

EDITORIAL COMMENT

Transcatheter Closure of Patent Foramen Ovale for Migraine Prophylaxis

Hope or Hype?*

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“But the quality which is considered of the highest order in surgical operations is self-possession. *The head must always direct the hand*, otherwise the operator is unfit to discover an effectual remedy. . . .”

—Sir Astley Cooper, Operating Theatre, St. Thomas’ Hospital, London (Lancet, October 5, 1823)

Migraine has generally been conceptualized as a primary disorder of the brainstem that mediates sensory input and neural influences on cranial vessels. It is estimated that 2,500,000 patients in the U.S. have at least one migraine per week, with a lifetime prevalence of 18%. Migraine is a risk factor for cryptogenic stroke, particularly in young patients without atherosclerosis risk factors. In fact, the prevalence of subclinical lesions in the cerebellum in patients with migraine with aura, particularly women, is up to 15-fold higher than controls (1). However, the underlying pathophysiology of migraine is not well understood, and new paradigms in understanding the underlying etiology and optimizing therapy are being explored.

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The foramen ovale is composed of the septum primum (left atrial side, fenestrated cranially) and the septum secundum (right atrial side, fenestrated caudally) joined in parallel forming a slit-like valve that shunts oxygenated blood to the systemic circulation during fetal development. A patent foramen ovale (PFO) results from lack of normal closure postnatally. Atrial septal defects (ASD) and PFO are present in approximately 25% of patients at autopsy and 45% of patients with cryptogenic stroke (2,3). An underlying mechanism of stroke in such patients includes transient right-to-left shunt during the release phase of Valsalva with passage of venous microemboli systemically (i.e., paradoxical

embolism). It is estimated that 70,000 strokes are associated with PFO annually in the U.S. (2).

In this issue of the *Journal*, two reports suggest an intriguing association between ASD/PFO closure and reduction in the incidence or even cure of migraine, particularly migraine associated with aura. Azarbal et al. (4) retrospectively evaluated changes in migraine patterns in 89 patients with cryptogenic stroke following ASD/PFO closure and showed a 42% migraine prevalence, with 62% having migraine with aura. At one-year follow-up, there was complete resolution of migraine, starting immediately postprocedure, in 60% of patients (75% in those with aura), and improvement in the remaining 40%. Reisman et al. (5), in a study of similar methodology, treated 162 patients with presumed paradoxical embolism and showed a 35% prevalence of migraine, with 68% having migraine with aura. Complete resolution of migraine was noted in 56% and significant improvement in 14%. In both groups, clopidogrel was given for three months and aspirin for at least six months postprocedure, and neurologists were involved in the design and/or interpretation of the studies. These two studies corroborate several recent studies showing similar results, with enhanced improvement in patients with migraine with aura (6–9) (Table 1).

Is there a plausible pathophysiologic link between ASD/PFO closure and relief or cure of migraine?

The hope. In patients with migraine with aura the prevalence of PFO, particularly those associated with right-to-left shunt, is significantly increased and similar to young patients with cryptogenic stroke, suggesting a common biologic link (10,11). Interestingly, patients with aura develop hypoperfusion in the occipital cortex, and paradoxical emboli seem to have a predilection for this area of the brain (12). The prevalence of PFO is increased in divers with migraine with aura, and precipitation of migraine has been documented immediately following diving or after placement of PFO devices in such patients (9). Migraine with aura also has occurred during contrast bubble studies, suggesting a causal mechanism, in patients with PFO, of paradoxical microembolization of gas, thrombi, or vasoactive neuromediators that are normally filtered and degraded by the lungs. Migraine with aura is associated with increased platelet hyperaggregability and is also more prevalent in young women who smoke and use oral contraceptives (13). Patent foramen ovale is also associated with transient global amnesia, another condition thought to be mediated by abrupt dysfunction of the vertebrobasilar circulation (14). Consistent with the hypothesis of paradoxical embolization, both aspirin and warfarin have been purported to decrease the incidence of migraine (15,16).

The hype. First, in all six studies combined, only 205 patients with migraine were included, with limited follow-up. Second, the majority of studies are retrospective and all are nonrandomized. Third, the data, although

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Table 1. Effect of PFO Closure Devices on Migraine Headache

Authors (Ref.)	Year	Type of Study	# of Subjects	# (%) With Migraine	Mean Follow-Up	Resolution %	Improved %
Willshurst et al. (9)	2000	Retrospective	37	21 (57)	17 months	48	38
Morandi et al. (6)	2003	Prospective	17	17 (100)	12 months	29	59
Post et al. (7)	2004	Retrospective	66	26 (39)	6 months	84	N/A
Schwerzmann et al. (8)	2004	Retrospective	215	47 (22)	24 months	N/A	83
Azarbal et al. (4)	2004	Retrospective	89	37 (42)	6 months	60	16
Reisman et al. (5)	2004	Retrospective	162	57 (35)	12 months	56	14
Total			586	205 (35)		55	42

N/A = not applicable; PFO = patent foramen ovale.

collected with well-validated measures, are based primarily on subjective recall of headache frequency rather than objectively gathered data, such as a headache diary and use of migraine medications. Fourth, patients and physicians were not blinded and it is not unreasonable to suspect that they were aware of the possibility of migraine improvement at the time of ASD/PFO device implantation. Fifth, a strong possibility exists for placebo effect, which can occur in 20% to 40% of subjects in any therapeutic study. However, the majority of patients either had complete resolution or improvement, suggesting additional mechanisms beyond placebo effect. Sixth, all patients were treated with clopidogrel and aspirin, which may have reduced migraine frequency (6). Seventh, two recent reports (17,18) have actually reported either new migraine with aura or transformation to daily occurrence following Amplatzer ASD closure (complete ASD closure was present and thrombus was ruled out by transesophageal echocardiography), questioning the proposed mechanism of migraine. Eighth, the completeness of PFO closure does not seem to be associated with migraine relief, which is disappointing from a pathophysiology perspective. Last, there is a small but real risk of significant complications related to placement of PFO devices (2).

These studies generate a strong rationale for further investigation in understanding the pathophysiology and treatment of migraine. However, before PFO closure can be proposed for migraine, a healthy skepticism should be in place, considering the high frequency of both migraine and PFO in the general population. It will be necessary to obtain definitive evidence with randomized controlled trials and to define the appropriate clinical indications. Design of such trials, which are already in the planning stages, will require adequate sample size and extended follow-up; optimal medical therapy, including antiplatelet and perhaps anticoagulation therapy; possibly an arm with a sham procedure; and blinding of follow-up physicians and nurses. Optimal design of such trials to seek an answer to the hypothesis that PFO closure can ameliorate migraine will enhance the concept of applying

evidence-based medicine in clinical decision-making that the cardiovascular community has promulgated so well over the past three decades. In addition, such trials can potentially lead to new paradigm shifts in the understanding and treatment of migraine.

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