Patent Foramen Ovale Closure Minimally Effective for Treating Refractory Migraines with Aura

Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention with STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008;117:1397–404.

Study Overview

Objective. To determine whether percutaneous closure of patent foramen ovale (PFO) is effective for preventing migraines in patients with severe, refractory, drug-resistant migraines with aura.

Design. Multicenter, randomized, double-blind, sham-controlled trial.

Setting and participants. Participants were recruited over the Web or from participating headache centers in the United Kingdom and were considered for inclusion if they had migraine with aura that started before age 50 years, had ≥ 5 headache days and ≥ 7 headache-free days per month, and failed ≥ 2 preventive medication regimens for migraine. Participants were excluded if they were pregnant, planning pregnancy, or breastfeeding; if they required PFO closure for another indication; if they had other medical problems, such as bleeding or platelet disorders, recent gastrointestinal bleeding, active infection, renal failure, pulmonary arteriovenous malformation, cirrhosis, portal hypertension, other neurologic disorders, or cardiovascular abnormalities; or if they could not tolerate aspirin or clopidogrel or any other components of the PFO closure procedure and recovery.

Intervention. Eligible participants underwent transthoracic echocardiography to evaluate for a right-to-left shunt. Presence of a shunt was interpreted as evidence of a PFO, and participants with a moderate to large shunt were referred for randomization. Patients were randomized to PFO closure with a STARFlex septal repair implant (NMT Medical Inc., Boston, MA) or a sham procedure while under anesthesia. All patients received antiplatelet therapy (aspirin and clopidogrel) for 24 hours prior to the procedure and 90 days postprocedure. Patients were permitted to use rescue medications to treat migraine.

Main outcome measures. Headache cessation between 90 and 180 days after the procedure, determined by patient diaries and evaluated by intent-to-treat analysis. Secondary endpoints included change in severity, frequency, or characteristics of migraine during the 90- to 180-day postoperative period, quality of life, or incidence of migraine during the 0- to 90-day postoperative period.

Main results. Of 432 screened participants, 143 were randomized (74 to the implant, 73 to sham). Most (60%) of those individuals screened had evidence of a right-to-left shunt. However, most shunts were small (ie, had small PFOs, pulmonary shunts, or rarely atrial septal defects), and only participants with moderate to large shunts were included. Mean age was approximately 44 years, most patients were female, and almost all patients were white. In both groups, the median number of headache days was approximately 30 during the 3 months prior to randomization. No difference was found between groups in the primary or secondary endpoints. Exploratory analysis, excluding 2 outliers in the implant group, revealed a significant reduction in the number of headache days per month in the implant group (P = 0.027). 7 patients (including 2 with pericardial effusions and 1 with a retroperitoneal bleed) in the implant group and 3 in the sham group experienced adverse events.

Conclusion. Treatment of refractory migraine headache with PFO closure was ineffective.

Commentary

Migraine with aura is a risk factor for ischemic stroke [1–4], and the increased prevalence of PFO in patients with migraine with aura has been implicated as a possible cause for this association [5–7]. Wilmshurst and Nightingale [8] have suggested that PFOs can directly cause migraines by creating a right-to-left shunt that allows for certain venous agents to bypass the lung, which otherwise would serve as a filter for these agents. As a result, the agents reach the brain and induce a migraine. These conclusions were fueled by observational data that found that migraine with aura resolved or significantly improved after percutaneous closure of PFOs was performed for other reasons (usually in the setting of a cerebrovascular event) [9–12]. Although most studies on PFO closure were small, the results were intriguing and several randomized clinical trials were planned as a result.

This well-designed trial by Dowson et al, funded by the

manufacturer of the device used for PFO closure, was sham-controlled and double-blind, had apparent adequate randomization, and used intent-to-treat analysis. The primary endpoint, cessation of migraine, was rigorous to account for the rather significant intervention pursued in this trial as a treatment for migraine.

This study confirmed the high prevalence of right-to-left shunt among patients with migraine with aura. However, Dowson et al found no significant benefit of the intervention with regard to the primary or any of the secondary endpoints. In further analysis, some benefit was found in reduced total headache days per month in the implant group, but this was discovered only when 2 outliers were removed from the analysis (due to a large number of headache days). The authors recount several reasons why the results were limited, including the rigorous primary endpoint, the decision to include migraine patients who are perhaps hardest to treat (those with significant refractory migraines), the allowance of preventive medications during the trial, and the inclusion of endpoints measured between 3 and 6 months after the intervention, when a lagged effect for migraine control is possible. Although these reasons are logical, it is important to note that this type of treatment cannot be pursued without use of very rigorous criteria to judge success. Of 68 patients who underwent PFO closure, 2 had pericardial effusions (including 1 with tamponade), 1 had a retroperitoneal bleed, and 2 experienced atrial fibrillation.

Applications for Clinical Practice

PFO closure was ineffective for the treatment of migraine with aura and therefore cannot be recommended in clinical practice. The results of ongoing clinical trials will contribute important information to the final determination of whether PFO closure for migraines with aura would be of any benefit.

—Review by Jason P. Block, MD, MPH

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