Therapy Group

Fisher exact probability method was used to make statistics on migraines at the 3rd and 6th month after treatment for patients of different genders (see Table 6 for details), and corresponding composition bar charts were drawn (see Figs. 5,6 for details). The results showed that there were significant differences in the distribution of headache among different gender subgroups in the interventional occlusion + drug therapy group at the 3rd month after treatment, and the difference was statistically significant ($p < 0.05$). The proportion of no or mild headache in female patients (85.72%) was higher than that in male group (63.05%). The degree of headache in female patients was less than that in male patients at 3rd month after operation. There were significant differences in the distribution of migraine between the two subgroups at the 6th month after treatment ($p < 0.01$). The proportion of no or mild headache in female patients (100%) was higher than that in male group (82.61%), and the degree of headache in female patients was less severe at the 6th month after treatment. The findings suggest that female patients benefit more from interventional occlusion than male patients.

Comparison of Migraine Improvement before and after Treatment in Different Gender Subgroups of Interventional Occlusion + Drug Therapy Group

GEE was used for generalized estimation analysis of migraine before treatment, migraine at the 3rd month after treatment and migraine at the 6th month after treatment for different gender subgroups of patients in the interventional occlusion + drug therapy group. The results showed that in the case of moderate or severe assignment in 1, the OR value of male patients compared with female patients was 2.22. That is, the risk of moderate or severe migraine in women was reduced by 55% (see Table 7 for details), and the generalized analysis results were statistically significant ($p < 0.01$).

Comparison of Preoperative RLS and Preoperative Migraine, Migraine at 3rd Month and Migraine at 6th Month after Surgery in Interventional Occlusion + Drug Therapy Group

Statistical analysis was performed for preoperative RLS and preoperative migraine and postoperative migraine at 3rd month and at 6th month statistical analysis respectively (see Table 8 for details), the results show that different RLS grading with preoperative migraine, postoperative at 3rd month and at 6th month of migraine difference had statistical significance ($p < 0.01, p < 0.01, p < 0.05$ respectively). In summary, the results show that compared with preoperative headache, patients with RLS grade 1 had the most significant headache relief at 3rd month after surgery, and patients with RLS grade 3 had the most significant

Table 6. Comparison of gender differences in migraine at 3rd and 6th month after treatment in patients with interventional occlusion and drug therapy.*

Headache grading	Female (n = 42)	Male (n = 46)	*p* value
Headache grading at 3rd month after treatment, n (%)			<0.05
No headache	6 (14.29%)	2 (4.35%)	
Mild	30 (71.43%)	27 (58.70%)	
Moderate	6 (14.29%)	15 (32.61%)	
Severe	0 (0.00%)	2 (4.35%)	
Headache grading at 6th month after treatment, n (%)			<0.01
No headache	7 (16.67%)	4 (8.70%)	
Mild	35 (83.33%)	34 (73.91%)	
Moderate	0 (0.00%)	8 (17.39%)	
Severe	0 (0.00%)	0 (0.00%)	

*Both tests all use fisher's exact probability method without statistics.

Table 7. Analysis of the generalized estimation equation for the difference of headache grading between genders in the interventional occlusion + drug therapy group.

Factors	OR	Standard error	95% CI	95% CI	*p* value
			Lower limit	Upper limit	
Gender (Male)	2.22	0.60	1.31	3.76	<0.01

Table 8. Comparison of preoperative RLS grading of patients in the interventional + drug therapy group with headache before surgery, at 3rd month after surgery, and at 6th month after surgery.*

Pain score	RLS grading = 1 (n = 7)	RLS grading = 2 (n = 27)	RLS grading = 3 (n = 54)
Preoperative headache score, mean (SD)	49.71 (7.87)	47.96 (5.87)	50.69 (3.11)
Headache score at 3rd month after surgery, mean (SD)	46.43 (7.14)	44.70 (5.46)	47.91 (3.07)
Headache score at 6th month after surgery, mean (SD)	45.00 (4.90)	44.00 (4.16)	44.48 (2.87)
F	22.56	8.34	1.605
p	<0.01	<0.01	<0.05

*For matching designs (e.g., three comparisons of headache scores for RLS of 1), repeated measure Analysis of Variance (ANOVA) was used with a statistic of F. RLS, right to left shunt.

headache relief at 6th month after surgery. Patients with RLS grade 3 had the most significant reduction in headache at 6th month compared to 3rd month after surgery. Considering that the number of patients classified as RLS 1 is small, its test efficacy is relatively insufficient, and its clinical significance is not obvious. Therefore, only the patients with grades 2 and 3 were finally compared. The results showed that patients with preoperative RLS grade 3 benefited more from intervention occlusion + drug therapy than patients with RLS grade 2.

Discussion

Currently, PFO combined with ischemic stroke is often defined as CS, the CS recurrence rate is about 1% and can be up to 50% in young patients [41]. Patients with PFO are prone to cerebrovascular embolism and stroke [42], and according to statistics, ischemic stroke was the leading cause of death and disability in the Chinese population between 1990 and 2017 [43]. Interventional closure can directly close the foramen ovale, the risk of recurrence is lower than the drug therapy, and the trauma is less than thoracotomy repair. PFO interventional occlusion, which is more convenient, less damaging, faster postoperative recovery and more beneficial to patients, is often recommended in clinical practice.

The study of this paper followed up the recurrence of stroke within 6 months after treatment in the two groups. The final results were that there were no recurrence of stroke in the interventional occlusion + drug therapy group, and 4 (6.35%) recurrence of stroke occurred in the drug therapy group alone. The results showed that the recurrence rate of stroke within 6 months in the interventional occlusion + drug therapy group was lower than that in the patients with drug therapy alone, and the interventional occlusion + drug therapy was more effective in reducing the risk of CS recurrence than that of drug therapy alone. The pathogenesis of CS induced by PFO is related to the anatomical structure of PFO and paradoxical embolism (PDE). Due to the presence of the RLS, Venous thrombosis in lower limb veins or situ thrombus in foramen ovale falls off into the right atrium, and it comes to the left atrium with blood

flow and pushed into the systemic circulation with the heart pump, forming arterial embolism, which can cause stroke, myocardial infarction, syncope, *etc*. [44]. There have been many previous studies on PFO interventional occlusion and the risk of stroke. In 2021, Varotto *et al*. [45] collected from three databases (Medline, EMbase, CENTRAL/CCTR) from December 2012 to 2019, and 3650 patients with CS with PFO were included in a network meta-analysis to study the safety and efficacy of transcatheter PFO interventional occlusion in preventing neurological events in stroke patients, and assess the risk of atrial fibrillation compared with the drug therapy (MT). The network Meta-analysis study supports interventional closure in CS patients, confirming that interventional closure is superior to medication, but increases the risk of atrial fibrillation. Also, one blocking device should not be considered superior to other blocking devices in reducing atrial fibrillation episodes because the comparison was not statistically significant. For patients with severe atrial fibrillation, receiving treatment has an advantage over receiving no treatment. The latest guidelines [46] from the American Academy of Neurology recommends that for patients under the age of 60 with PFO and embolic stroke without other stroke mechanisms, PFO intervention may reduce the risk of recurrent stroke (3.4% reduction in absolute risk of recurrent stroke after 5 years). An international large non-randomized controlled clinical trial study showed that for patients with unexplained cerebral ischemia (including stroke, transient ischemic attack, magnetic resonance related ischemic damage), PFO blocking not only reduces the risk of ischemic event recurrence, and significantly reduce the incidence of migraine, hypoxia, syncope [47].

The World Health Organization 2013 Global Disease Survey identified migraine is now the sixth most common disease and the second most disabling disease worldwide [48]. Typical migraine presents as recurrent unilateral or bilateral, moderate or severe intensity pain, with physical activity aggravating the attacks and rest relieving the headache [49,50]. The possible theories of migraine caused by PFO include the theory of vasoactive substances, abnormal embolism theory, genetic theory and unilateral lateral defect theory [51,52]. Migraine caused by PFO is mainly related to the accumulation of serotonin. Due to RLS, part of the serotonin in the blood skips the pulmonary circulation filtration and directly enter the left heart and systemic circulation, resulting in a significant increase in the content of serotonin in the cerebral artery, thus causing migraine [53]. Some scholars also believe that the occurrence of migraine is related to the inflammatory factors, serotonin or microthrombus in the venous system caused by the right to left shunt directly entering the left heart system and then entering the brain to activate the corresponding receptors [54–56].

The results of this study showed that the proportion of headache free and mild headache cases in the patients with interventional occlusion + drug therapy was higher than that in the group of drug therapy alone. Under the test level of alpha = 0.05, there was a statistical difference in the distribution of migraine in the 3rd month after treatment among different therapy groups ($p < 0.01$). It can be understood that patients with interventional occlusion + drug therapy had less migraine at 3rd month after treatment than patients with medication alone. According to the analysis of headache in the 6th month of patients in different therapy groups, the results showed that under the test level of alpha = 0.05, migraine in the 6th month in different therapy groups had a decreasing trend, but there was no significant statistical difference between the two groups ($p > 0.05$). Longitudinal analysis of migraine before treatment, migraine at 3rd month after treatment, and migraine at 6th month after treatment in the two groups showed that the risk of moderate or severe migraine in the interventional occlusion + drug therapy group was 0.6 times higher than that in the drug alone group, that is, the risk was reduced by 40% (OR = 0.60, $p < 0.05$). In conclusion, patients treated with interventional occlusion + drug therapy had less severe migraine at 3rd month and a 40% lower risk of developing moderate or severe migraine after treatment than those treated with medication alone. Patients in the interventional occlusion + drug therapy group benefited more after treatment. A 2021 Meta-analysis of the efficacy of percutaneous foramen ovale closure in migraine confirmed that foramen ovale occlusion was a benefit in patients with migraine [57]. Also in 2021, Mojadidi *et al*. [58] pooled the data from two randomised trials, PRIMA [59] and PREMIUM [60] and set efficacy endpoints as mean days of monthly migraine reduction, headache response rate (defined as 50% reduction in monthly migraine attacks) and percentage of patients who had complete migraine cessation, the results showed that foramen ovale occlusion significantly reduced the mean number of migraine days per month and migraine attacks per month.

In order to facilitate clinicians to recommend treatment plans for patients with different genders as a reference, this study conducted a statistical analysis of migraine scores of patients with different genders in the interventional occlusion + drug therapy group before surgery, migraine at 3rd month and migraine at 6th month after surgery to evaluate the difference in efficacy between different genders. The results showed that the proportion of no or mild headache (85.72%) in female subgroup was higher than that in male subgroup (63.05%), and the degree of migraine in female patients was less severe. The proportion of headache no or mild at 6th month after surgery (100%) in the female group was higher than that in the male subgroup (82.61%), indicating that migraine severity in female patients was generally less severe. Under the test level of alpha = 0.05, the difference of migraine scores at the 3rd and 6th month after surgery in different gender subgroups was statistically significant. The analysis results of headache improvement before and after treatment in different gender subgroups of interventional blocking + drug therapy group also showed

that the risk of moderate or severe headache in males was 2.22 times that in females (OR = 2.22, $p < 0.01$), that is, the risk of moderate or severe headache in females was reduced by 55%. In summary, the results show that female patients with interventional occlusion + drug therapy have lower migraine degree and lower risk of moderate or severe headache than male patients at the 3rd and 6th month after surgery. Female patients benefit more from interventional occlusion + drug therapy.

In 2022, a matched case-control study found that the incidence of RLS was significantly higher in patients with unexplained syncope than in normal controls, the total incidence of RLS of all grades in the 52 patients with unexplained syncope was 48.1% (25/52), compared with only 21.2% (11/52) of the 52 control patients, moreover, the logistic regression analysis showed a significant correlation between RLS and unexplained syncope (OR = 1.988; 95% CI = 1.233~3.205; $p = 0.005$) [61]. Studies have shown that the frequency of headache and HIT-6 score in patients with RLS is significantly higher than those without RLS, patients with moderate or substantial RLS had a higher frequency of migraine attacks compared with those with mild or no RLS [8]. According to the relevant Chinese expert guidelines in 2021, the clinical benefit of PFO occlusion is related to the right-to-left shunt volume, and patients with moderate to large RLS volume have greater benefit after treatment, while patients with small RLS volume and deep cerebral small infarction have poor effect [62]. On this basis, the difference of preoperative RLS shunt volume and preoperative and postoperative migraine in the interventional occlusion + drug therapy group was statistically analyzed. The results showed that patients with different RLS grading had different headache relief. Patients with preoperative RLS grading of 1 had more headache relief at 3rd month after surgery, patients with preoperative RLS grading of 3 had more headache relief at 6th month after surgery, and patients with preoperative RLS grading of 3 had more benefit after surgery.

Conclusion

In summary, this retrospective study discussed and evaluated the clinical efficacy of interventional occlusion in the treatment of PFO with positive foam test in the treatment of CS, and concluded as follows: Compared with the drug therapy, interventional occlusion + drug therapy could better reduce the risk of CS recurrence and improve the prognosis, and the degree of migraine in patients is significantly reduced; patients with different genders received interventional occlusion + drug therapy had different degrees of migraine after surgery. Women had less severe migraine and a lower risk of moderate or severe migraine, and women benefited more after treatment; postoperative migraine relief was different among patients with different RLS grading. Patients with preoperative RLS grading of 3 had the most significant postoperative migraine relief, so patients with preoperative RLS grading of 3 had more benefits after treatment.

Limitations

In this study, since most patients were lost to follow-up after one year during the follow-up process, only the recurrence of stroke within 6 months was counted, and the long-term efficacy of the two treatments was not explored. More research data are needed to support this conclusion. There are many factors affecting migraine, such as the education level, living habits and self-care ability. Although this study excluded migraine patients with definite etiology as well as other psychiatric patients with headache during the collection process, this study did not collect information on patient education, smoking and drinking. The number of cases in this study was relatively small. As a result, some statistical results are not high enough, more data are needed to further confirm the conclusions of this study.

Abbreviations

PFO, Patent Foramen Ovale; CS, Cryptogenic Stroke; ASA, Atrial Septal Aneurysm; OR, Odds Ratio; TIA, Transient Ischemic Attack; FDA, US Food and Drugs Administration; SCAI, The American Society of Cardiovascular Angiography and Interventions; RLS, Right to Left Shunt; PDE, Paradoxical Embolism; c-TCD, Contrast-enhanced Transcranial Doppler; c-TTE, Contrast-enhanced Transthoracic Echocardiography; c-TEE, Contrast Transesophageal Echocardiography; RoPE, The Risk of Paradoxical Embolism; RRR, The Relative Risk Reduction; ICE, Intracardiac Echocardiography; 95% CI, 95% Confidence Interval; GEE, Generalized Estimatingequations.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author Contributions

ZL and WX conceptualized this study. ZL conducted and collected the data, and drafted the manuscript. WX generated the figures. WX reviewed and edited the language. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. Both authors read and approved the final manuscript. Both authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Nanchong Central Hospital (No.: 2022 Annual Review (095)). We confirm that all methods were carried out in accordance with relevant guidelines and regulations based on Declaration of Helsinki. All of the patients had signed the informed consent form.

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Conflict of Interest

The authors declare no conflict of interest.

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