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PATENT FORAMEN OVALE AND MIGRAINE

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EXECUTIVE SUMMARY

Migraine headache is a disabling condition without a cure. Pharmacotherapy can currently only reduce the frequency and intensity of these headaches, highlighting the need for more definite treatment options. Observational studies have shown a possible association between migraine headache and the presence of a patent foramen ovale (PFO). Further evidence has shown that migraine headaches are significantly eased in patients undergoing PFO closure for cardiovascular reasons. The first prospective randomized trial evaluating the effect of PFO closure on migraine headaches, the MIST trial, did not reach its primary endpoint of a significant elimination of migraine headaches, but did show a significant reduction in headache days and migraine burden. A larger US trial, MIST II, is being conducted with more patients, revised endpoints, and a longer follow-up. Other trials evaluating alternative PFO closure devices (ESCAPE, PREMIUM) are also underway. While the current data do not support the use of PFO closure as a first-line treatment for migraine headaches, these ongoing studies will provide valuable insights into the clinical benefit of this procedure in all or a subset of migraine sufferers.

Introduction

Migraine headache is a common and disabling condition which, with a prevalence of 10-12%, ranks 19th among diseases causing worldwide morbidity (1). The suffering associated with migraine headaches accounts for a significant loss in productivity and a substantial increase in health care-related costs. In one report, migraine headaches were estimated to cost between \$5.6-\$17.2 billion in sick days and lost productivity (2). Another HMO-based study found that migraineurs submit up to twice as many health care claims and up to 2.5 times as many pharmacy claims as non-migraineurs (3). In defining effective treatment for migraine headache, a commonly accepted endpoint is a 50% reduction in headache frequency after 6 months of therapy. While this may be considered efficacious therapy by some, others might argue for a more definitive treatment.

Association Between Migraine Headache and PFO

In the 1990s, an interesting theory was put forward based on two apparently unrelated observations: 1) Several studies had shown migraine headache to be a risk factor for stroke, particularly in young women (4); and 2) younger stroke patients had been found to have a higher incidence of patent foramen ovale (PFO) (5). Consequently, it was speculated that PFO could play a causative role in the pathogenesis of migraine headaches. PFO has a prevalence of approximately 25% in the general population, and up to 50% in the migraine patient population. Theoretically, right-to-left shunting of blood through a PFO could allow “substances” from the venous system to bypass the natural filter of the lungs and expose the brain to higher than normal concentrations, triggering the development of a migraine. These substances may include vasoactive agents such as atrial natriuretic peptide, platelet factors, and amines, which in elevated concentrations can cause a migraine in susceptible individuals even without a PFO (6). These substances may also include paradoxical microemboli traveling to the terminal branches of the basovertebral arteries and affecting blood flow to the brain stem. Rather than inducing a stroke, the small embolus or platelet aggregate may precipitate a spreading wave of depolarization that is recognized as the first step in the generation of a migraine (7).

Evidence Linking Migraine Headaches to PFO

Several observational studies have examined the prevalence of PFO among migraineurs, both with and without aura (Table 1). While Del Sette et al. (8) showed a statistically significant association between the prevalence of PFO among migraineurs versus controls; Anzola et al. (9) found that the association varied with migraine subtype, as only those patients with aura had a higher occurrence of PFO when compared with controls.

Other observational studies have examined populations of patients undergoing a PFO closure procedure for cardiovascular reasons (or divers for decompression sickness) and found that comorbid migraine headaches were either significantly improved or completely cured in a substantial percentage of cases (Table 2). At the same time, two cases have been reported in which interatrial shunt closure resulted in transformation from intermittent migraine headaches to daily migraine headaches (10). A distinction, however, is that in both cases the interatrial shunting was through a relatively large atrial septal defect as opposed to a PFO. This change in

migraine pattern may be related to a change in interatrial pressure following closure. Wilmshurst et al. (11) reported that 4 out of 11 patients undergoing PFO closure noted fortification spectra (bright, shimmering, jagged lines spreading across the visual field) just after closure, indicating that migraine immediately after PFO closure is not rare.

Until recently, the body of evidence linking PFO and migraine headaches has been intriguing, but limited. In particular, none of the reports showing improvement of migraine after PFO closure had a control group. The first prospective, randomized, double-blind, placebo controlled study evaluating the effect of PFO closure on migraine headaches was the MIST (Migraine Intervention with STARFlex® Technology) trial sponsored by NMT Medical, Inc. (Boston, MA) (12). From January 2005 to July 2005, 13 centers in the United Kingdom randomized 147 patients with migraine headache plus aura in a 1:1 fashion to either percutaneous PFO closure with the STARFlex septal closure system (Figure 1) or to a sham procedure, which included general anesthesia, an incision in the groin, and identical pre- and post-procedural treatment and follow-up. Participants had to have had a history of frequent migraine attacks (≥ 5 days per month) and be refractory to prophylactic medications (previous failure of two medication classes). Of the 432 migraine with aura patients originally screened for this study, over 60% were found to have a right-to-left shunt. Of these, almost 40% had a moderate to large PFO, which is a 6-fold increase compared to the general population.

The preliminary results showed that 42% of treated patients experienced at least a 50% reduction in their headache days compared with 23% of controls ($p = 0.038$). There was also a 37% reduction in migraine burden (frequency x duration) in the treated patients compared with a 17% reduction in the controls ($p = 0.033$). This translated to a mean reduction in headache burden of 50 hours per month in the treated group. However, the trial did not reach its primary endpoint, which was 40% elimination in migraine headache at 6 months in the treatment group. Still, the investigators felt there were enough positive trends to suggest that PFO closure may be an effective way to treat certain types of migraine. Further analysis of the MIST data may indicate which patients are most likely to show a significant treatment response.

In order to validate the treatment trends seen in MIST I, a second trial is underway in the US. MIST II will have a similar study design, but with a larger patient population (600 migraine patients), modified endpoints, and a longer follow-up period (1 year). Enrollment is expected to be complete by the end of 2006. In addition, NMT Medical, Inc. announced in October 2005 its approval of MIST III, a study designed to expand data and follow-up on MIST migraine patients.

Advances in the technology of PFO closure devices may eventually be relevant for migraine sufferers. For example, the BioSTAR™ septal repair implant (NMT Medical, Inc., Boston, MA) is the first bioabsorbable device designed to promote a more natural, rapid, and complete sealing of heart defects such as PFOs. It consists of a bioabsorbable acellular collagen matrix mounted on the STARflex alloy framework. Preliminary results of the BEST (BioSTAR Evaluation Study) trial, showing safety and efficacy of the BioSTAR device, were presented at EuroPCR 2006. It remains to be seen whether the BioSTAR will provide migraine patients with a better PFO-related treatment option.

Ongoing Trials Evaluating PFO Closure and Migraine Headaches

The ESCAPE (Effect of Septal Closure of Atrial PFO on Events of Migraine with Premere™) trial is a randomized, double-blind, placebo controlled, multi-center US trial sponsored by St. Jude Medical, Inc. (St. Paul, MN) (13). The trial intends to determine the safety and efficacy of PFO closure in reducing the frequency of migraine headaches using the Premere PFO closure device (St Jude Medical, Inc.) (Figure 2). Anticipated enrollment is 500 patients with an echocardiographically-documented PFO and a related right-to-left shunt. All randomized subjects with refractory migraine (for at least 1 year) will undergo right heart catheterization, with the treatment arm also undergoing PFO closure. The primary endpoint will be the proportion of patients experiencing a 50% or greater reduction in migraine headaches.

The PREMIUM (Prospective Randomized investigation to Evaluate the incidence of headache reduction in subjects with Migraine and PFO Using the AMPLATZER® PFO occluder) trial is a randomized, two-arm, double-blind, multi-center US trial designed to determine whether patients who undergo PFO closure with an AMPLATZER PFO occluder (AGA Medical, Minneapolis, MN) (Figure 3) have a reduction in both the frequency and severity of migraine headaches (14). The study is expected to enroll approximately 400 patients at up to 30 medical centers.

Conclusions

Whether the association between PFO and migraine headaches is causal or coincidental remains unresolved. Despite the relative safety of the transcatheter PFO closure procedure (more than 13,000 PFO closure procedures have been performed worldwide), PFO closure as a first-line treatment for migraine headaches is currently not recommended. The lack of universal improvement with PFO closure in patients suffering from migraine headaches may result in the invasive procedure being an option only for certain migraine subgroups, such as refractory cases. Trials such as MIST I-III, ESCAPE, and PREMIUM will determine if closure of a PFO might be a conventional option for the treatment of migraine headaches in the future.

Table 1. Prevalence of PFO among Migraine Headache Patients vs. Controls

Study	N	Migraine patients with PFO %	Control with PFO %	Odds ratio	95% confidence interval	P-value
Del Sette et al. (1998; Cerebrovasc Dis;8:327)	94	18/44 (41%)	8/50 (16%)	3.2	1.4-7.2	<0.005
Anzola et al. (1999; Neurology;52:1622)	191	Aura: 54/113 (48%) No aura: 12/53(23%)	5/25 (20%)	Aura: 3.66 No aura: 1.17	Aura: 1.21-13.25 No aura: 0.32-4.45	Aura: 0.01 No aura: NS

Table 2. Observational Studies: % of Patients with Migraine Improvement after PFO Closure for Stroke or Decompression Sickness

Published study	% migraine improved/cured	Follow up (months)
Wilmshurst et al. (2000; Lancet;356:1648)	86%	Up to 30
Morandi et al. (2003; J Interv Cardiol;16:39)	88%	6
Post et al. (2004; Neurology;62:1439)	75%	3
Reisman et al. (2005; J Am Coll Cardiol;45:493)	70%	12
Azarbal et al. (2005; J Am Coll Cardiol;45:489)	76%	3

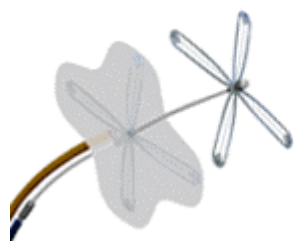
Figure 1. The STARFlex® Septal Repair Implant



The STARFlex® Septal Closure System. Image, with permission, From NMT Medical Inc.

This STARFlex implant incorporates a self adjusting, flexible spring system so that it can automatically adjust to different shapes and locations of defects. (Image courtesy of and reproduced with permission from NMT Medical, Inc., Boston, MA, USA)

Figure 2. The Premere™ PFO Closure Device



Premere PFO Closure System

Designed to conform to the unique anatomy for more confident PFO closure procedures.

The Premere device has two anchors that pivot independently and are connected by a tether, allowing them to be adjusted and fit to any length PFO. The device is designed to be retrievable. (Image courtesy of and reproduced with permission from St. Jude Medical, Inc., St. Paul, MN, USA)

Figure 3. The AMPLATZER® PFO Occluder



The AMPLATZER PFO occluder is a self-expandable, double disc device made from a Nitinol™ wire mesh and containing thin polyester fabric. The two discs are linked together by a short connecting waist. (Image courtesy of and reproduced with permission from AGA Medical, Minneapolis, MN, USA)

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