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Guest Editorials

Vagus Nerve Stimulation for the Acute Treatment of Cluster Headache

In this issue, Silberstein et al[1] attempted to learn whether external stimulation of the vagal nerve could abort a cluster headache. Sixty vagal nerve stimulation (VNS)-treated patients were compared to 73 sham-treated patients. Results in these two groups were compared using a "response rate" defined by the authors as the percentage of patients achieving reduction of pain to a pain-free (0) or mild (1) level. Patients were encouraged to begin treatment at the very first sign of a cluster headache, which could consist of mild pain. A secondary end point was "sustained response" during the 15–60 minutes following the attack. The authors found no significant differences with regard to the primary and secondary endpoints between the verum and sham groups. But, when a subgroup analysis was done, focusing on episodic cluster (EC) patients versus chronic cluster (CC) patients, significant differences were seen for both the primary and secondary endpoints between subjects with episodic cluster headaches in the treatment and sham group. No significant differences were seen in the chronic cluster headaches subgroup. The authors assert that their subgroup analysis of results was done in a "prespecified" manner. They concluded that VNS was potentially useful for patients with episodic cluster headaches: "Considering the tolerability, dosing, and/or practicality issues associated with currently available symptomatic treatments, nVNS provides a safe, well-tolerated, effective, and easy-to-use non-invasive option for acute CH treatment. . .in patients with episodic cluster headache."

This was a large, well-designed sham-controlled trial suggesting treatment effectiveness and safety, and addressing an unmet need. On the surface, therefore, this would appear to be good news for desperate cluster headache patients as well as for the manufacturer of the vagal nerve stimulator device. Digging a bit deeper, however, dampens our enthusiasm somewhat, at least for now.

The design of this study was appropriate for the research question, and followed an accepted format, with subjects randomly assigned to one of two blinded groups. Several headaches were treated but only the first one was assessed for the primary treatment endpoint. A blinded period of one month allowed several attacks per patient to be captured, and a subsequent open-label period allowed some further post hoc analysis. Exclusion criteria were standard. Inter-group variations were insignificant. Sample size determination was done appropriately and the numbers needed to satisfy statistical analysis needs were enrolled. An intent-to-treat analysis was employed.

The effectiveness of subject blinding was assessed after the first treatment. Authors noted that "a considerable proportion of patients correctly guessed their treatment allocation." They went on to state that "successful blinding was achieved at the end. . .[of the blinded period]." This, unfortunately, does not mitigate the clear problem of inadequate blinding, a common obstacle in device and injection studies, as pointed out succinctly by Asano and Goadsby.[2]

The primary endpoint was not achieved in this study – ie, differences in reduction in pain severity between active and sham groups were not significant. The authors point to a significant response in a prespecified subgroup – the subjects with episodic cluster headache. Unfortunately, there are inherent

problems with assigning importance to results derived from subgroup analyses.[3] First, they tend to fall under the category that the discerning reader might call "spin," since every data set could be made to find two subgroups where one group is statistically significant for a particular end point, and the other is not. Also, conclusions drawn in this way are notorious for failing to replicate. The risk of interpreting these subgroups can be lessened by a formal test of interaction which examines whether the response is statistically different in the two subgroups. The authors did not do this. As a result, type 1 error cannot be excluded. On the other hand, the "expected" probability of there being a better response in EC patients than in CC patients is reasonably high – thus adding some credence to the authors' conclusion.

The device used in this study seems safe. It is imperative to assure this as there might be conceivable adverse effects due to vagal (both left and right vagus nerves) impact on cardiac conduction and laryngeal function. Fortunately, years of observation of VNS used for controlling intractable epilepsy suggest little cause for alarm.[4] Further observation of adverse effects with this and other vagal stimulation devices will hopefully set our minds at rest. Interestingly, in this study, adverse effects were more often seen in subjects using the sham device. For example, skin irritation affected no subjects using the verum stimulation, but 12% of those using the sham device. Three percent of those using the active stimulation reported burning/tingling/soreness/stinging, while 9% of the sham group reported symptoms along these lines. And overall, 31% in the sham group reported some adverse effects compared to 15% in the verum group. This begs the question of how inactive the sham stimulator was and why it was found to be irritating. (The authors suggested differences in DNIC activity between the two groups as the cause, but this is entirely speculative). And again, this also raises questions about the success of blinding.

Post hoc analyses done by the authors of this study raised interesting questions for further investigation, as is so often the case. The significant differences in response rate (percentage of patients achieving $\geq 50\%$ of headaches relieved) in EC subjects might suggest this as a meaningful endpoint in future studies. The reduction in headache duration for both active subgroups suggests this as another meaningful endpoint to explore in the future. The authors, when exploring drawbacks in their study suggested that the 15 minute assessment time as being too short, and that a later time point for pain assessment might have improved the results. However, the low overall satisfaction with this treatment in the verum group (38%) speaks against this.

Finding successful alternatives for the acute treatment of cluster headache is an important goal, especially for patients who are relatively refractory to current options (subcutaneous and nasal triptan, oxygen, and parenteral dihydroergotamine). This study did not provide evidence for efficacy in the intended group, but despite the limitations in subgroup analysis in general, it suggested benefit for patients with episodic cluster headache. Further study is definitely worthwhile, with clear endpoint assessment and with successful blinding, as difficult as that might be.

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