Novel approaches to managing migraine and cluster headaches

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The use of botulinum toxin type A purified neurotoxin complex and peripheral neurostimulation are now established approaches in the management of the highly disabling primary headache syndromes migraine and cluster headache.

Migraine and cluster headaches are highly disabling primary headache syndromes. There is a continuing need to add novel, safe and practical treatments to our current therapeutic armamentarium. This article reviews the use of botulinum toxin type A purified neurotoxin complex and peripheral neurostimulation for these headaches.

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Botulinum toxin type A for chronic migraine

The purified neurotoxin complex preparation of botulinum toxin type A (Botox) is currently listed on the PBS in Australia for use in chronic migraine if the patient meets the clinical criteria (Box). The injections should be given by a fixed -site, fixed-dose protocol. The PREEMPT [Phase III Research Evaluating Migraine Prophylaxis Therapy clinical program] protocol comprises 31 fixed-site, fixed-dose (5 units) intramuscular/ subcutaneous injections, with the option of additional injections (Figure 1).[1]

The mechanism of action of botulinum toxin type A purified neurotoxin complex in chronic migraine is unclear, but is postulated to result from inhibition of release of nociceptive neuropeptides (such as calcitonin gene-related peptide, substance P and glutamate) from sensory C fibres, reducing peripheral and central sensitisation of pain.[2]

The pivotal clinical trials were the two PREEMPT trials in 2010, the pooled results of which showed a response rate (50% reduction in headache days) of 47% with injections of onabotulinumtoxinA (the US generic name for Botox) versus 35% with placebo injections at 24 weeks. Perhaps even more impressive was the reduction in headache hours per month by 120 hours in the onabotulinumtoxinA group versus 80 hours for placebo.[3] Treatment-related adverse events were mild, with the most common being neck pain, muscular weakness, eyelid ptosis, musculoskeletal pain, injection site pain and headache.[3]

The cost of botulinum toxin type A purified neurotoxin complex to the patient is up to $38.30 per treatment course under the PBS (as a prescription fee) plus consultation and injection item numbers. It should be noted that the various botulinum toxins possess individual potencies, and only the purified neurotoxin complex preparation of botulinum toxin type A (Botox) is PBS and TGA approved for chronic migraine; the other brands have not been shown to be efficacious in migraine.

PBS CRITERIA FOR USE OF BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX IN CHRONIC MIGRAINE

Clinical criteria

The patient must have experienced an average of 15 or more headache days per month, with at least eight days of migraine, over a period of at least six months, prior to commencement of treatment with botulinum toxin type A neurotoxin

AND

The patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications* prior to commencement of treatment with botulinum toxin type A neurotoxin

AND

The patient must have achieved and maintained a 50% or greater reduction from baseline in the number of headache days per month after two treatment cycles (each of 12 weeks duration) in order to be eligible for continuing PBS-subsidised treatment

AND

The patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with botulinum toxin

Population criterion

The patient must be aged 18 years or older

Treatment criteria

The patient must be treated by a neurologist

Prophylactic migraine medications are propranolol, amitriptyline, methysergide,* pizotifen, cyproheptadine or topiramate

* Methysergide is no longer available in Australia but a patient who has failed it in the past can count it as one of the three previous treatments.

Neurostimulation for migraine and cluster headache

Peripheral neurostimulation can be minimally invasive and non-destructive and is increasingly available to patients. Its analgesic effects have been attributed to activation of afferent Aβ fibres and gate control in the spinal cord and descending supraspinal control from the rostroventromedial medulla or the periaqueductal grey matter.[4]

Supraorbital nerve stimulation (using the Cefaly® device) is effective in the prevention of episodic migraine headaches, and vagus nerve stimulation (using the gammaCore® device) is effective in the prevention of both chronic migraine and chronic cluster headache. Cefaly is TGA registered for the treatment and prevention of migraine and tension headache, and gammaCore for the treatment and prevention of migraine and cluster headache.

Occipital nerve stimulation (using an implantable pulse generator) may improve headaches for some people who try the therapy but long-term results are limited.

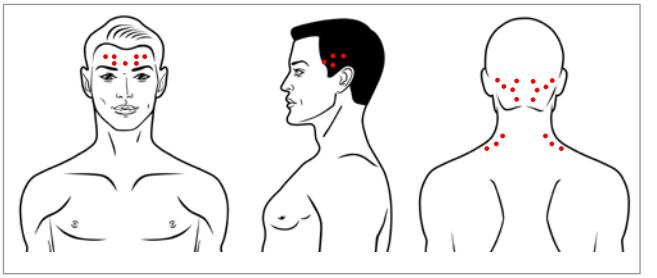

Figure 1. Botox headache treatment. A fixed dose (5 units) of botulinum toxin type A purified neurotoxin complex is injected into each of 31 fixed sites in the PREEMPT injection protocol. These sites are in the corrugator, procerus and frontalis muscles (above left), temporalis muscle (above centre) and occipitalis, cervical paraspinal and trapezius muscles (above right).

Supraorbital nerve stimulation: Cefaly® device

The Cefaly device provides bilateral external supraorbital transcutaneous neurostimulation (STS) in a simple to use, portable device (Figure 2). The Prevention of Migraine Using the STS Cefaly (PREMICE) clinical trial showed that daily stimulation for 20 minutes in patients with episodic migraine (two or more episodes per month) resulted in a response rate (50% reduction in migraine days per month) of 38% in the stimulation group versus 12% for sham stimulation at three months.[5] Side effects were reported in 4.3% of users and were mild and fully reversible.[5] These side effects included intolerance to the paraesthesia induced by the electrical stimulation of Cefaly on the forehead, arousal and sleep changes, headache and allergic skin reaction to the electrode.[6]

The cost of the device to the patient is about $400, and the device may be rented (www.cefaly.com.au). It may be an option for a drug-averse or drug-intolerant patient.

Vagus nerve stimulation: gammaCore® device

The gammaCore device is a handheld, portable noninvasive vagus nerve stimulator that is applied to the neck (Figure 3). The device comes preloaded with either 150 doses or 300 doses. Each 'dose' consists of stimulation for about 90 seconds after which the device automatically turns off. Once the preloaded doses have been used up, the device needs to be replaced as it is nonrechargeable.

The Preventative Treatment of Chronic Migraine (EVENT) study in patients with chronic migraine showed that prophylactic use at two doses three times a day, resulted in a response rate (a more than 25% reduction in number of headache days per month) in 15% of patients with the device and 4% with a sham device at eight weeks.[7]

The Prevention and Acute Treatment of Chronic Cluster Headache (PREVA) study in patients with chronic cluster headache showed that the number of cluster headache attacks

Figure 2. Cefaly® device for supraorbital nerve stimulation.

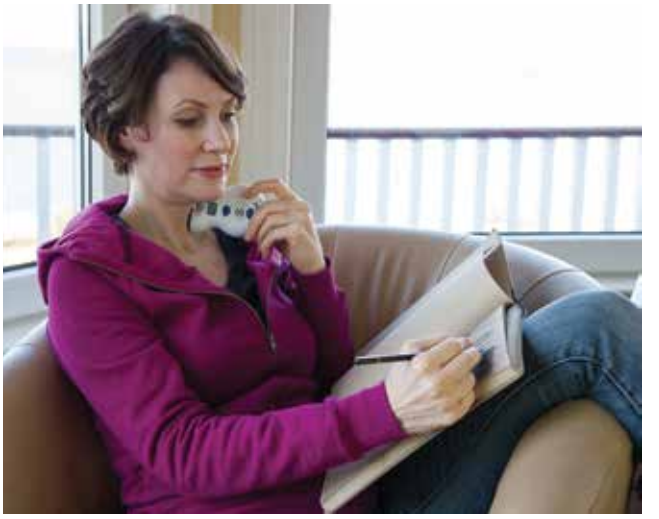

Figure 3. gammaCore® device for vagus nerve stimulation.
Image courtesy of electrocore.com

per week was reduced compared with patients treated with standard of care alone (-7.6 *vs* -2.0). The prophylactic regimen was three doses twice a day. Acute treatment was three doses at onset of pain.[8]

Side effects include twitching of the eyelids and lips, which resolve once the stimulus is turned off. The device is not suitable for use in patients with any implanted devices (including pacemakers and hearing aid implants) or with carotid stenosis.

The cost of gammaCore to the patient is about $400 for a 300-dose device (http://gammacore.com/en/healthcareproviders/contact-us). A doctor has to authorise the patient via the company before the device can be ordered.

Occipital nerve stimulation

Occipital nerve stimulation is moderately invasive. Leads (unilateral or bilateral) are placed on either side of the midline caudally along or perpendicular to the occipital nerve at the craniocervical junction. A subcutaneous pocket is created in the chest wall or abdomen for the implantable pulse generator. A subcutaneous tunnel is made from the lead incision site to the pocket and connected with a lead/extension.

Multiple case series of patients with chronic cluster headache collectively show a 67% response rate (at least 50% improvement in headache frequency and/or intensity) with occipital nerve stimulation.[9-14] However, no randomised controlled trial confirming these preliminary open-label findings has been conducted.

Three large randomised controlled trials of this form of peripheral neurostimulation have failed to show a statistically significant response in their experimental period in the active phase of treatment in patients with refractory chronic migraine.[15-17]

The adverse effects of occipital nerve stimulation are either device-related (electrode migration, lead breakage, local infections, irritation from lead insulation and battery depletion) or stimulation-related (irritation within the receptive field of the occipital nerve, muscle contractions and local pain around the impulse generator.[18]

The cost to the patient of occipital nerve stimulation is variable but may be substantial, and depends on the proceduralist and the details of private health cover.

Conclusion

Prevention of migraine and cluster headache have in the past focused on standard pharmacological agents. There is now interest and progress in neurostimulation and other novel methods to help these patients. Botulinum toxin type A purified neurotoxin complex and peripheral neurostimulation now have established roles in the treatment and prevention of these headaches. Other novel approaches are being trialled, including calcitonin gene-related peptide antibodies for migraine and sphenopalatine ganglion stimulation for cluster headache. Real progress is being made in helping patients with these difficult and often disabling disorders. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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