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Review article

A systematic review of closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and cryptogenic stroke or transient ischemic attack

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ABSTRACT

The optimal treatment for secondary prevention in patients who have a patent foramen ovale (PFO) and history of cryptogenic stroke is still uncertain and controversial. In view of this, we performed a systematic review of randomized controlled trials (RCTs) to investigate whether PFO closure was superior to medical therapy for prevention of recurrent stroke or transient ischemic attack (TIA) in patients with PFO after cryptogenic stroke. We searched the Cochrane Central Register of Controlled Trials, Embase, PubMed, Web of Science, and ClinicalTrials.gov. Three randomized controlled trials with a total of 2303 patients were included and analyzed. A fixed-effect model was used by Review Manager 5.2 (RevMan 5.2) software. The pooled risk ratio (RR) of recurrent stroke or TIA was 0.70, with 95% confidence interval (CI) = 0.47 to 1.04, $p = 0.08$. The results were similar in the incidence of death and adverse events, and the pooled RR was 0.92 (95% CI = 0.34 to 2.45, $p = 0.86$) and 1.08 (95% CI = 0.93 to 1.26, $p = 0.32$), respectively. The data of this systematic review did not show superiority of closure over medical therapy for secondary prevention after cryptogenic stroke. Due to some limitations of the included studies, more randomized controlled trials are needed for further investigation regarding this field.

Contents

1. Introduction

The etiology of ischemic stroke remains unknown in approximately 40% of stroke patients despite an extensive diagnostic evaluation, and such strokes are classified as cryptogenic stroke [1]. Oval foramen is an interatrial communication that serves to shunt blood from the right

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atrium directly into the left atrium before birth. The foramen usually closes as the left-sided pressure rises and is typically sealed within the first year of life. However, it still exists in about 24% of healthy adults and 38% of patients with cryptogenic stroke [2]. It is widely accepted that venous thrombus can gain access to the left atrium through an oval foramen [3]. Thus, paradoxical embolism has been implied as the most likely mechanism of cryptogenic stroke related to PFO, particularly in younger patients. An embolus may enter the systemic circulation from the right to the left atrium via the PFO and cause blockage of a cerebral artery [4]. Therefore, therapeutic measures for secondary prevention are aimed at inhibiting thrombus formation, or occluding the path of the paradoxical embolism [5]. At present, the treatments for preventing recurrent stroke or TIA include medical therapy with antiplatelet agents or anticoagulants, transcatheter PFO closure, and open surgical repair. With the rapid development of interventional technologies, transcatheter device closure has become a feasible and relatively safe treatment option, with high implant success rate and low incidence of device-related complications reported in several observational studies [6,7], and primary surgical repair is rarely advocated. At present, the predominant treatments include PFO closure and medical therapy. A significant controversy surrounds the optimal strategy for treatment of cryptogenic stroke or TIA and concomitant PFO. Transcatheter device closure is superior to medical therapy in the prevention of recurrent stroke or TIA according to the conclusions of several meta-analyses [7–10]. However, all reviews relate to nonrandom trials, and it is inappropriate to answer the questions about therapeutic efficacy due to the imbalance of baseline characteristics, follow-up, and outcome assessment. Therefore, it is necessary to review all relevant randomized controlled trials on this issue to make an objective comparison of the safety and efficacy of the two treatments.

2. Materials and methods

2.1. Search strategy

We searched the Cochrane Central Register of Controlled Trials, Embase, PubMed, Web of Science, and ClinicalTrials.gov, and selected potentially relevant studies through a manual search of references from all eligible studies and review articles. If necessary, we contacted authors to obtain additional unpublished data. When the same patient population was included in several publications, only the most recent or complete study would be included.

2.2. Inclusion criteria

Studies that met the following criteria were included: (1) randomized controlled trials; (2) comparing transcatheter device closure with medical therapy for prevention of recurrent stroke or TIA in patients with PFO-related cryptogenic stroke or TIA; (3) reporting the data of recurrent stroke or TIA, death, and adverse events; and (4) follow-up period was 12 months at least.

2.3. Types of outcome measures

Primary outcome was defined as recurrent stroke or TIA during the follow-up period. Secondary outcomes were specified as follows: 1. Death from any cause after randomization. 2. Adverse events directly related to the device, procedure, or medical therapy during the follow-up period.

2.4. Data extraction and statistical analysis

Two authors independently assessed each paper for relevance, eligibility and quality. We independently extracted data from each eligible trial, and assessed each study for risk of bias using the Cochrane Collaboration's tool including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. We graded these items as having high, low, or unclear risk.

All statistical analyses were performed using the RevMan 5.2 program. We calculated a weighted treatment effect using the Mantel–Haenszel method, and expressed results as risk ratio, 95% confidence interval, and *p*-value. Heterogeneity assumption was assessed by Chi^2 test and I^2 test. The heterogeneity was considered insignificant when $p > 0.1$ or $I^2 < 50\%$, and the treatment effect of each study was calculated by the fixed-effect model. Otherwise, the random effect model was utilized (http://handbook.cochrane.org).

3. Results

3.1. Description of studies

The study selection process is detailed in Fig. 1. Ultimately, three randomized controlled trials [11–13] with 2303 patients in total were included, and several trials that had registered in ClinicalTrials.gov were still in progress. All the included articles that were published in *The New England Journal of Medicine* from 2012 to 2013 were prospective, multicenter, randomized, controlled trials. They provided a comparison of transcatheter PFO closure with medical therapy in patients with PFO and a history of cryptogenic stroke or TIA. These trials were carried out in Europe, the United States of America, Canada, Brazil, and Australia. Patients were included if they were between 18 and 60 years of age, had a cryptogenic stroke or TIA and evidence of a patent foramen ovale. PFO was diagnosed by transesophageal echocardiography with a bubble study. Exclusion criterion was any identified potential cause of stroke or TIA other than the patent foramen ovale. Patients from two groups accepted the PFO closure operation and medical therapy. The therapeutic regimen included an antiplatelet agent, anticoagulant or both of them. The follow-up period was from two to eight years. The end-point events were adjudicated by an independent, expert clinical events committee using a blind method. The distribution of patients in different study groups, along with part of their baseline characteristics, is demonstrated in Table 1. There were no significant differences between the two groups with respect to medical history,

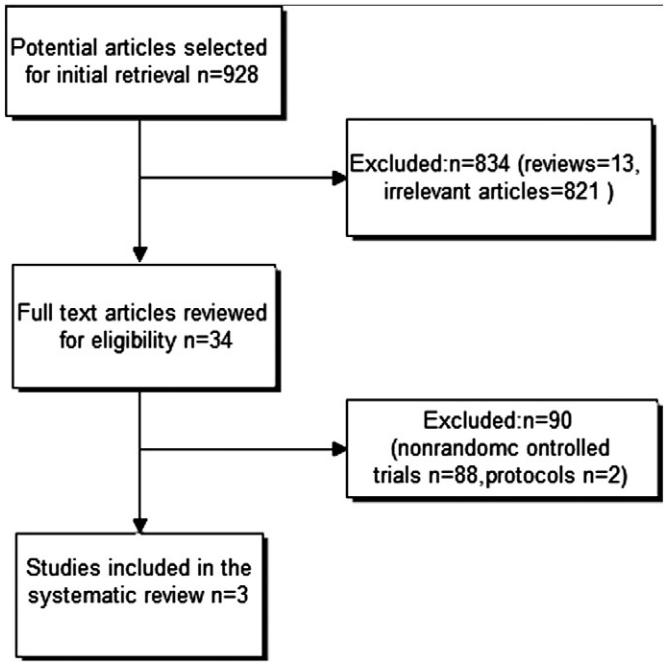

Fig. 1. Flow diagram demonstrating selection of studies.