Occipital nerve stimulation for chronic migraine—interpreting the ONSTIM feasibility trial

Todd J Schwedt

Chronic migraine, which affects approximately 2% of the population, results in substantial costs to individual sufferers and to society (1). Current treatment options for chronic migraine are often inadequate, with a proportion of chronic migraine patients being intractable to conventional therapy. Clearly, better treatment strategies are needed to reduce the burden from this common and disabling disorder.

Dr Saper and co-investigators report the results from the ONSTIM trial, a Medtronic sponsored study of occipital nerve stimulation for the treatment of chronic migraine patients who had been intractable to standard pharmacotherapy (2). Subjects had suffered from migraine for an average of 22 years and chronic migraine for 10 years, had approximately 23 days per month with headache, had pain in the distribution of the occipital nerves, were intractable to prophylactic medications from at least two standard classes and had transient relief of pain following occipital nerve block. These subjects were randomized to one of three groups: (i) adjustable stimulation ($N = 33$); (ii) sham stimulation (pre-set stimulation for one minute daily) ($N = 17$); or (iii) continued medical management ($N = 17$). In order to assess whether or not response to occipital nerve block was a useful predictor for response to occipital nerve stimulation, a subset of subjects who did not benefit from the blocks were placed into an ancillary group that also received treatment with adjustable stimulation ($N = 8$). Safety and efficacy data were derived from three months of follow-up.

The primary aim of this study was to collect preliminary data regarding the safety and efficacy of occipital nerve stimulation for the treatment of chronic migraine. The study was not designed to yield conclusions regarding this treatment modality. Consistent with the study goals, the sample size was small and multiple outcomes were investigated independently. Many of these outcomes showed numerical superiority (although not necessarily statistically significant superiority) of adjustable stimulation over sham stimulation and over continued medical management. Despite the small sample size, adjustable stimulation was associated with statistically superior benefit for a few disability and quality-of-life outcomes when independently analyzed (not corrected for multiple comparisons). These results suggest that occipital nerve stimulation is a promising treatment for chronic migraine and that further clinical trials are warranted.

In addition to the study power and methods of analysis, a few other study specifics should be considered when interpreting the results.

- This study excluded subjects who were overusing abortive headache medications. Because a substantial proportion of subjects with very frequent migraines do overuse abortive medications, it would be reasonable to test occipital nerve stimulation in this group of subjects as well. Although it has traditionally been believed that medication overuse results in a group of patients who are more refractory to treatment, this differential intractability has not been noted in some recent clinical trials (3).
- The placebo-response rate to an implantation procedure is likely to be quite substantial. In this study, a pre-set stimulation subject group who received stimulation for one minute daily served as the sham-stimulation control group. Unquestionably, there are numerous difficulties in designing sham control groups to study surgical treatments for migraine. Although the pre-set stimulation group comes close to a true control, as the investigators of this study discuss, it does fall short. In the adjustable-stimulation group, it is possible that paresthesias secondary to stimulation and the ability to control stimulator parameters resulted in immeasurable placebo effects. Technical and ethical debates regarding sham control groups are needed when designing future stimulator trials.

Washington University Headache Center, USA

Corresponding author: Todd J. Schwedt, Director, Washington University Headache Center, 660 South Euclid Ave, Campus Box 8111, St. Louis, MO, 63110, USA
Email: schwedt@neuro.wustl.edu
Patient selection for this trial included intra-operative paresthesia testing during placement of the stimulator. In other words, prior to permanent implantation it was required that stimulation caused paresthesias in regions of the head in which the patient had pain. Unlike some of the other occipital nerve stimulation studies, there was not an initial five-to-seven–day trial of percutaneous stimulation. Although the positive predictive value of such a pre-implant trial for tolerability and clinical effects of stimulation is yet to be determined, it is reasonable to think that such a trial may be predictive for these outcomes.

Patients were allowed into this study even if they were taking migraine prophylactic medications, as long as the medications and doses had not changed during the four weeks preceding enrollment. Although there may be ethical concerns about withdrawing chronic migraine patients from prophylactic medications, the effect of these medications on study results cannot be determined. Future studies might consider excluding patients taking prophylactics or consider powering the study to examine the effects of their use on results.

The subjects in this study had migraine for an average of 22 years and chronic migraine for an average of 10 years prior to enrollment. Although it is important to ensure intractability of chronic migraine prior to considering implantation of a stimulator, it is possible that patients with a shorter duration of disease may be more responsive and/or respond more quickly to occipital nerve stimulation.

Complication rates would need to be reduced if occipital nerve stimulation was to be used more widely for treatment of intractable chronic migraine. The complication rate associated with stimulation in this feasibility trial was substantial, with 24% of subjects having lead migration and 14% having infection, all within three months of stimulator implantation. Reduced complication rates are likely achievable as surgical techniques and stimulator equipment evolve. Furthermore, although not an issue in this study, which reported only three months of follow-up, battery depletion eventually occurs. The need for battery replacement has to be considered when discussing stimulator therapy.

Although the results from this feasibility study are promising, they also demonstrate the continued need for better therapies for chronic migraine. Realizing that this study included only patients who had already demonstrated that they are intractable to conventional therapies, only 39% had benefits that met a priori criteria for response. This, of course, leaves 61% as non-responders. Patients in the adjustable-stimulation group had a reduction in days with headache from 22.4 days per month to 15.7 days per month. Although this decline in number of headache days is clinically relevant, subjects were still suffering from very frequent migraines. Therefore, if these results were to translate into clinical practice, many of these patients would require prophylactic therapies in addition to occipital nerve stimulation.

Because many patients with chronic migraine have pain in frontal head regions in addition to C2-inner-vated regions, it is possible that combined supraorbital and occipital nerve stimulation would result in even better outcomes. Reed and colleagues have published preliminary data suggesting that this combined approach to stimulation may be superior to occipital nerve stimulation alone (4). Future trials should explore this possibility.

The three-month follow-up data from the ONSTIM trial supports the call for further studies of occipital nerve stimulation for the treatment of intractable chronic migraine. Results from the continued follow-up of these subjects are highly anticipated. If occipital nerve stimulation is to be considered a viable therapy, benefits must be persistent over a prolonged duration of time with acceptable complication rates and battery life.

Disclosures

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References