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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

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Background—Patent foramen ovale (PFO) is prevalent in patients with migraine with aura. Observational studies show that PFO closure resulted in migraine cessation or improvement in ≈80% of such patients. We investigated the effects of PFO closure for migraine in a randomized, double-blind, sham-controlled trial.

Methods and Results—Patients who suffered from migraine with aura, experienced frequent migraine attacks, had previously failed ≥2 classes of prophylactic treatments, and had moderate or large right-to-left shunts consistent with the presence of a PFO were randomized to transcatheter PFO closure with the STARFlex implant or to a sham procedure. Patients were followed up for 6 months. The primary efficacy end point was cessation of migraine headache 91 to 180 days after the procedure. In total, 163 of 432 patients (38%) had right-to-left shunts consistent with a moderate or large PFO. One hundred forty-seven patients were randomized. No significant difference was observed in the primary end point of migraine headache cessation between implant and sham groups (3 of 74 versus 3 of 73, respectively; $P=0.51$). Secondary end points also were not achieved. On exploratory analysis, excluding 2 outliers, the implant group demonstrated a greater reduction in total migraine headache days ($P=0.027$). As expected, the implant arm experienced more procedural serious adverse events. All events were transient.

Conclusions—This trial confirmed the high prevalence of right-to-left shunts in patients with migraine with aura. Although no significant effect was found for primary or secondary end points, the exploratory analysis supports further investigation. The robust design of this study has served as the model for larger trials that are currently underway in the United States and Europe. **(*Circulation*. 2008;117:1397-1404.)**

Key Words: foramen ovale, patent ■ heart septal defects ■ migraine disorders ■ migraine with aura ■ treatment

Migraine affects ≈13% of the general population between 20 and 64 years of age[1] with a male-to-female ratio of 1:3, and in ≈36% of patients, the attack is preceded by an aura.[2] Migraine with aura is associated with patent foramen ovale (PFO), a remnant of the fetal anatomy, and with other causes of right-to-left shunts (RLSs).[3] In patients

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with significant PFOs and/or RLSs, the prevalence of migraine with aura is increased.[4] In cadaver[5] and live population studies,[6] total PFO prevalence is reported at 27%, of which 4.9% were large at rest and an additional 2.4% were on Valsalva maneuver. It has been postulated that in some migraine patients, venous blood contains agents normally removed by passage through the lungs that can trigger an attack of migraine if they reach the brain in sufficient concentrations; alternatively, long-term shunting of the agents may reduce the threshold for migraine generation in the brain.[7]

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About 80% of patients who underwent PFO closure for nonmigraine indications reported cessation or improvement in their migraine attacks after PFO closure.[6,8–10] These studies are limited by being predominantly retrospective, nonrandomized, and conducted in highly selected populations of patients. Furthermore, the highly variable course of migraine and the known placebo effect in previous migraine trials[11] mean that for proper conclusions to be drawn, a controlled and blinded trial design is imperative. The Migraine Intervention With STARFlex Technology (MIST) trial was a randomized controlled study designed to assess the effect of PFO closure on migraine headache in patients with frequent, disabling, and drug-resistant migraine with aura.

Methods

This was a prospective, multicenter, randomized, double-blind, sham-controlled clinical trial. The study was approved by a multicenter research ethics committee in the United Kingdom. Patients gave written informed consent at each of the 3 stages of the screening process (at medical screening with a headache specialist, at the cardiology contrast echocardiography visit, and before randomization at an implantation center). All procedures were conducted in accordance with the most recent revision (2004) of the Declaration of Helsinki.

Patients

Patients were identified from records of participating headache centers or by self-referral after preliminary screening on a Web site (www.migraine-mist.org). They were offered a headache specialist screening visit if they were 18 to 60 years of age with a history of migraine with aura as defined by the criteria of the International Headache Society[12] starting before 50 years of age; had ≥5 migraine headache days per month but at least 7 headache-free days per month; and reported a history of having failed at least 2 classes (β-blockers, anticonvulsants, calcium channel blockers, tricyclics, and serotonin antagonists) of preventive medication because of inefficacy or intolerability as judged by an investigator. Patient history at the first visit to the headache doctor determined the inclusion criteria, and patients were not excluded after the minimum 30-day baseline period if the number of headache days fell outside the inclusion criteria.

Exclusion criteria included other cardiovascular defects, the presence of intracardiac thrombi, active endocarditis, coagulopathy, bacteremia or active infections, elevated serum creatinine, platelet disorder, other neurological disorders, recent history of active peptic ulcer or gastrointestinal bleeding, cirrhosis, portal hypertension or pulmonary arteriovenous malformation, contraindication to aspirin or clopidogrel, or any other medical condition or contraindication to the procedures and treatments used in the study. Patients also were excluded if they were pregnant, were planning pregnancy, or were nursing over the duration of the study, as were those who required PFO closure for reasons unrelated to migraine, ie, stroke or decompression illness. The patient flow through the study is illustrated in Figure 1.

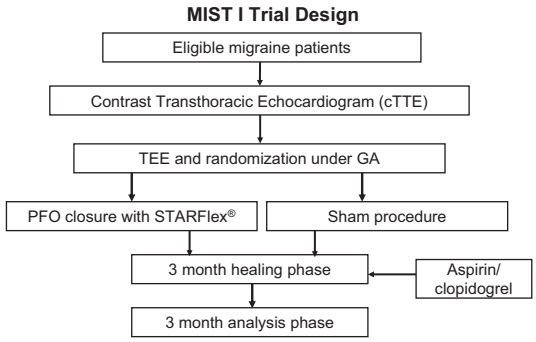

Figure 1. Patient flow through the study. cTTE indicates contrast transthoracic echocardiography; TEE, transesophageal echocardiographic asessment; and GA, general anesthesia.

Eligible patients were referred for assessment for the presence of an RLS by contrast transthoracic echocardiography at 1 of 2 echocardiography laboratories according to a specified protocol. This diagnostic method was selected because it combined a low-risk approach compared with transesophageal echocardiography with a high degree of sensitivity and specificity.[13] Images were acquired in the apical 4-chamber view using second harmonic imaging. Agitated saline was injected into an antecubital vein at rest and during provocative maneuvers (Valsalva maneuver, sniff, cough). Shunt size was determined using a practical, clinical hybrid method based on approximate count and visual appearance of bubbles in the left heart during the first 5 cardiac cycles of contrast entering the right atrium. See the online-only data supplement for more details. Patients with small or no shunts were excluded and referred back to the headache specialist for further care. Patients with evidence of a moderate or large RLS, interpreted as resulting from the presence of a PFO, were referred to a trained and experienced (minimum of 10 PFO closure procedures) interventional cardiology center for randomization. Headache diaries were recorded for at least 30 days before randomization (baseline phase).

Randomization: PFO Closure Procedure or Sham Procedure

Aspirin and clopidogrel were given to all patients as a loading dose in the 24 hours before the procedure (300 mg each) and for 90 days after the procedure (75 mg each daily). After induction of general anesthesia, all patients underwent transesophageal echocardiographic assessment of the interatrial septal anatomy to ensure that no anatomic contraindication to PFO closure was present. The patient was then randomized by the investigator who telephoned a central computerized service. Patients were randomized in a 1:1 ratio (blocks of 4) to either PFO closure with the STARFlex septal repair implant (NMT Medical Inc, Boston, Mass) or a sham procedure (skin incision in the groin). Patients randomized to implant were given intravenous heparin 100 IU/kg periprocedurally as required to keep activated clotting time >200 seconds. Only the staff present in the cardiac catheterization laboratory knew the treatment allocation. All patients were subsequently managed in an identical fashion and were reviewed before discharge. Patients and headache specialists were not informed of treatment allocation during follow-up.

Follow-Up

Patients attended headache clinics after the procedure for 6 visits at intervals of 30±7 days. Days 0 to 90 were defined as the healing phase; days 91 to 180, as the analysis phase. During this time, patients were encouraged to continue with existing migraine prophylactic medications and not to initiate new medications. Patients were allowed to use rescue medications at any time to treat migraine attacks. A final study visit was conducted by the implanting

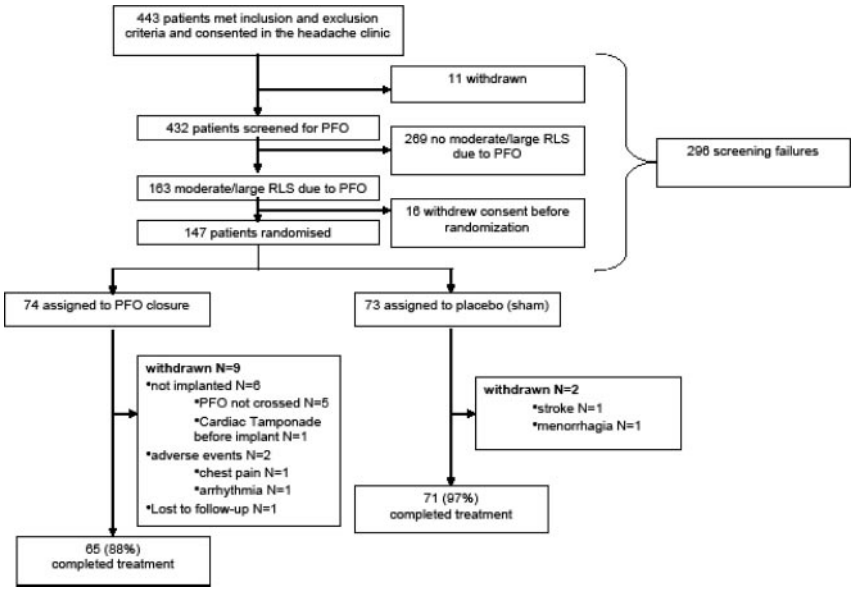

Figure 2. Study flow and patient disposition.

cardiologist, who informed the patient of his or her treatment allocation and assessed the implant arm for residual shunts by repeat transthoracic echocardiography.

Outcomes

Daily headache diaries were kept, and at each clinic visit, patients completed the Headache Impact test (HIT-6)[14] and the Short-Form 36 (SF-36v2) Quality of Life questionnaire.[15] At baseline, the end of the healing phase, and the end of the analysis phase, patients completed the Migraine Disability Assessment (MIDAS) questionnaire.[16]

Primary Efficacy End Point

The primary efficacy end point was migraine headache cessation during the analysis phase. It was derived from diary data.

Secondary Efficacy End Points

Secondary efficacy comparisons were incidence of migraine during the healing phase; change in the severity of migraine attacks based on MIDAS (over a 3-month retrospective period) and HIT-6 (over a 1-month retrospective period) scores; change in the frequency of migraine attacks other than elimination of attacks; change in the characteristics of migraine (with or without aura and change thereof); change in the severity, frequency, and character of migraine relative to effective closure rate or presence of residual leak; and change in quality of life based on the SF-36v2 questionnaire (over a 1-month retrospective period).

Unless indicated otherwise, secondary efficacy comparisons were of the change between the baseline and analysis phases. The estimation of total migraine headache days was defined as the number of migraine headaches times the average length of the migraine in hours divided by 24 and rounded up to the nearest day.

Secondary Safety End Points

Adverse events were recorded at all clinic visits. Prespecified safety end points included device and procedural success and the incidence of major adverse events, including death, stroke, bleeding complications, and adverse drug reactions. Adverse events were monitored by a data, safety and adverse events monitoring board (DSAEMB) that included 4 physicians (3 cardiologists and 1 neurologist), a medical ethicist, and a biostatistician who were independent of the trial investigators.

Statistical Analyses

All randomized patients formed the intention-to-treat population, which was the population for the primary analyses of efficacy and safety. Efficacy analyses also were conducted on a per-protocol population, defined as all randomized patients who received the allocated treatment and who had completed follow-up.

On the basis of previous observational studies,[6,8,9] we anticipated cessation of migraine in 40% of the implant group compared with 15% of the sham group. A sample size of 132 patients was required for 80% power using a 2-sided test with $P=0.05$. Allowing for a 10% dropout rate and a further 4% loss of blinding for medical reasons, we aimed to randomize 150 patients.

All significance testing between the 2 groups was 2 sided and performed at $P=0.05$, with no adjustment for multiple comparisons. The primary efficacy end point was analyzed with Fisher exact test because of the low incidences involved. Secondary end points were analyzed with the χ^2 test if the data were dichotomous (eg, migraine incidence and device success) or by the Wilcoxon rank-sum test if they were continuous (eg, attack frequency). Adverse event frequency was compared with the χ^2 test.

The study was funded by NMT Medical Inc and designed jointly by NMT Medical Inc and a scientific advisory board (the MIST Trial Design Physician Advisory Group), together with additional advisors on bioethics, biostatistics, and patient groups. The study was managed by a steering committee and the DSAEMB.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Population

Patient flow through the trial is shown in Figure 2. A total of 432 patients were assessed for an RLS by transthoracic

Table 1. Types of RLSs Detected by the Contrast Transthoracic Echocardiography Procedure

	Patients, n	Patients, %
Patients, n	432	100
Atrial septal defect	1	0.2
Moderate and large PFO	163	37.7
Other shunts (all types)	96	22.2
Total shunts	260	60.2

Table 2. Patient Demographic and Baseline Characteristics

	Implant (n=74)	Sham Procedure (n=73)
Age, mean±SD (range), y	44.3±10.6 (21–60)	44.6±10.4 (20–61)
Sex, M/F	12/62	11/62
White, n (%)	73 (99)	72 (99)
Migraine attacks in 30 d before procedure, mean±SD, n	4.82±2.44	4.51±2.17
Headache d/3 mo, median (range)	27 (0–70)	30 (5–80)
MIDAS score, median (range)	36 (3–108)	34 (2–189)
HIT-6 score, mean±SD	67.2±4.7	66.2±5.1
Preventive medications used, median, n	1	1
Acute medications used, median (range), n	3 (0–8)	2 (0–9)
Atrial septal aneurysm (>10-mm excursion), n (%)	25 (34)	Not recorded

echocardiography. The types of RLS detected by the procedure are shown in Table 1. A shunt was detected in 260 patients (60%), of which 163 (38%) were interpreted as being due to a moderate or large PFO. Of the patients with other shunts, 96 (22.2%) had small shunts or large pulmonary shunts and 1 (0.2%) ASD. The baseline characteristics of the 147 patients (16 patients did not progress to randomization: 6 because of personal reasons or lost to follow up, 6 for medical reasons including pregnancy, dental treatment, sinusitis, hysterectomy, steroid treatment and late declaration of aspirin sensitivity, and 4 others after transoesophageal echocardiography; 2 were diagnosed as having an ASD and it was not possible to confirm PFO in the other 2) who subsequently underwent randomization (74 to PFO closure, 73 to sham) are given in Table 2. The 2 groups were well matched in terms of age, gender, and race. At baseline, patients also were similarly matched in terms of the average frequency of migraine attacks, headache impact (MIDAS and HIT-6 scores), and median number of acute and preventive medications being taken.

No PFO was found or crossed in 5 of the 74 patients (7%) randomized to closure. In 1 patient, a 23 mm device embolised to right atrium after release and in a second patient, the initial implant position was unsatisfactory, with prolapse of left atrial arms into the right atrium. This device was withdrawn from the PFO but subsequently embolised to the left pulmonary artery whilst being withdrawn into the delivery sheath. Both devices were successfully retrieved using snares. In a third patient, the initial implant could not be deployed and was retrieved without being detached. All 3 patients had a second device successfully implanted and continued in the study. One randomized patient was withdrawn because of procedure-related cardiac tamponade before device deployment. Two patients in each group withdrew as a result of adverse events in the follow-up period. One patient was withdrawn after being lost to follow-up. Therefore, the study population consisted of 147 patients in the intention-to-treat and 136 in the per-protocol analyses.

Efficacy

The major efficacy analyses are presented for both the intention-to-treat and per-protocol populations in Tables 3 and 4. The primary end point of migraine cessation was observed for 3 patients in each group. Secondary end points did not differ significantly between groups for either the intention-to-treat or per-protocol populations.

Recognizing the failure to achieve predefined endpoints, we conducted exploratory analysis[17] to aid hypothesis generation and future study design. Two patients in the implant group were noted to account for 20% of all headache days in the implant group during the analysis period (Figure 3) and differed from the rest of the population (Shapiro-Wilk test, $P=0.0014$). When these patients were excluded from the per-protocol population, a significant 2.2 d/mo (from 6.0 to 3.8 d/mo; 37%) reduction was noted in median total migraine headache days for the implant group compared with 1.3 d/mo (from 5.0 to 3.7 d/mo; 26%) in the sham group ($P=0.027$).

Residual moderate or large atrial level shunts were reported in 4 patients when assessed at 6 months by the treating cardiologists, with no differences seen in treatment effect

Table 3. Efficacy Analyses: Intention-to-Treat Population

	Implant (n=74)		Sham procedure (n=73)		Statistical Analyses*	
	Baseline	Analysis Phase	Baseline	Analysis Phase	Difference Between Implant and Sham Arms (95% CI)	P
Patients with no migraine attacks, n	0	3	1	3	−0.06% (−6.45–6.34)	1.0
Frequency of migraine attacks/mo, mean±SD	4.82±2.44	3.23±1.80	4.51±2.17	3.53±2.13	0.45 (−0.16–1.05)	0.14
n	66	66	73	73	...	...
Total MIDAS score, median (range)	36 (3–108)	17 (0–270)	34 (2–189)	18 (0–240)	1 (−11–10)	0.88
n	66	67	69	72	...	...
Headache d/3 mo (MIDAS), median (range)	27 (0–70)	18 (0–90)	30 (5–80)	21 (0–80)	1 (−5–6)	0.79
n	66	67	69	72	...	...
HIT-6 total score, mean±SD	67.2±4.7	59.5±9.3	66.2±5.1	58.5±8.6	0 (−3–2)	0.77
n	67	67	69	73	...	...

Missing data were replaced by last observation carried forward. CI indicates confidence interval.

Table 4. Efficacy Analyses: Per-Protocol Population

	Implant (n=64)*		Sham (n=71)		Statistical Analyses	
	Baseline	Analysis Phase	Baseline	Analysis Phase	Difference Between Implant and Sham Arms (95% CI)	*P*
Patients with no migraine attacks, n	0	3	1	3	0.46% (−6.50–7.42)	1.0
Frequency of migraine attacks/mo, mean±SD	4.88±2.43	3.26±1.82	4.55±2.18	3.55±2.14	0.47 (−0.15–1.08)	0.13
n	64	64	71	71	...	...
Total MIDAS score, median (range)	40 (3–108)	16 (0–270)	34 (2–189)	18 (0–240)	1 (−10–10)	0.89
n	57	64	67	71	...	...
Headache d/3 mo (MIDAS), median (range)	26 (0–70)	19 (0–90)	30 (5–80)	21 (0–80)	1 (−5–6)	0.85
n	57	64	67	70	...	...
HIT-6 total score, mean±SD	67±4.6	60±10	66±4.9	59±8.8	0 (−3–2)	0.79
n	57	64	67	71	...	...
Total migraine headache d/m,† median (range)	6.0 (1–17.0)	3.8 (0–13.3)	5.0 (0–20.0)	3.7 (0–16.7)	1.3 (0–2.3)	0.027
n	62	62	70	71	...	...

Missing data were replaced by last observation carried forward. CI indicates confidence interval.

*One subject was missing baseline diary cards.

†Determined as follows: No. of headaches/month)×(average length in hours)/24, rounded up to nearest day. Two outliers were removed.

between those closed versus those with a residual shunt. No significant changes could be observed in the severity end points of the MIDAS or HIT-6 scales or in the quality of life end point SF-36v2.

Tolerability and Safety

Most patients in both groups reported ≥1 minor adverse events, most commonly attributed to trial antiplatelet medication. Serious adverse events occurred in 16 patients (Table 5). Other procedural complications included pericardial effusion in 2 patients, 1 of which required percutaneous drainage, and a retroperitoneal bleed in 1 patient in the implant group, which was managed conservatively. Patients in the sham group experienced 3 serious adverse events that were probably related to antiplatelet medication (incision site bleed, anemia, and nosebleed). The patient in the sham arm who suffered a stroke 4 months after the procedure and 1 month after withdrawal of antiplatelet medication was withdrawn and later underwent PFO closure. In 3 patients, devices were withdrawn due to dissatisfaction with the initial implant position. A second device was deployed in a satisfactory position during the same procedure in all 3 patients.

Discussion

The premise of closure of PFO to reduce migraine frequency continues to be researched[9,18,19]; however, the MIST trial is the first prospective, randomized, placebo (sham) -controlled trial of PFO closure for the treatment of migraine with aura. The lack of objective measures of migraine and the known placebo effect seen in previous pharmacological studies[20] meant that adequate blinding of both patients and headache physicians was an important element in the design of the MIST trial. Although not assessed formally, we believe blinding was achieved with the sham procedure. We have demonstrated that a sham procedure is feasible in a device trial and

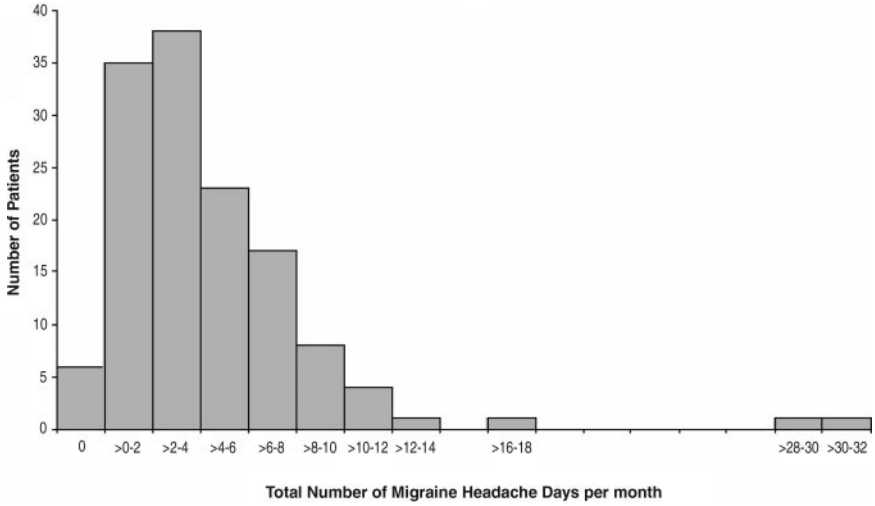

Figure 3. Histogram of the total number of migraine headache days per month for each patient of the per-protocol population in the analysis period.

Table 5. Incidence of All Serious Adverse Events in All Randomized Patients

Event	Arm of Study	Relationship to Study Device, Procedure, or NIM as Adjudicated by DSAEMB and Medical Monitor
Postprocedure atrial fibrillation with aberrant conduction	Implant	Possibly related to device and procedure
Sinusitis	Prerandomization	None
Tamponade	Implant	Definitely related to procedure
Pericardial effusion	Implant	Definitely related to procedure
Retroperitoneal bleed	Implant	Definitely related to procedure
Chest pain*	Implant	Possibly related to device
Epistaxis	Sham	Probably related to NIM
Chest infection and asthma	Sham	None
Atrial fibrillation	Implant	Possibly related to device
Removal of right ovarian cyst	Sham	None
Brainstem stroke	Sham	None
Central chest pain	Implant	Possibly related to device, procedure, and NIM
Removal of infected sacral nerve stimulator†	Implant	None
Menorrhagia leading to anemia	Sham	Possibly related to NIM
Injection of botulinum into bladder†	Implant	None
Pregnant	Implant	None
Oozing of groin postprocedure	Sham	Definitely related to procedure; possibly related to NIM

NIM indicates noninvestigational medication.
*This patient had 2 events of chest pain.
†Same patient.

recommend that it become the standard for future trials of PFO closure for migraine. Placebo control can be problematic in surgical procedures, but a sham procedure has been used in 3 controlled studies of acupuncture for migraine and led to valid results.[21–23]

The criteria for patient selection included only migraine with aura patients with frequent and refractory attacks. Our results demonstrated that the study patients had ≈5 migraine attacks in the month before treatment (diary), with ≈30 days of headache in the previous 3 months (MIDAS). The baseline MIDAS score was 36 and the HIT-6 score was 67, both in the range of severe headache impact.[14,16] It should be noted that it is possible for patients with >5 migraine headache days per month but effective acute/rescue medications to score low on MIDAS because the score is calculated by adding time lost and time at <50% of normal capability in daily activities.[16] The patient selection criteria were therefore met in the study population, which was well matched between the 2 groups. In general, patients were taking few prophylactic medications at baseline, supporting the suggestion of relative failure of these treatments in the past (entry criteria was failure of ≥2 classes of prophylactic medications). However, on average, patients were taking >1 acute medication to treat their attacks.

Consistent with previous studies, we demonstrated a much higher incidence of RLS in migraine with aura patients than reported in the general population.[3,24] Thirty-eight percent of patients were found to have a large PFO, and 60% had shunts of any type.

The demanding primary end point of complete cessation of migraine headache, which in this study was underpowered, was chosen on the basis of observational studies and ethical considerations that demanded the demonstration of a major clinical effect in a population with severe refractory migraine. A significant effect on this end point and the specified secondary end points was not demonstrated. Exploratory analysis was undertaken when it was evident that 2 statistical outliers accounted for more than one third of the overall migraine headaches experienced. When these 2 patients were removed, the implant arm demonstrated a significant reduction in total migraine headache days, consistent with but not proof of a causal relationship between PFO and migraine with aura. Some patients may benefit from closure, but a potential for short-term deterioration exists in a minority of patients.[25] Larger randomized controlled studies that are ongoing will help further define the risk-to-benefit ratio.

Results from the MIST trial did not support the efficacy seen in previous observational reports.[6,8–10,18,19,26] A simple placebo response cannot explain the lack of efficacy because patients were not being treated for migraine in the observational studies and therefore had no expectation of efficacy. The discrepancies, however, can be explained in a number of ways. First, in the observational studies, the PFO was closed because it was thought to be responsible for a clinical event, usually stroke or decompression illness,[6,8,9,18,19,26] whereas the MIST trial patients were different in that their PFO was not related pathophysiologically to any such clinical event. Indeed the types of patients in the observational studies were specifically excluded from MIST. Second, MIST trial patients were selected because they had particularly severe and refractory migraine, whereas in the observational studies, migraine was incidental to the reason for closure.[27] Severe refractory migraine, particularly if associated with chronic frequent headache, depression, or other comorbidities, may prove less amenable to treatment than mild or moderate migraine. Moreover, the continued use of prophylactic migraine medication throughout the trial in both treatment arms (in contrast to most pharmacological studies) may have limited the impact of PFO closure. This patient population typically is excluded from pharmacological migraine trials because they have been shown to be resistant to other drug therapies.

Third, the primary study end point of migraine cessation may have been unrealistic and less clinically relevant than reduction in migraine frequency. Even the best-designed studies of preventive medications show a responder rate (reduction of migraine frequency of ≥50%) of only ≈50%.[28]

The most commonly used primary end point in such studies is the change in mean monthly migraine frequency, with the responder rate used as a key secondary end point.[11,28] In addition, in light of the observed effect size, the secondary end points were underpowered in the MIST trial.

Finally, a number of additional methodological issues may have influenced the results. We chose to analyze the benefit of PFO closure from 3 to 6 months after device implant. The effect of PFO closure during this relatively early analysis phase may have been confounded by a hangover effect of clopidogrel,[29] incomplete closure of the defect, concomitant pulmonary shunts, and a possible early transient adverse effect of device implant.[25,30] Therefore, a longer analysis phase might have demonstrated additional benefit accrued over time. Residual shunts were assessed by the investigators using contrast transthoracic echocardiography at 6 months. Closure rates were consistent with those previously reported for the STARFlex device.[31] However, it is likely that more residual shunts persisted earlier during the analysis phase, and atrial or pulmonary shunts below the detection threshold of this technique[32] might have had an impact on the treatment effect in this population.

In 5 patients, the PFO was not crossed. The screening echocardiograms of the patients in whom a PFO was not found were reviewed again, and the conclusions were consistent with the original assessment. The choice of transthoracic echocardiography as a screening method was based on logistical and ethical imperatives, and we believe it has been shown to have acceptable sensitivity and specificity. However, differentiation of the degree and site of shunt may be difficult,[33] and additional sources of shunting such as pulmonary atriovenous malformation may be overrepresented in a migraine population. Furthermore, a number of the investigators reported greater difficulty in finding and crossing the PFOs in our study population compared with previous patients with stroke and decompression illness. This might reflect smaller or more serpiginous defects and may have contributed to the adverse events in the study.

It should be noted that the side effects in this trial were transient. Although it is true that discontinuing prophylactic drugs can eliminate side effects, severe persistent side effects are known. The safety profile in this study was consistent with previous reports[34] and the known STARFlex safety profile.[31] To date, >25 000 PFOs have been closed in clinical practice through 4 generations of technology (NMT Medical Inc, data on file).

The many lessons learned during the conduct and final analysis of this study are crucial to the design of future research. All studies currently approved by the Food and Drug Administration have different study designs with improvements based on lessons from MIST. MIST III, designed to openly follow up patients in the MIST trial, is ongoing, and larger randomized controlled trials with longer-term follow-up are currently underway. Modifications of the patient selection criteria, the primary end point to assess a responder rate, and duration of follow-up, as well as beginning assessments once the implant is fully healed, are some of the necessary changes for new studies.

Conclusions

This trial has confirmed the high prevalence of RLS in migraine with aura patients. Although no significant effect was found for the primary or secondary end points, the exploratory analysis supports further investigation. MIST emphasizes the critical importance of blinding in the evaluation of novel interventions and illustrates that blinding can be achieved even in complex trials. The robust design of this study has served as the model for other larger trials that are currently underway in the United States and Europe.

Appendix

Study Contributors

Professor Horst Sievert, cardiologist chairman of DSAEMB; Professor Eric Eeckhout, cardiologist member of DSAEMB; Professor Len Doyal, medical ethicist member of DSAEMB; Dr Ralph Kern, neurologist member of DSAEMB; Dr Francis Baudet, pain specialist member of DSAEMB; Roy Taylor, biostatistician member of DSAEMB; Dr Luc Missault, cardiologist medical monitor and member of DSAEMB; Geoff Fournie, NMT Medical Inc, member of the steering committee; and Gill Glennon, NMT Medical Inc, member of the steering committee.

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Disclosures

All study sites received research grants. Drs Hildick-Smith and Mullen have ownership interests in NMT Medical Inc. Dr Mullen has received teaching honoraria and has acted as a consultant to NMT. The remaining authors report no disclosures.

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CLINICAL PERSPECTIVE

The Migraine Intervention With STARFlex Technology (MIST) trial was the first randomized controlled clinical trial to evaluate closure of a patent foramen ovale to treat refractory migraine headaches. All other reports to date of migraine improvement after patent foramen ovale closure were on patients with comorbid conditions such as stroke, transient ischemic attack, or decompression illness. The unique study design of the trial demonstrated that a double-blind sham-controlled study was both feasible and ethically justifiable in this condition. Although the study failed to achieve its primary end point of complete cure of recurrent migraine headaches, the modest treatment effect demonstrated in this trial may have been mitigated by a number of confounding factors. The length of follow-up, the assessment period, or the impact of study medications in both arms may have affected the results. Longer-term follow-up of the current study group (including the crossover from the sham arm of the study) and future trials should shed light on the efficacy and risk-to-benefit ratio of patent foramen ovale closure for migraine.

Go to http://cme.ahajournals.org to take the CME quiz for this article.

Correction

In the article, "The MIST Trial (Migraine Intervention with STARFlex Technology): A prospective, multicentre, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache" by Dowson et al that appeared in the March 18, 2008, issue of the journal (*Circulation*. 2008;117:1397–1404), a number of errors and omissions occurred.

Investigators Drs Peter Wilmshurst and Simon Nightingale did not sign the Copyright Transfer Agreement because of an internal disagreement about the conduct of study. Therefore, they were not listed as authors on the final accepted version of the manuscript that was published in the journal.

The description for assessing intracardiac shunts was brief in the original manuscript because of the limitation of word count. Shunt size was determined using a practical clinical hybrid method based on approximate count and visual appearance of bubbles in the left heart during the first 5 cardiac cycles of contrast entering the right atrium. See the newly posted online-only Data supplement for more details.

For clarification, unsatisfactory implant position was not considered a serious adverse event per protocol. No patent foramen ovale was found or crossed in 5 of the 74 patients (7%) randomized to closure. In one patient a 23-mm device embolized to right atrium after release, and in a second patient the initial implant position was unsatisfactory with prolapse of left atrial arms into the right atrium. This device was withdrawn from the patent foramen ovale but subsequently embolized to the left pulmonary artery while being withdrawn into the delivery sheath. Both devices were successfully retrieved using snares. In a third patient, the initial implant could not be deployed and was retrieved without being detached. All 3 patients had a second device successfully implanted and continued in the study. There are no additional unreported serious adverse events that occurred during the study.

To display the withdrawn patients in more depth, a revised Figure 2 (study flow and patient disposition) has been provided. The original text is correct. Of the 443 patients consented as fulfilling the headache inclusion/exclusion criteria, there were 296 patients who were not eligible for the randomization visit. Eleven patients withdrew before diagnostic transthoracic echocardiogram where 163 (37.7%) were found to have moderate or large patent foramen ovale, 172 (39.8%) had no shunt and, as in amended Table 1, 96 (22.2%) had small shunts or large pulmonary shunts, and 1 (0.2%) had an atrial septal defect. A further 16 patients did not progress to randomization, 6 for personal reasons or because they were lost to follow up, 6 for medical reasons (pregnancy, dental treatment, sinusitis, hysterectomy, steroid treatment, and late declaration of aspirin sensitivity), and 4 others after transesophageal echocardiography. Two patients were diagnosed as having an atrial septal defect, and it was not possible to confirm patent foramen ovale in the other 2.

In the text of the original article under Efficacy, a reference to Figure 3, a histogram of the total number of migraine headache days per month for each patient, was inadvertently calculated on migraine headache hours as opposed to the correctly stated migraine headache days. The original histogram displaying the distribution of outliers in the study is consistent with the corrected text of the manuscript as follows:

Two patients in the implant group were noted to account for 20% of all headache days in the implant group during the analysis period (Figure 3) and differed from the rest of the population

(*Circulation.* 2009;120:e71-e72.)

***Circulation* is available at http://circ.ahajournals.org**

(Shapiro-Wilk test, $P=0.0014$). When these patients were excluded from the per-protocol population, a significant 2.2 d/mo reduction (from 6.0 to 3.8 d/mo; 37%) was noted in median total migraine headache days for the implant group compared with 1.3 d/mo (from 5.0 to 3.7 d/mo; 26%) in the sham group ($P=0.027$). The statistical calculations were based on headache days as indicated in the manuscript, and the justification of removal of these outliers has not changed.

The authors confirm that they disclosed all relevant relationships and potential conflicts of interest that were present during the 2 years leading up to manuscript submission, as required by the American Heart Association.

The online version of the article has been updated to address these issues. The authors regret the errors and have offered clarification where requested.

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STANDARDISATION OF ECHOCARDIOGRAPHIC PROCEDURE

Applicable to: All echocardiograms performed during the course of the trial where contrast valsalva bubble trial is required.

Background: Patent foramen ovale (PFO) may vary in both anatomical and functional size, and as such the clinical impact of a PFO may differ. [1] Quantification of the volume of right to left shunting through a patent foramen ovale (PFO) has been attempted in prior studies, in part using a bubble counting mechanism, with classification schemes based on the absolute number of microbubbles seen in the left atrium after complete opacification of the right atrium. This technique, has not been completely validated with correlation to large anatomical studies, with 2- dimensional measurements on transesophageal echocardiography, or balloon sizing techniques of PFO size; and as such is not uniformly accepted as a "gold standard" for PFO sizing in the echocardiography community.[2, 3] Part of the differences in detection and sizing of PFO are due to inherent limitations in the technique.[4, 5]

Most literature reports on PFO closure, while often uutilising classification schemes that attempt to quantify the number of microbubbles crossing into the left atrium, have not uutilised a core echocardiography lab to validate the method or its accuracy, leaving the validity of bubble counting as an accurate, reproducible, and correlative method potentially suspect.[6, 7] As such, significant differences can exist with regard to the exact frame and moment used for interpretation at a trial site versus at the core laboratory, potentially resulting in significant inter-observer variability.

The most recent example of this comes from a report published by Mas et al.[8] In this trial of PFO and atrial septal aneurysm and the risk of cerebrovascular events, contrast echocardiograms were reviewed by multiple observers to validate microbubble count and thus presence of a PFO. In that trial there was significant intra-observer variability, with disagreement in PFO in 13.9% of patients, and in shunt quantification in 26.6%.

The central hypothesis of our trial is based on three premises:

- The patient has echo demonstration of a PFO.
- The patient has a documented history of refractory migraine.
- The patient does or does not experience ongoing migraines during the trial period.

Based on these premises, and the potential weaknesses of hard counting methods, our trial proposes to use a practical, clinical hybrid method that describes the shunt capacity based on count and visual appearance of the shunt (bubbles).

Recommended Supplies/Preparation

• 20 gauge Venflon needle.

• Three way stopcock connected to Venflon with a 6-inch extension tubing, primed with saline (stopcock connected to end away from patient).

• One empty 10 cc syringe.

• Three 10 cc syringes filled with 8-9cc saline plus 0.3-0.5ml of air in each syringe. (Three syringes are for three separate injections-manoeuvres.)

Recommended Procedure

1. Note that echo equipment preparations, including probe insertion and equipment settings are not listed in the following steps. The TTE probe should be well prepared or inserted prior to the bubble trial being performed. Optimal PFO viewing windows and ultrasound unit parameters should be optimised prior to performing the bubble trial.

2. Explain the procedure to the patient, and have patient perform practice valsalva.

3. Start IV in right antecubital vein. (Note: Post implant bubble trial may be performed using a catheter inserted via the groin access site provided the catheter is placed in the SVC such that contrast injectate enters the right atrium from the SVC.). Insure good patency. Secure with adhesives.

4. Connect the empty syringe to one port of the stopcock and draw 0.5cc of blood into syringe.

5. Connect saline-filled syringe to the “straight thru” port of the stopcock.

6. Turn the stopcock off to the patient, create the bubbles in solution by pushing the saline back and forth between the two syringes a minimum of 10 exchanges to insure proper agitation of media.

7. When the sonographer is ready, turn the stopcock off to the empty syringe, inject the agitated saline into the patient, injecting through the “straight flow” pathway of the syringe and stopcock. Raise the patient’s right arm.

8. On appearance and filling of right atrium with bubble solution, have the patient perform valsalva pressure and hold until instructed to release (5-7 seconds).

9. Repeat the process for a minimum of three manoeuvres or as needed to achieve adequate evaluation of shunt.

10. If patient is not able to perform valsalva manoeuvre, they will be asked to cough or to take deep respiration.

Presence of Shunt

• **Yes:** Based on appearance of bubbles in the left heart either spontaneously or after provocative manoeuvre within 5 cardiac cycles after opacification of the right atrium.

• **No:** Based on no bubbles in left herat either spontaneously or after provocative manoeuvre within 5 cardiac cycles after opacification of the right atrium.

Assessment of Flow

The appearance of contrast in the left heart will be characterised as occurring before or during Valsalva strain or with/after release and will be graded according to the scale below. Classifications are based on bubbles appearing in left heart either spontaneously or after provocative manoeuvre within 5 cardiac cycles after opacification of the right atrium.

• **Grade 0: None**

No bubbles appearing in the left heart on valsalva.

• **Grade 1: Trace**

The distinct appearance of between one and approximately ten bubble(s) in the left heart during the manoeuvre, but at no time does the appearance of the bubbles constitute a concentration that could be circumscribed as a section within the left atrial cavity.

• **Grade 2: Moderate**

The distinct appearance of a moderate quantity (approximately ten to twenty five) of bubbles in the left heart such that a distinct circumscribable section of the LA cavity can be described as filled.

• **Grade 3: Substantial**

The distinct appearance of a significant quantity (approximately 25 or more) of bubbles in the left heart, some of said bubbles reaching the contralateral left atrial wall, such that complete filling of LA chamber can be described.

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