ORIGINAL ARTICLE

Ischemic Stroke in Patients with Percutaneous Patent Foramen Ovale Closure

Accidente cerebrovascular isquémico en pacientes con cierre percutáneo del foramen oval permeable

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ABSTRACT

Background: The prevalence of patent foramen ovale is approximately 50% in patients who have suffered a cryptogenic stroke. The recurrence of ischemic stroke after percutaneous patent foramen ovale closure is approximately 1% per year.
Objective: The aim of this study was to evaluate the prevalence of recurrent ischemic stroke in our population undergoing percutaneous patent foramen ovale closure.
Methods: All patients with diagnosis of cryptogenic ischemic stroke who underwent percutaneous patent foramen ovale closure between January 2007 and September 2015 were retrospectively included. Follow-up detected patients who had either a recurrent stroke and/or a transient ischemic attack after percutaneous patent foramen ovale closure.
Results: Twenty eight patients with average age of 47 years (20-71 years) at the time of the procedure were included in the study. Fifty percent of patients were females, 79% had previous history of stroke and 21% of transient ischemic attack. The RoPE score was 7.07 points (3-10 points) and percutaneous closure was successful in all cases. During follow-up (median 989 days, interquartile range 670-1766 days), two patients (7%) had a new stroke. In both patients, transesophageal echocardiography revealed closed patent foramen ovale without residual leak.
Conclusions: The incidence of a recurrent stroke is low after percutaneous patent foramen ovale closure and it is possible that a significant number of recurrent cases will not be preventable with its closure.

Key words: Foramen Ovale, Patent - Stroke - Heart Septal Defects, Atrial/surgery - Septal Occluder Device

RESUMEN

Introducción: El foramen oval permeable se encuentra en alrededor del 50% de los pacientes que han sufrido un accidente cerebrovascular criptogénico. La recurrencia de un accidente cerebrovascular isquémico luego del cierre percutáneo del foramen oval permeable es de alrededor del 1% anual.
Objetivo: Evaluar la prevalencia de recurrencia de accidente cerebrovascular isquémico en nuestra población tratada con cierre percutáneo del foramen oval permeable.
Material y métodos: Se incluyeron en forma retrospectiva desde enero de 2007 hasta septiembre de 2015 todos los pacientes con diagnóstico de accidente cerebrovascular isquémico criptogénico a quienes mediante técnica percutánea se les ocluyó un foramen oval permeable. En el seguimiento se detectaron los casos en los que se diagnosticó recurrencia de evento en la forma de un nuevo accidente cerebrovascular isquémico y/o ataque isquémico transitorio posterior al cierre percutáneo.
Resultados: Se incluyeron 28 pacientes, con edad promedio al momento del procedimiento de 47 años (20-71 años), el 50% eran mujeres, el 79% habían tenido un accidente cerebrovascular y el 21% un ataque isquémico transitorio. El puntaje de RoPE fue de 7,07 puntos (3-10 puntos). El cierre percutáneo fue exitoso en todos los casos. En un período de seguimiento (mediana 989 días, intervalo intercuartil 670-1.766 días) se identificaron dos pacientes (7%) que tuvieron un nuevo accidente cerebrovascular. En ambos pacientes se repitió un ecocardiograma transesofágico y se encontró foramen oval permeable cerrado sin fugas residuales.
Conclusiones: La frecuencia de recurrencia de accidente cerebrovasculares baja luego del cierre percutáneo del foramen oval permeable y posiblemente un buen número de los casos recurrentes no sean prevenibles con su cierre.

Palabras clave: Foramen oval permeable - Accidente cerebrovascular - Defectos del tabique interatrial/Cirugía - Dispositivo Oclusor Septal

Abbreviations

AF	Atrial fibrillation	**TIA**	Transient ischemic attack
PFO	Patent foramen ovale		

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INTRODUCTION

Patent foramen ovale (PFO) is found in approximately 25% of individuals in the overall population and increases to 50% in patients who have suffered a cryptogenic stroke. (1) During the last decade, its inclusion as a risk factor for an ischemic neurologic event has been controversial.

Clinical studies comparing medical therapy versus percutaneous PFO closure in young patients who suffered a cryptogenic stroke did not show significant differences regarding recurrences. (2) In these studies, recurrence of ischemic stroke was approximately 1% per year. Recent evidence during reanalysis of one of these studies (RESPECT) suggested a lower rate of cryptogenic ischemic stroke recurrence in patients treated with percutaneous closure. (3)

The aim of this study was to evaluate the prevalence of ischemic stroke recurrence in our population undergoing percutaneous PFO closure.

METHODS

All patients with diagnosis of cryptogenic ischemic stroke who underwent percutaneous PFO closure between January 2007 and September 2015 were retrospectively included. Cases diagnosed with event recurrence, either as new ischemic stroke and/or transient ischemic attack (TIA) after percutaneous closure were identified in this cohort of patients. Patients with a probable cause for stroke [e.g. atrial fibrillation (AF)] or migraine were excluded from the study. In all cases, bubble contrast transesophageal echocardiogram with agitated saline solution injection and Valsalva maneuver was used for PFO diagnosis. The criterion for the diagnosis of PFO and atrial septal aneurysm followed current guideline recommendations. (4) A large PFO was considered with passage of >20 bubbles. All patients were evaluated with brain imaging studies (diffusion nuclear magnetic resonance imaging) to confirm the ischemic stroke and/or TIA diagnosis. In addition, other causes responsible for an ischemic event were ruled out by means of electrocardiogram, 24-hour Holter monitoring, color Doppler echocardiography of neck vessels, transesophageal echocardiography and complete thrombophilia panel excluding the presence of elevated levels of anticardiolipin antibodies, lupus anticoagulant, hyperhomocysteinemia, protein C deficit, protein S deficit, antithrombin III and factor V Leiden deficit and prothrombin gene mutations.

All patients were assessed by a neurology specialist. The decision to perform percutaneous PFO closure treatment was debated among specialists in neurology, clinical cardiology, echocardiography, angiology and interventional cardiology. The family doctor's opinion and patient preference were considered in problematic cases.

The device used for each intervention was selected according to the total atrial septal length and the presence of aneurysm in the interatrial septum. All procedures of device implantation were performed under general anesthesia with intravenous sodium heparin administration and routine antibiotic prophylaxis.

Fluoroscopy and transesophageal echocardiography were used to guide all the procedures. During follow-up, the patients were indefinitely maintained with aspirin 100/mg/day.

Statistical analysis

InfoStat/P (Universidad Nacional de Córdoba, 2015) software was used to perform statistical analyses. Categorical variables were expressed as percentage and continuous variables as average and range.

Ethical considerations

The study was performed following regulations for observational studies, in compliance with the Declaration of Helsinki principles.

RESULTS

During the study period, 40 patients undergoing percutaneous PFO closure were identified. Twelve patients were excluded: 9 were operated on for migraine, 1 patient had AF, 1 patient embolism in other non-cerebral vascular territories and 1 patient thrombosis of the retinal artery.

The remaining 28 patients with previous history of cryptogenic ischemic stroke or TIA were included in the study. Average age was 47 years (20-71 years) at the time of the procedure, 50% were women and 79% had suffered a stroke. The RoPE (Risk of Paradoxical Embolism) score was 7.07 points (3-10 points) for the whole cohort and no patient had presented AF, heart failure, coronary artery disease and/or peripheral vascular disease (Table 1).

The percutaneous closure was successful in all cases and the devices used were pfm Nit Occlud™ PFO in 14 patients (50%), Amplatzer™ PFO in 9 patients (32%), OcclutechFigulla™ PFO in 4 patients (14%) and Cardia Atriasept™ in 1 patient (4%).

During the follow-up period (median of 989 days, interquartile range 670-1766 days), two patients (7%) were identified with a new stroke, confirmed both by a clinical neurologist and neurological imaging. The first patient with recurrence was a 69-year-old man, with an initial RoPE score of 4 points, in whom the event occurred 124 days after PFO closure. The second patient was also a 53-year-old man, with a RoPE score of 6 points, who had a new event 1705 days following percutaneous closure. Both patients had complete neurological recovery after the recurrence. In both cases, a transesophageal echocardiogram was

Table 1. Population characteristics

Variable	
Age	47 years (20-71 years)
Stroke / Transient ischemic attack	22 (79%) / 6 (21%)
Diabetes	3 (11%)
Smoking	2 (7%)
Dyslipidemia	2 (7%)
Hypertension	6 (21%)
RoPE score	7.07 points (3-10 points)
Large patent foramen ovale	25 (96.1%)
Atrial septal aneurysm	12 (48%)

performed including simultaneous bubble test with agitated saline solution injection, ruling out residual short-circuits through the devices (absence of right to left bubble passage at rest and with Valsalva maneuver); it was also seen that both occluders were adequately positioned in the interatrial septum. However, the mechanism eliciting the stroke could not be identified.

DISCUSSION

The risk of long-term recurrent stroke is approximately 10% at one year, 25% at 5 years and 40% at 10 years, and this risk is higher in patients with symptomatic atherosclerotic disease, active vascular or thrombogenic disease and those interrupting antiplatelet and/or antihypertensive treatment. (5) The main finding of our series of patients was the low recurrence of ischemic stroke after percutaneous PFO closure. Only two patients had ischemic stroke recurrence (7%).

Three recently published randomized clinical studies compared percutaneous closure versus conservative treatment (aspirin, antiplatelet or anticoagulant therapy) in patients with PFO and ischemic stroke.

The first of these studies, the CLOSURE I trial, which included 909 patients with a 2-year follow-up period, found no differences in the rate of stroke recurrence, with a prevalence of 2.9% in the percutaneous treatment branch. (6) The second study, the PC Trial, including 414 patients with a longer follow-up period of up to 4 years, detected 0.5% stroke recurrence in the percutaneous treatment group, not significantly different from the medical treatment group. (7) Finally, the RESPECT trial, including 980 patients with a 2.5-year follow-up, found 2% ischemic stroke recurrence, similar to that of the medical treatment branch. However, this last study was the only one including a pre-specified analysis comparing recurrences according to the treatment received and not by intention-to-treat. In this analysis, percutaneous treatment was superior to medical treatment (HR 0.27, 95% CI 0.10-0.75, p <0.007). (8)

It is interesting to point out that in the CLOSURE I trial, another probable cause of ischemic stroke was identified in most recurrent events, which was different from paradoxical embolism through the PFO. (6)

The long-term follow-up of patients in the recently presented RESPECT study showed that percutaneous closure has benefits to prevent a recurrent cryptogenic stroke. (3) In our experience, as the two cases of recurrent ischemic stroke presented absence of residual shunt, we assumed that they were not secondary events to paradoxical embolism.

Decision-making on the secondary prevention management of cryptogenic stroke is still a dilemma, influenced by the increased prevalence of PFO detected in the general population. A RoPE score based on 12 studies,which included variables such as age, risk factors and imaging studies, could be useful in this difficult clinical scenario. In patients with a low score (0 to 3 points), PFO may be just a coincidence and the estimated recurrence rate is approximately 20% at 2 years, while in patients with a high score (9-10 points), it is highly probable that PFO may be the cause of ischemic stroke with a recurrence rate of approximately 2% at 2 years. In our patients, the average RoPE score was 7 points, with 72% chance that the index event (ischemic stroke or TIA) were secondarily ascribed to paradoxical embolism and with an estimated recurrence rate of approximately 6% (between 2% and 10%). (9) The two cases of recurrence detected had RoPE score of 4 and 6 points, which added to absence of residual shunt by transesophageal echocardiography suggests that they were probably initially wrongly selected cases for percutaneous treatment.

There is no precise indication about which patients would benefit from percutaneous treatment of PFO associated to ischemic stroke; however, patients below 60 years of age, with atrial septal aneurysm, large right to left short-circuit of their PFO and high RoPE score (9-10 points) currently seem to be the best candidates for this intervention. (10)

Finally, the rate of recurrence also seems to depend on the implanted device and in this sense the studies with AMPLATZER™PFO occluder, the most widely used worldwide, would be the one with the best results and the lowest rate of complications. (11) In our experience, we did not encounter complications (e.g. thrombosis) associated to the device in the recurrence cases.

CONCLUSIONS

We observed that the prevalence of stroke recurrence was low, in agreement with the one reported in the described randomized clinical trials, although we must acknowledge the limitations of our work (small sample size and retrospective design). Possibly, a large number of recurrent cases are nor preventable with PFO closure, which warns us on a strict selection of patients candidates for percutaneous treatment.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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