PFO Closure Falls Short in MIST Migraine Trial

BY MELINDA TANZOLA
Contributing Writer

ATLANTA — Patent foramen ovale closure with a septal repair implant gave a modest benefit to patients with migraine and PFO, according to preliminary results of a study with 163 patients.

The enrollment phase of the sham-controlled study also showed that right-to-left cardiac shunts occurred in 60% of the patients with migraine who were screened, Dr. Peter Wilmshurst reported at the annual meeting of the American College of Cardiology.

This prevalence is "very, very high," commented Dr. David O. Williams, director of interventional cardiology at Rhode Island Hospital in Providence. "The usual prevalence [in the general population] is about 15%-20%," Dr. Williams said.

Insertion of a STARFlex septal repair implant provided complete migraine relief in 3 of 74 patients (4%) during 6 months of follow-up, the same rate as in the 73 patients who received a sham procedure. Thus the catheter-based device, developed by NMT Medical Inc. (which also sponsored the study) failed to achieve the primary end point of complete headache relief.

"However, using more conventional migraine trial end points, significant differences were found," noted study investigator Dr. Andrew Dowson, a headache specialist at King's College Hospital in London. Forty-two percent of patients receiving the implant had a 50% reduction in headache days, compared with 23% of sham-treated patients, a statistically significant difference.

The Migraine Intervention with STARFlex Technology (MIST) trial was a prospective, randomized, placebo-controlled, double-blind study that initially screened 432 individuals with migraine. The study was done at 13 centers in the United Kingdom during January-July 2005. Patients were aged 18-60 years, with a minimum 1-year history of migraine with an age at onset no later than 50 years, and frequent migraines (at least 5 days per month but at least 7 headache-free days per month). The study was restricted to those with migraine with aura, because previous studies have shown an association between PFO and these types of migraines, said Dr. Dowson.

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DR. DOWSON

Contrast transthoracic echocardiograms revealed that 72 patients had small shunts (atrial and pulmonary), 22 had large pulmonary shunts, 3 had atrial septal defects, and 163 had large patent foramen ovales (PFOs), for a total of 260 shunts, reported Dr. Wilmshurst, a coinvestigator and cardiologist at Royal Shrewsbury (U.K.) Hospital.

The 163 patients with large PFOs were targeted for the study, and after 16 were excluded 147 patients were randomized to receive either PFO closure or a sham operation. Sham patients underwent general anesthesia and woke up with a groin incision. Patients underwent a 3-month healing phase after surgery, followed by a 3-month analysis phase in which migraine occurrences were continually monitored.

Patients were maintained on their prophylactic migraine medication, although those who overused migraine medication were excluded from the study. Other exclusion criteria included prior stroke or transient ischemic attack or cardiac contraindications.

In addition to the significant reduction in headache days, the implant also provided a significantly greater reduction than did sham in headache burden, a measure that incorporates both the frequency and duration of headaches. Patients receiving the implant achieved a 37% reduction in headache burden, from 136 at baseline to 86 at last follow-up, whereas those receiving the sham operation improved from 117 at baseline to 96 at the last 6-month follow-up, a 17% reduction.

The MIST investigators noted that the difference in the magnitude of the reduction between the implant and sham groups was statistically significant.

The results sent "a little bit of a mixed message" commented Dr. Williams. The low rate of complete headache resolution suggests that PFOs may not have an etiologic role in migraine. "On the other hand, there was some improvement, and we wonder whether the closure process may not have been complete." The high prevalence of cardiac shunts in patients with migraine suggests that screening selected patients with transthoracic echocardiography and then performing repairs when indicated may be a good idea. "It's something to consider for disabled patients," he said. In addition, "in skilled hands, the risks of PFO closure are very low. The procedural risk is like that for cardiac catheterization."

With STARFlex, an umbrellalike Dacron patch is mounted on a pacing lead framework and threaded by catheter through the femoral vein to the right heart. The catheter is then passed into the left atrium through the PFO. After the first umbrella is opened, the catheter is pulled back into the right atrium. Then the second umbrella opened, and the two patches come together, forming a tight seal.

In the implant group, five serious adverse events occurred in one patient each: cardiac tamponade, pericardial effusion, retroperitoneal bleeding, atrial fibrillation, and chest pain. For the sham group, one patient had incision site bleeding, two patients had effects of antiplatelet therapy (anemia, nosebleed), and one patient had a brainstem ischemic stroke 4 months into the follow-up.

The study investigators plan to evaluate residual shunting in the patients who had repairs, Dr. Dawson said. He also proposed that a longer follow-up may show greater benefit from the implants. ■

Philadelphia Bureau Chief Mitchel L. Zoler contributed to this report.

GUEST EDITORIAL

MIST: Not the End of the Story

BY DAVID DODICK, M.D.

For years the exact relationship, if any, between migraine and patent foramen ovale was long on speculation and short on data. In the late 1990s, anecdotal evidence began to hint at some relationship when migraineurs who had a PFO closed for decompression illness began reporting decreases in—and even complete cessation of—migraine. But our only data sources were retrospective studies.

To be sure, these studies came to tantalizing conclusions. First, they confirmed that migraineurs, particularly those with aura, have a significantly higher incidence of PFO than the general population. And second, up to 80% of migraineurs who had a PFO closure experienced up to a 50% decrease in their migraine frequency.

But until last month, when NMT Medical Inc. released the results of its Migraine Intervention with STARFlex Technology (MIST) trial, we lacked good randomized, controlled, and prospective data. Unfortunately, the MIST trial failed to meet its primary end point—a 40% cure rate among the 147 patients who underwent the procedure. Insertion of a device designed to repair patent foramen ovale provided complete migraine relief in 4% of patients during a 6-month follow-up, the same rate as that in patients who received a sham procedure.

Does this mean that PFO closure for migraine is a failed therapy? I don't think so, and negative results shouldn't dampen enthusiasm for the three randomized, controlled trials now recruiting patients in the United States.

MIST did have some encouraging findings. It strengthened the hypothesis that PFO and migraine are linked: More than 60% of the 432 migraineurs screened for the study had a right-to-left shunt. Of those, almost 40% had a moderate or large PFO. This is six times greater than what we see in the general population.

MIST also found that PFO closure had a significant effect on migraine, although not as strong as had been hoped. Forty-two percent of those who received the closure device had a greater than 50% reduction in migraine attacks, compared with 23% of the sham surgery patients. The so-called "headache burden"—a combination of frequency and duration—also decreased significantly in those who received the device, compared with the sham procedure group (37% vs. 17% reduction).

But these results don't really provide us with any new, concrete data upon which to build a surgical treatment for migraine. What we have learned instead, perhaps, is that future trials should choose more realistic end points.

To reach for a 40% "cure rate" over a 3-month period for what is a chronic and sometimes lifelong disease is unrealistic and, perhaps, not even feasible. A longer follow-up time would make more sense. Additionally, using the "headache burden" as a measure of effectiveness is questionable. We're looking to prevent attacks, not just reduce their duration or intensity.

PFO closure is not a trivial procedure. With a complication rate of approximately 6% and the potential for serious adverse events, migraine patients shouldn't be undergoing cardiac catheterizations unless we can prove that the procedure eliminates their headaches. If there is a particular subgroup of patients that improves with PFO closure, it is vital that the clinical features of that subgroup be identified so that patients who will not benefit are not unnecessarily subjected to the risk of the procedure.

Finally, it's important to remember that PFO closure, if it's ever proved effective for migraine, will likely benefit only a small percentage of patients.

Migraine is a complex disorder, and attacks may occur spontaneously or be triggered by a variety of factors. It's conceivable that PFO may be the major trigger for some migraineurs and that its closure would eliminate most, or even all, of their attacks. Finding those patients, if they exist, will be our next big challenge—if future studies are positive. ■

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