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A meta-analysis of the effectiveness and safety of occlusion of patent foramen ovale versus pharmacological treatment for the prevention of recurrent cryptogenic stroke

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 August 2023 and was last updated on 16 August 2023.

INTRODUCTION

Review question / Objective The aim of this study was to systematically investigate the efficacy and safety of both blockade and pharmacological treatment in the prevention of stroke recurrence. By conducting a large-scale randomized controlled trial, we will comprehensively assess the advantages and disadvantages of these two treatments and provide reliable scientific evidence to guide clinical treatment decisions. Additionally, we will strictly follow ethical standards to ensure patient rights and safety, contributing to the advancement of medicine and the development of more accurate and effective treatment strategies for stroke patients. This study is expected to provide accurate guidance for clinical treatment and nursing practice, as well as reliable evidence to support clinical practice guidelines for the care of stroke patients with patent foramen ovale.

Condition being studied Stroke is a disease with high global morbidity, disability, and mortality. It can be classified into Hemorrhagic Stroke (Hemorrhagic Stroke) and Ischemic Stroke (Cerebral Ischemic Stroke). Cryptogenic stroke (CS), also known as cryptogenic stroke, is a subtype of ischemic stroke without a clear etiology . It accounts for 10% to 40% of all ischemic strokes, and the patients are predominantly young . Patent Foramen Ovale (PFO), an embryonic defect of the interatrial septum , is a common cause of cryptogenic stroke and has received increasing attention. During the embryonic period, the foramen ovale is a normal physiological channel for blood circulation. However, after birth, the foramen ovale gradually closes due to an increase in pressure in the left atrium. In some cases, the foramen ovale does not close after 36 months of life, leading to a condition known as patent foramen ovale . A patent foramen ovale allows oxygenated blood to pass from the right atrium into the left atrium . The prevalence of patent foramen ovale failure (PFO) in the adult population is 20% to 25%, and in people with cryptogenic stroke, 40% to 50% of patients have PFO . Currently, the main treatments for PFO

include PFO occlusion and pharmacological therapy.

METHODS

Search strategy The searches were conducted using a combination of subject terms and free words , and the search strategy was determined after several pre-searches. The key words "Foramen Ovale, Patent", "Heart Septal Defects, Atrial", "patent foramen Foramen Ovale, Patent", "Heart Septal Defects, Atrial", "patent foramen ovale", "atrial septal defects", "PFO", "right to left shunt ", "atrial septal aneurysm", "ASA", "interatrial shunt ", "Stroke", "Brain Infarction", "Cerebral Infarction ", "Stroke, Lacunar", "Cerebrovascular Disorders", "Brain Ischemia", "Ischemic Attack, Transient", "stroke", "ischemic stroke", "cryptogenic stroke", "current stroke", "transient ischemic attack", "TIA", "brain infarction", "drug therapy ", "antithrombins", "factor Xa Inhibitors", "warfarin ", "platelet aggregation inhibitors", "platelet aggregation", " Aspirin", "medical therapy", "platelet aggregation", " clopidogrel", "Aspirin", "anticoagulants", "antiplatelet ", "novel oral anticoagulant", "new oral anticoagulant", "non-vi", "medical therapy tamin K antagonist". medical therapy tamin K antagonist oral anticoagulant", "catheterisation", "cardiac catheterisation", "septal occluder device", "percutaneous closure", "transcatheter closure", "cardiac catheterisation", "heart catheterisation ", "septal occluder device".

Participant or population Subjects participating in the study had to meet the following conditions: age ranging from 18 to 60 years and a history of stroke. Additionally, they must have undergone clinical or imaging examinations to confirm their stroke type, which can be ischemic stroke, transient ischemic attack (TIA), or peripheral embolism. Furthermore, there needs to be a basis for diagnostic imaging such as transesophageal echocardiography (TEE), transcranial doppler (TCD), or other appropriate tests to confirm the presence of a patent foramen ovale. Finally, after rigorous assessment, other potential causes of the stroke event, such as atherosclerotic type of large arteries, cardiac source of embolism, or occlusion of small arteries, must have been ruled out.

Intervention After undergoing PFO occlusion therapy, the test group patients were administered one or two antiplatelet drugs, either in a single or combined form, for a minimum period of three months post-occlusion.

Comparator The control group patients received drug treatment with a follow-up period of at least 1 year. This treatment included either a single or combined use of anticoagulant or antiplatelet drugs, or the combined use of two drugs.

Study designs to be included This meta-analysis was designed to compare the efficacy and safety of interventional PFO closure vs medical therapy for secondary prevention of cryptogenic ischemic stroke in patients with PFO.

Eligibility criteria Inclusion: criteriaSubjects participating in the study had to meet the following conditions: age ranging from 18 to 60 years and a history of stroke. Additionally, they must have undergone clinical or imaging examinations to confirm their stroke type, which can be ischemic stroke, transient ischemic attack (TIA), or peripheral embolism. Furthermore, there needs to be a basis for diagnostic imaging such as transesophageal echocardiography (TEE), transcranial doppler (TCD), or other appropriate tests to confirm the presence of a patent foramen ovale. Finally, after rigorous assessment, other potential causes of the stroke event, such as atherosclerotic type of large arteries, cardiac source of embolism, or occlusion of small arteries, must have been ruled out.

Information sources Computer searches of the Cochrane Library, Joanna Briggs Institute Library, MEDLINE, RNAO, OVID, Web of Knowledge, Nursing Consult, EMbase, CINAHL (Cumulative Index to Nursing and Allied Health literature), Elsevier (Science Direct), CALIS (China Academic Library & Information System), China Biomedical Literature Database (CBM), Chinese Journal Full Text Database (CNKI) and Wanfang Data Resources System. Our literature search was limited to the period from 2012 to December 2022 and covered literature in Chinese and English only.

Main outcome(s) (1) recurrent stroke events; (2) transient ischaemic attack (TIA)events.

Additional outcome(s) (1) haemorrhage; (2) new atrial fibrillation or atrial flutter; and (3) all-cause mortality throughout the follow-up period.

Quality assessment / Risk of bias analysis The publication bias of the literature was assessed using a funnel plot and Egger's test.

Strategy of data synthesis Meta-analysis was performed using Stata17.0 software to ensure accuracy and reliability of the study results. The heterogeneity between the results of each included

study was tested using the I2 test. Methodological heterogeneity was classified as very low if I2 ≤ 25%, low if 25% < I2 ≤ 50%, high if 50% < I2 ≤ 75%, and very high if I2 > 75%. A fixed-effects model was employed if I2 ≤ 50%, while a random-effects model was used if I2 > 50%. The combined effect sizes were expressed as relative risk (RR value) and its 95% confidence interval (95% CI). A statistically significant difference in the incidence of ischaemic stroke, haemorrhage, TIA, and all-cause mortality between the two interventions was determined when the 95% CI of the RR value did not include 1 ($P < 0.05$). If the 95% CI of the combined RR value was both > 1, it was considered a risk factor, whereas if it was both < 1, it was considered a protective factor. The data included in the literature were imported and a forest plot was automatically generated using the software.

Subgroup analysis Subgroup analyses will be performed if at least 2 studies report data on specific populations. Subgroup analyses will include (i) type of occlusion; (ii) type of antiplatelet drug.

Sensitivity analysis To investigate the robustness of the findings, sensitivity analyses were conducted through the one-by-one exclusion method using the "metaninf" module of Stata 17.0 software.

Language restriction English.

Country(ies) involved China.

Keywords foramen ovale inhibition, stroke, occlusion, meta-analysis, randomized controlled trial.

Contributions of each author

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