Nerve Stimulation Shows Efficacy for Migraine

Technique associated with fewer headache days, less intense pain in patients with refractory headache.

BY DIANA MAHONEY
New England Bureau

BOSTON — The efficacy of occipital nerve stimulation in the first clinical trial of its use in the treatment of refractory migraines suggests that the technique may be a promising option for individuals who have not responded to medication or other established therapies, according to Dr. Joel Saper.

The neurostimulation technique was associated with a significant reduction in both the number of headache days per month and the intensity of pain in nearly 40% of patients with chronic migraine who were randomized to its use in a multicenter feasibility trial, reported Dr. Saper, founder and director of a head pain treatment and research center in Ann Arbor, Mich.

Occipital nerve stimulation (ONS) is achieved by the delivery of asymmetric biphasic electrical pulses via subcutaneous wires attached to the tissue surrounding the occipital nerve, located between the back of the neck and the skull. This form of peripheral nerve stimulation is thought to modulate the path of the migraine circuit and, by so doing, to interrupt the pain signals, said Dr. Saper.

Although previous studies have assessed ONS for the treatment of migraine and other headaches, as well as for occipital neuralgia, these have mostly been retrospective analyses, case series, or uncontrolled trials, he noted.

In the current investigation, called the ONSTIM (Occipital Nerve Stimulation for the Treatment of Intractable Migraine) study, Dr. Saper and colleagues randomized, in a 2:1:1 design, 110 patients from nine centers to one of three conditions: adjustable stimulation, in which patients received the neurostimulator and were able to control the level of stimulation; preset stimulation, or the device-control group, in which the level of stimulation was not adjustable; and standard medical management.

All of the patients included in the study experienced 15 headache days per month, as per ICHD-II (International Classification of Headache Disorders, second edition) criteria for chronic migraine, and none were responsive to available medical therapies. Prior to randomization, all of the patients received diagnostic occipital nerve block (ONB). The first eight patients who failed ONB formed an ancillary group and were offered ONS.

Of the 110 patients, 66 completed the electronic diary data for the 3-month follow-up period, including 28 in the adjustable-stimulation group; 16 in the preset-stimulation group; 17 in the medical-management group; and 5 in the ancillary group.

In the final analysis, the investigators used nonparametric methods to compare the ONS intervention group with the two control-condition groups for reduction in headache days per month, decrease in overall pain intensity on a 0-10 scale, and responder rate (defined as a 50% drop in headache days per month and a minimum 3-point drop in overall pain intensity from baseline), Dr. Saper explained.

Two patients who failed occipital nerve block responded to the stimulation technique.

DR. SAPER

With respect to headache days per month, the mean reduction from baseline in the device-intervention group was 27%, compared with 9% and 4% for the device- and medication-control groups, respectively. The mean drop in overall pain intensity was 1.5 points for patients in the intervention group, compared with 0.5 and 0.6 in the device and medication controls, he said.

In terms of treatment response, 39% of the patients in the intervention group experienced at least a 50% decrease in headache days per month and a minimum 3-point drop in pain intensity at 3 months, Dr. Saper said. In contrast, only 6% of the device-control group and none of the medically managed patients responded to therapy, he said at the annual meeting of the American Headache Society.

Of interest, he noted, "two of the patients in the ancillary group—all of whom failed ONB—responded to ONS, indicating that ONB may not be predictive of response to ONS."

No adverse events and no "unanticipated" adverse device events occurred, said Dr. Saper.

"The most common adverse device event was lead migration, which occurred in 12 of the 51 implanted subjects." Other adverse device events, particularly battery failure, "were consistent with the literature," he said.

Although additional randomized controlled trials are needed, the findings are important, "particularly to the population of chronic migraine sufferers who do not respond to aggressive medical therapy," Dr. David Dodick, one of the ONSTIM investigators, said in a symposium on neurostimulation for refractory primary headache disorders at the annual meeting.

If further studies demonstrate the safety and efficacy of ONS, leading to approval and commercialization of the technology, he said, "there may be some relief in sight for these patients."

The ONSTIM study was sponsored by Medtronic Inc., the developer of the neurostimulation device, and was conducted under an investigational device exemption according to the Food and Drug Administration's device-approval procedures. ■

Milnacipran Could Improve Fibromyalgia-Related Pain

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — The antidepressant milnacipran appears to provide sustained pain relief in patients with fibromyalgia.

In a 28-week, randomized blinded extension trial in 449 patients with fibromyalgia, durable pain relief and improved overall well-being was reported after 1 year of use by patients who responded to milnacipran during the trial's lead-in phase, lead investigator Dr. Don Goldenberg and associates reported in a poster at the annual meeting of the American Academy of Neurology. No new safety concerns emerged.

"Milnacipran is safe and effective for long-term use in fibromyalgia patients," concluded Dr. Goldenberg of Massachusetts General Hospital in Boston, who disclosed receiving personal consulting fees from Forest Laboratories, one of the companies—along with Cypress Bioscience Inc.—that sponsored this trial.

Milnacipran is a dual-reuptake inhibitor that is unique in that it raises levels of the neurotransmitter norepinephrine more than serotonin.

Marketed as Ixel for depression in Europe and Asia for years, milnacipran is not approved for any use in the United States. Despite its lack of Food and Drug Administration approval, word about milnacipran has spread on fibromyalgia patient Web sites.

The antidepressant milnacipran has not been approved for any use by the Food and Drug Administration, but word about the drug has spread on fibromyalgia patient Web sites.

A new drug application for milnacipran as a fibromyalgia treatment was filed with the FDA in December 2007 by Forest Laboratories Inc. and Cypress Bioscience Inc.

Patients enrolled in the trial had successfully completed a 6-month lead-in trial and were maintained on milnacipran 200 mg/day or rerandomized from placebo or milnacipran 100 mg/day to either milnacipran 100 mg/day or 200 mg/day for an additional 6 months of treatment. Their mean age was 50 years, more than 95% were female, and the mean duration of fibromyalgia was about 5.5 years.

Efficacy was measured as mean change from lead-in baseline to week 55 in pain recall scores, in Patient Global Impression of Change (PGIC) Scale scores, and in total Fibromyalgia Impact Questionnaire (FIQ) scores. No statistical analyses were performed to determine significance for the efficacy outcomes. This is noteworthy, as a pivotal phase III trial in 888 patients with fibromyalgia reported in September 2005 that its primary efficacy assessments failed to demonstrate statistical significance.

The current analyses were based on 147 of 209 patients maintained on milnacipran 200 mg/day for both phases of the study; 63 of 92 patients switched from milnacipran 100 mg/day to 200 mg/day; and 65 of 100 patients who switched from placebo to milnacipran 200 mg/day.

Efficacy data were not available on the 48 patients receiving milnacipran 100 mg in the extension phase.

Patients continuing on milnacipran 200 mg/day in the extension study showed a 46% improvement in mean pain recall scores, the investigators reported.

Patients switched from milnacipran 100 mg/day to 200 mg/day maintained the pain relief achieved in the lead-in trial and showed an additional 12% reduction in pain scores at the higher dose. Overall, their mean pain scores improved 52% from lead-in baseline.

Mean scores on the 7-point PGIC scale were 2.18 for patients continuing on milnacipran 200 mg/day and 1.91 for patients switching from 100 mg/day to 200 mg/day, indicating improvements in both groups after 1 year, according to the investigators. A score of 1 equals "very much improved" and 2 equals "much improved."

At week 55, the improvement in total FIQ scores was 49% among patients who switched from 100 mg/day to 200 mg/day and 41.5% among those maintained on 200 mg.

Patients switched from placebo to milnacipran 200 mg in the extension trial experienced a 47% improvement in their mean pain total scores after 28 weeks of treatment.

Similar improvements were observed in PGIC and FIQ, according to Dr. Goldenberg, who disclosed that along with fees from Forest Laboratories, he has received personal consulting fees from Eli Lilly & Co. and Merck & Co.

The drug was well tolerated at doses of 100 mg/day and 200 mg/day, and the majority of adverse events were mild to moderate. Data on serious adverse events were not presented in the poster and were not available from the investigators at press time.

The most common newly emergent adverse event during the extension phase in patients continuing on milnacipran was nausea, which was reported in 13% of these patients. ■