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PRISM study: occipital nerve stimulation for treatment-refractory migraine
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Objectives: To investigate the safety and efficacy of occipital nerve stimulation (ONS) for the preventive treatment of refractory migraine.
Background: ONS may offer a safe and effective alternative to the currently limited therapeutic options available to migraine sufferers that fail pharmacological management.
Methods: This multi-center, double-blind, randomized controlled trial enrolled participants who (1) met the 2004 International Classification of Headache Disorders (ICHD-2) diagnostic criteria for migraine with aura, migraine without aura, and/or chronic migraine; (2) presented as drug-refractory (failed therapy with at least two acute and two preventive medications); and (3) had ≥6 days per month of long-duration (≥4 hours) migraine with moderate/severe pain (migraine day). Those overusing acute medications at baseline, per ICHD-2 criteria, were included as a pre-specified analysis subgroup. Prior to implantation, both arms received 5–10 days of percutaneous trial stimulation, using their randomized settings, to evaluate the predictive value of a treatment trial on 12-week outcome. Subjects were randomized 1:1, to receive bilateral active (250 μsec pulses, 60 Hz, 0–12.7 mA) versus sham (10 μsec pulses, 2 Hz, <1 mA, 1 sec on/90 min off duty cycle) stimulation for 12-weeks post-implantation of an ONS device. The primary endpoint, captured by daily electronic diary entries, was the change from baseline in migraine days/month evaluated 12 weeks after implantation. At 12 weeks, sham subjects were converted to active settings. Diary follow-up continued for 52 weeks.

Results: Of 179 patients screened for enrollment, 140 eligible subjects were randomized, 132 were implanted and 125 completed 12-week follow-up. For the primary endpoint, reduction in migraine days/month, the difference across treatment arms was not significant (-5.5 vs.-3.9 days/month, P = 0.29, Table 1). There was a trend towards a greater difference between treatment arms for those not overusing medication (-5.9 vs.-2.6) in comparison with the medication overuse subgroup (-5.0 vs.-4.8). In the active arm, a favorable response to the percutaneous treatment trial was moderately predictive of 12-week response (positive likelihood ratio = 2.0, 95% CI [1.4 2.9]; negative likelihood ratio = 0.21, CI [0.06 0.78]). Two-year aggregate safety data revealed infection, non-target area sensory symptoms, and implant site pain as the most-frequent device related adverse events.

Conclusions: Active ONS did not produce statistically significant benefits in relation to sham stimulation on the primary endpoint. Heterogeneity in treatment response suggests that there may be a treatment responsive subgroup. Future studies should endeavor to identify and randomize patients likely to respond to stimulation, based in part on the absence of medication overuse and a favorable response to a trial of percutaneous treatment.
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Table 1.

<table>
<thead>
<tr>
<th></th>
<th>$n$</th>
<th>Baseline days/month (mean ± SD)</th>
<th>Change at 12-weeks (mean ± SD)</th>
<th>$P$-value</th>
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</thead>
<tbody>
<tr>
<td>Active</td>
<td>63</td>
<td>20.2 ± 7.2</td>
<td>-5.5 ± 8.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Sham</td>
<td>62</td>
<td>19.2 ± 7.9</td>
<td>-3.9 ± 8.2</td>
<td></td>
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</tbody>
</table>

Conclusions: Active ONS did not produce statistically significant benefits in relation to sham stimulation on the primary endpoint. Heterogeneity in treatment response suggests that there may be a treatment responsive subgroup. Future studies should endeavor to identify and randomize patients likely to respond to stimulation, based in part on the absence of medication overuse and a favorable response to a trial of percutaneous treatment.