

# CNS NEWS

McMahon Publishing Group 

CLINICAL REVIEWS AND UPDATES IN NEUROLOGY AND PSYCHIATRY • CNSNEWSONLINE.COM

SEPTEMBER 2006 • Vol. 8 No. 9

## EDUCATIONAL REVIEW



Irritable  
Bowel  
Syndrome:  
The Brain-  
Gut Axis

see pages 23–27

*Splitting Headache Experts:*

# The Debate Over Migraine Surgery

SAN DIEGO—Patients who suffer from chronic migraines say they would do anything to rid themselves of the pain—but heart surgery?

Arising from research in stroke and cardiology, the controversial new approach is based on observations that individuals with the debilitating headaches also often have a small hole known as a patent foramen ovale (PFO) in the septum between the left and right atria of the heart,<sup>1,2</sup> and that surgical closure of the opening (for other reasons) results in fewer migraines.<sup>2-4</sup>

Now, the first prospective, randomized, double-blind, placebo-controlled study specifically looking at whether closure of such a hole can alleviate migraine is causing a stir in neurology circles—but not because it worked.

In the MIST (Migraine Intervention with STARFlex Technology) trial, which enrolled 147 subjects at 13 different centers in the United Kingdom, migraine pain was completely eliminated in only six subjects—three of whom underwent the real surgery and three from a control group that underwent a “sham procedure.” The study was an unequivocal failure.

It generated more interest in the subject, however, as was evident during a half-day course on PFO—which



played out more like a debate—during the 2006 annual meeting of the American Academy of Neurology.

## Pros, Cons and Dollar Signs

Proponents of the procedure say that complete elimination of migraine pain (the treatment end point used in MIST) is unrealistic. Rather, they maintain, one should

see **SURGERY**, page 30 ►

*'This might be interpreted as a half-full glass, which some might see as a positive prompt to do more procedures, without the perspective of examining the full data. We all look forward to more studies.'*

—Joel Saper, MD

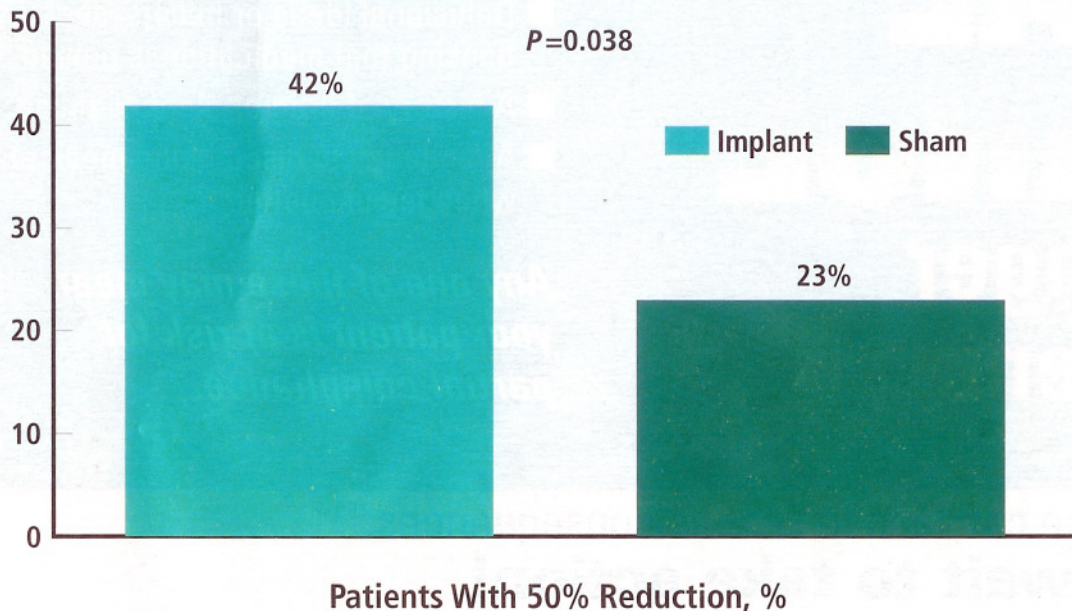


## A Host of Theories, Potential Treatments

In developing fetuses, an opening in the septum between the left and right atria of the heart allows blood to bypass the lungs, which are not used until birth. An opening that fails to close naturally shortly after birth is a PFO. Most cases of PFO as an isolated finding warrant no special intervention, but in the setting of an otherwise unexplained neurologic

event, treatment includes antiplatelet and/or warfarin therapy to prevent cryptogenic stroke.

For individuals who suffer from recurrent cryptogenic strokes, surgical closure of the PFO also is



MIST, Migraine Intervention With STARFlex Technology Trial

**Figure 1. MIST: 50% reduction in headache days.**

indicated. In the past, this entailed a risky, invasive, costly procedure, but more recently, catheter-based devices have been approved. Among them are the Amplatzer PFO Occluder, from AGA Medical Corporation, in Golden Valley, Minn.; the CardioSEAL Septal Occlusion System, from NMT Medical; the Premere PFO Closure System, from Velocimed, in Minneapolis; the Sideris Buttoned Device, from Custom Medical Devices, in Amarillo, Texas; and the Guardian Angel, from Microvena Corporation, in Whitebear Lake, Minn. STARFlex, the newer version of CardioSEAL, is not yet approved in the United States. It consists of two wire frameworks holding polyester fabric, which look like two tiny open umbrellas. Spring coils hold the device in place, with one umbrella on each side of the hole. Over time, the patient's own tissue grows into and around the fabric and metal framework.

The two main theories behind the PFO-migraine link are related to blood flow between the left and right atria, Dr. Mauskop said. "The first suggests that an embolic event, facilitated by the right-to-left shunt, triggers a migraine. The second theory proposes that the right-to-left shunt permits certain vasoactive substances to access the brain because they are not filtered out by the lungs, and these substances, as yet uncharacterized, trigger a migraine."

## Not a Cure, but Effective Treatment

In previous observational studies, PFO closure was associated with unexpected self-reports of an 80% decrease in migraines among stroke patients and deep sea divers—who are prone to migraine: because of decreased ventilation. Other research, led

# MIGRAINE

## SURGERY

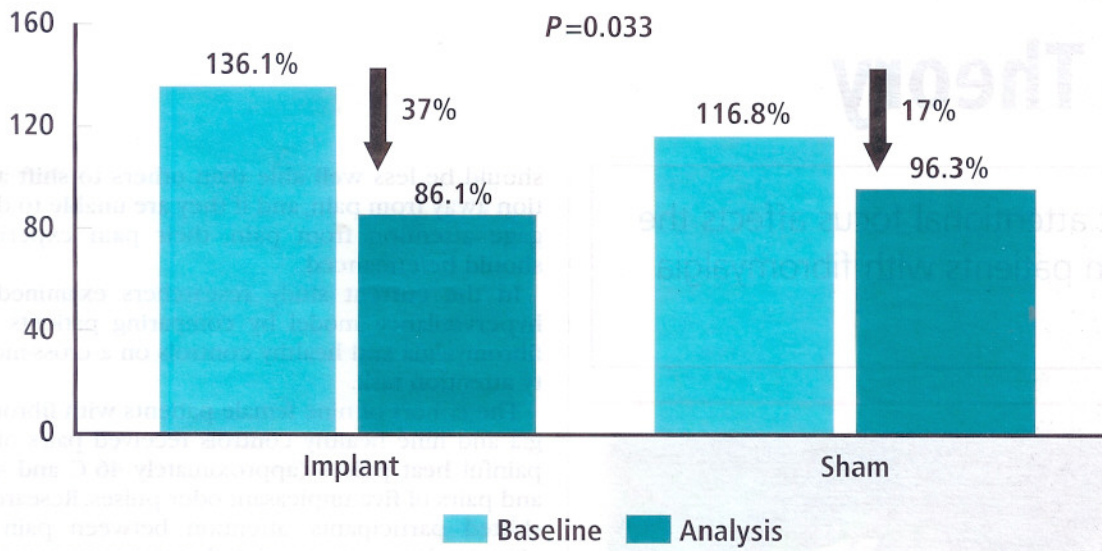
continued from page 1 ▼

focus on the 42% of patients who had a 50% reduction in headache, which was nearly double the number of patients who had a similar response (23%) after the sham procedure ( $P=0.038$ ). The opposition counters by likening the MIST results to those of a 1958 investigation into surgical treatment for angina. In that report, 68% of patients who underwent bilateral internal mammary artery ligation, a procedure now known to be useless, reported a slight or moderate reduction in their angina.

The stakes are high, both for patients and for companies that stand to gain from a new application (the technology is approved for use in the prevention of stroke) for devices that seal a PFO, like Boston-based NMT Medical, which manufactures the STARFlex transcatheter used in MIST. Migraine and PFO are extremely common in the general population, with estimated prevalence rates of 10% to 12% and 25% to 30%, respectively.<sup>5</sup> If all migraineurs with a PFO became candidates for a surgical procedure, the market for the devices could expand to include millions of people.

A potential connection between migraine and stroke has been studied in the past. What makes the new approach so attractive—to the point where physicians are recommending a surgical procedure that is not conclusively proven effective—is the promise, some believe, of one procedure easing migraine pain and also protecting the patient from a stroke later in life.

“The concept that treating a patent foramen ovale may relieve migraine as well as decrease the risk of stroke in patients with migraine with aura is dramatic,” said Alexander Mauskop, MD, director of the New York Headache Center in New York City.



MIST, Migraine Intervention With STARFlex Technology Trial

**Figure 2. MIST: reduction in headache burden (frequency × duration).**

by Vladimir Kummer, MD, a neurologist at the Sarah Network of Rehabilitation Hospitals in Brasilia, Brazil, has described a greater prevalence of PFO in migraine with aura than in other types of headaches.<sup>5</sup>

"We have not done closing procedures to treat migraine, Dr. Kummer said. "Most of these patients have had good response to conventional migraine treatments. We advise patients with PFO to avoid smoking and hormonal contraception, and to watch their cholesterol and blood pressure."

The MIST trial, which was sponsored by NMT Medical along with two UK advocacy groups, Migraine Action Association and Migraine in Primary Care Advisors, studied patients who had migraine with aura, 74 of whom were randomized to percutaneous endovascular closure with STARFlex and 73 to the sham procedure. The subjects were found to be six times more likely than the general population to have large right-to-left shunts, most of which were considered PFOs. The results did not indicate that PFO closure provides a complete cure for migraine, but they did show a mean reduction in headache burden of 50 hours per month and a 50% reduction in headache in 42% of patients who underwent the surgery.

### Debate Continues

Whether the association is causal or coincidental remains unresolved.<sup>6</sup> The Quality Standards Subcommittee of the American Academy of Neurology concluded that "there is insufficient evidence to evaluate the efficacy of surgical or endovascular closure" (of a PFO to prevent recurrent stroke).<sup>7</sup>

The surgery is not without its complications. In MIST, 6.8% of patients in the surgical group had serious adverse events, some of which were life-threatening. Even in the sham procedure group, 5.5% had a serious adverse event. Further, at 12 months, up to 9% of the patients had a persistent PFO.

"The MIST data cannot rule in or rule out a treatment effect of PFO on migraine with aura. If there is an effect, it appears to be modest and no greater than seen with medical therapy like topiramate [Topamax, Ortho-McNeil]," said Robert Shapiro, MD, PhD, director of the Headache Clinic at the University of Vermont College of Medicine in Burlington. "All these limitations make it difficult to make one enthusiastic about these results. Off-label closure of PFO solely for migraine prevention is totally unjustified. Phase III trials are needed."

Despite a lack of convincing clinical trials, some

physicians have recommended percutaneous endovascular closure of PFO to their patients with migraine. A recent survey revealed that cardiologists were significantly more likely to recommend PFO closure for migraine than were neurologists ( $P=0.01$ ).<sup>8</sup>

"It is a disservice to everyone when a study that covers a large number of variables and outcomes presents only selected data at one time point, some of which is positive," commented Joel Saper, MD, founder and director of the Michigan Head-Pain and Neurological Institute, in Ann Arbor, Mich. "This might be interpreted as a half-full glass, which some might see as a positive prompt to do more procedures, without the perspective of examining the full data. We all look forward to more studies."

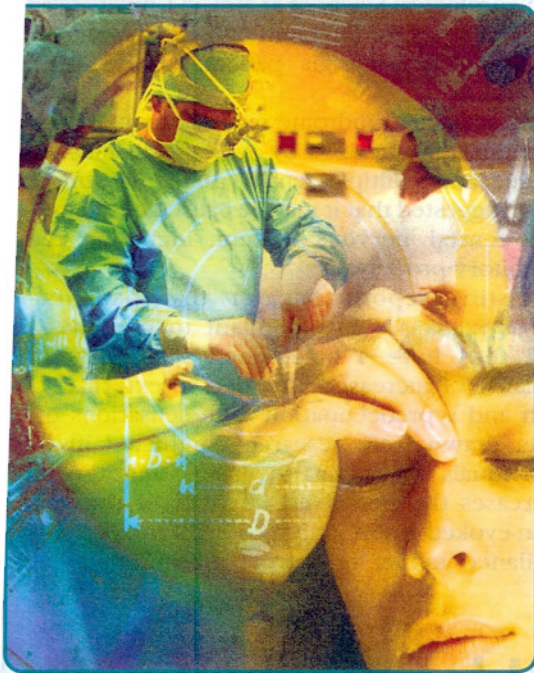
At least three are currently recruiting (Sidebar), seeking out just those patients who would try anything—*anything*—to beat a migraine.

—Andrew N. Wilner, MD, FAAN, FACP  
and Jennifer Kulpa

### References

1. Reisman M, Christofferson RD, Jesurun J, et al. Migraine headache relief after transcatheter closure of patent foramen ovale. *J Am Coll Cardiol*. 2005;45:493-495.
2. Scherzmann M, Wiher S, Nedelchev K, et al. Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. *Neurology*. 2004;62:1399-1401.
3. Post MC, Thijs V, Herroelen L, Budts WIHL. Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. *Neurology*. 2004;62:1439-1440.
4. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet*. 2000;356:1648-1651.
5. Artal FJC, Kummer W, Ribeiro L, Braga H, Mesquita HM, Vargas AP. Prevalence of patent foramen ovale in migraine patients with and without aura compared to stroke patients. A transcranial Doppler study [abstract]. Presented at: 58th annual meeting of the American Academy of Neurology; San Diego, Calif.; April 1-8, 2006. Abstract P03.195.
6. Diener HC, Weimar C, Katsarava Z. Patent foramen ovale: paradoxical connection to migraine and stroke. *Curr Opin Neurol*. 2005;18:299-304.
7. Messe SR, Cucchiara B, Luciano J, Kasner SE. PFO management: neurologists vs. cardiologists. *Neurology*. 2005;65:172-173.
8. Messe SR, Silverman IE, Kizer JR, et al. Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;62:1042-1050.

# MIGRAINE



## Migraine Surgery Trials Seek Patients

**MIST II** (a Prospective, Multicenter, Double-Blinded, Placebo-Controlled Trial To Evaluate the Effectiveness of Patent Foramen Ovale Closure With the STARFlex Septal Repair Implant To Resolve Refractory Migraine Headache With Aura)

**Purpose:** To investigate the safety and effectiveness of PFO closure with the STARFlex Septal Repair Implant System in migraine reduction

**Criteria:** age between 18 and 60 years, history of migraine before age 50, refractory migraine with aura, PFO

**Sponsor:** NMT Medical

**Contact:** Karen Doyle, kbd@nmtmedical.com

**Study ID Number:** G050119; MIST II

**ClinicalTrials.gov Identifier:** NCT00283738

**PREMIUM** (Prospective Randomized Investigation To Evaluate the Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder Compared to Medical Management)

**Purpose:** To evaluate the impact of percutaneous closure of a PFO, with use of the AMPLATZER PFO Occluder, on the incidence of migraine headaches

**Criteria:** age between 18 and 55 years, refractory migraine with or without aura, PFO

**Sponsor:** AGA Medical Corporation

**Contact:** Maren Yurick, myurick@amplatzer.com

**Study ID Number:** AGA-010; G050054

**ClinicalTrials.gov Identifier:** NCT00355056

**ESCAPE** (Effect of Septal Closure of Atrial PFO on Events of Migraine With Premere)

**Purpose:** To determine the safety and effectiveness of PFO closure in reducing the frequency of migraine headaches compared with medical therapy alone

**Criteria:** age between 28 and 55 years, refractory migraine, PFO

**Sponsor:** St. Jude Medical

**Contact:** Barb Denardo, cdresearch@sjm.com

**Study ID Number:** 1202-001

**ClinicalTrials.gov Identifier:** NCT00267371