Dr Chris Blatchley on treating migraine with botulinum toxin simply and effectively

In my aesthetic clinic, it is common to hear patients say, “I know it is time to get my botox done when my headaches start again.” At least one in 10 women suffer from migraines and even more from migraine-related headaches, so it is important to know how to refine your injection technique to treat them effectively. Treat them well and your patients will tell their friends with migraines to come to you, and you can have the satisfaction of greatly improving their quality of life. And it is not difficult to do!

WHAT CAUSES MIGRAINES?
Unsurprisingly for such a common affliction, there are many different theories to explain their cause. Osteopaths see it as a neck problem, dentists as a TMJ problem and neurologists as a brain problem. In a sense they are all correct but research behind how botulinum toxin works has been helpful in providing a unifying theory.

Historically neurologists have classified primary headaches (i.e. those not cause by pathologies such as tumours, haemorrhage etc) into many different subtypes. More recently, noted neurologists specialising in headaches, such as Dr Russell Lane and Dr Paul Davies, have come to the view that all primary headaches are driven by the same fundamental process – the “migraine mechanism” – even if they present in different ways. Migraine sufferers will often be clear about the difference between a “headache” and a “migraine”, and indeed most will suffer far more frequently from headaches than a full blown migraine even though the same mechanism is operating.

Primary headaches probably result from an imbalance of the normal excitatory and inhibitory control processes. These trigger a wave of cortical neural excitation followed by suppression of electrical activity which slowly sweeps over the brain and

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results in activation of neural pathways that modulate pain. This wave also causes secondary constriction and then dilation in cerebral blood vessels, notably in the meninges, which generates the pain. Visual and other auras can occur in the constriction phase before the pain starts. Full-blown migraines can result in cognitive disorientation, hypersensitivity to light and sound, nausea and vomiting, vertigo and other autonomic disturbances that may well be more troublesome than the headache.

Although it is important to exclude secondary headaches, migraines are diagnosed from the history, and most people have had them for years and have already been diagnosed. As long as there has been no change in the headache pattern then you do not need to worry about missing other causes.

Genetics determines susceptibility to migraine in a complex manner. This susceptibility cannot be ‘cured’, so the clinical imperative is to manage the symptoms. The first effective treatment for migraine headaches was ergot, derived from a mould that grows on rye and caused St Anthony’s Fire, from which ergotamine and related drugs were developed. In the last 30 years, these compounds have been replaced by the far less toxic triptans. For prevention, beta blockers, anti-depressants, anti-epileptic drugs and calcium antagonists are all useful but often cause side effects such as tiredness which limit their usefulness. More recently botulinum toxin has been shown to be effective.

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For many years doctors have observed that headaches follow the distribution of the ophthalmic branch of the trigeminal nerve (V1) and the greater occipital nerve (from the second cervical nerve, C2) in the neck. The pain centres for both these nerves overlap in the trigemino-cervical tract in the brain stem, which acts as a relay station for pathways involved in the migraine mechanism. One interesting idea is that this structural overlap is related to the avoidance reflex to protect the eye by closing the eyelids and turning the head. Tiredness, hunger, visual and auditory stimuli and smells can also trigger attacks, provoking the wave of cortical depolarisation discussed earlier, but the various different sensory stimuli interact in concert, so that reducing the peripheral stimulation of the brain-stem pain centres helps reduce the potential for an attack.

Botox acts on free nerve endings which carry pain stimuli to the brainstem over unmyelinated fibres; such fibres are also present in the autonomic nervous system. These free nerve endings are found in the connective tissue, particularly in the fascia and fascial attachments of muscles to bone. Within them are vesicles that contain substance P, a neuropeptide that is released when a painful stimulus is experienced. This stimulates other free nerve endings to amplify the stimulus and start an inflammatory process that results in vasodilation via neuronal reflexes to local blood vessels and also by the chemical inflammatory pathway, which attracts pro-inflammatory cells into the area. Botox works by preventing the release of neurotransmitters from the vesicles in the same way as it does at neuromuscular junctions, thus reducing the afferent pain signals to the trigemino-cervical complex.

There is considerable debate as to whether botox affects the brain centrally. Recent evidence suggests active botox can travel retrogradely along the natural axonal cytoplasmic flow. However, even though it may modify the synapses of the same neuron at a central level there is little evidence to suggest this has a clinical effect. The “infective” botulinum toxin molecule attaches to the vesicle as it is reabsorbed into the neurone, and is activated by splitting into a heavy and light chain as it actively passes through vesicle wall into the cytoplasm. Only the light chain is active, and it also loses its infectivity in the process. This is unlike its close cousin tetanus toxin, which can easily pass between neurones.

The effect of botox on migraine was noticed in the 1990s by Bahman Guyuron, a plastic surgeon in Cleveland. It was found that patients experiencing a variety of headaches, and treated with botox to prevent excessive movement of the facial muscles, had less frequent and less intense headaches. Further research showed that botox injections into the head, neck and upper part of the spine can reduce the frequency and severity of migraines. The exact mechanism of action is not fully understood, but it is believed that botox acts on the pain relay centres in the brain stem, reducing the activity of the afferent pain signals to the trigemino-cervical complex.

**HOW DOES BOTOX WORK?**

Botox works by preventing the release of neurotransmitters from the vesicles in the same way as it does at neuromuscular junctions, thus reducing the afferent pain signals to the trigemino-cervical complex. This reduces the activity of the pain relay centres in the brain stem, which are instrumental in kick-starting migraines. Botox acts on free nerve endings which carry pain stimuli to the brainstem over unmyelinated fibres; such fibres are also present in the autonomic nervous system. These free nerve endings are found in the connective tissue, particularly in the fascia and fascial attachments of muscles to bone. Within them are vesicles that contain substance P, a neuropeptide that is released when a painful stimulus is experienced. This stimulates other free nerve endings to amplify the stimulus and start an inflammatory process that results in vasodilation via neuronal reflexes to local blood vessels and also by the chemical inflammatory pathway, which attracts pro-inflammatory cells into the area. Botox works by preventing the release of neurotransmitters from the vesicles in the same way as it does at neuromuscular junctions, thus reducing the afferent pain signals to the trigemino-cervical complex.
Ohio. He developed a theory that migraines were caused by irritation of the supratrochlear nerve, a branch of V1, as it passed through the corrugator muscles, and that excision of the corrugators would treat migraines permanently. Initially he had very variable success but started to use a “Botox Test” in which a large dose of BoNT-Botox is injected into the corrugators. He observed that the corrugator operation was more successful if patients’ migraines responded well to botox first. It would be an understatement to say that neurologists have dismissed this theory and have been damning about migraine surgery. My view is that any response to corrugator surgery is the consequence of the destruction of unmyelinated pain fibres that pass from the corrugators into the supratrochlear and supraorbital nerves, rather than through inhibiting “mechanical irritation” of the nerve fibres, though there may also be a mechanical element in stimulating the free nerve endings.

Meanwhile Allergan developed the PREEMPT Protocol for Botox® administration, in which multiple injections are placed into the neck, temples and forehead. However, essentially none is injected into the corrugators, even though the protocol claims to inject the glabella. Indeed Allergan teaches injectors to point the needle away from the corrugators, so that it is unlikely that any Botox® reaches the corrugators within their fascial compartment, since BoTN-A is far too large a molecule to diffuse through fascial layers. The ‘infective’ element of the BoTN-A molecule is 150kDaltons, which equates to several tens of thousands of atoms (one carbon atom weighs 12 Daltons), while Botox® is about six times as large. It appears that Allergan wanted a standard method that could be used in a double-blind controlled study for the American FDA where there would be no danger of lid ptosis due to poor injection technique. At the time Allergan were being investigated by the Department of Justice for making claims they could not substantiate and badly needed proof of efficacy. The FDA licenced Botox® for migraines in October 2010 but Allergan decided to pay a $600 million fine a month before in September 2010 to settle the DoJ investigation “in the interests of shareholders”, presumably because they knew that they were about to get FDA approval. Armed with FDA approval, Allergan filed a patent for its use in all neurological pain and have no plans to do further research improving on the PREEMPT Protocol. These comments are not made to knock either Allergan or their protocol. It was ground-breaking at the time because it showed for the first time in a double-blind controlled study that BoTN-A is effective in migraine. However the PREEMPT Protocol is now five years old and I suggest that it is possible to improve the outcome in migraine by injecting the corrugators simply and effectively, as is done in the surgeon’s Botox Test.

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**HOW TO INJECT BOTOX – COMBINING THE PREEMPT PROTOCOL AND THE BOTOX TEST**

I have been using “botox” as a generic term for botulinum toxin A (BoTN/A), the active strain present in the three commercially available forms in the UK. In fact, I use Xeomin by Merz to excellent effect and there is no reason to think that Dysport/Azzalure from Galderma will be less effective. They all work by the same mechanism to prevent neurotransmitter release. Although only Allergan’s Botox® has a licence for use in migraines, most of the work we do in aesthetic treatments is off-licence. The main thing to understand is how to inject 50/60U Botox®/Xeomin or 120/150U Dysport/Azzalure into the corrugators to avoid the largely theoretical danger of lid ptosis.

The simple protocol I use is only a small variation from the standard points that you use every day and combines elements of both the PREEMPT Protocol and the Botox Test. It does not usually require injections into the neck/temples so that one uses only half the amount of BoTN/A compared to 150-180U Botox® in the full PREEMPT protocol. This keeps the costs for the patient down to not much more than for an aesthetic treatment. One can always add injections to the neck/temples later if indicated.
I dilute 100U Xeomin in 2.5ml bacteriostatic saline. The main principle when deciding dosage is to use that which is sufficient. If the migraines are well controlled on a normal aesthetic dose of ~15-20U to the forehead and 20U to the corrugators then there is no need to increase this. However people presenting with migraines will usually require the higher dose of 60U to the corrugators and 15-30U to the forehead. This will ensure that the full height of the frontalis and the entire mass of the corrugators are injected.

Aesthetic practitioners are well versed in injecting the forehead, and the principles remain the same when treating migraines. They may be more nervous about injecting 60U directly into the corrugators, and they key is to understand the anatomy. The area around the eye is composed of multiple fascial compartments that protect the eye from spread of infection and, as discussed earlier, BoTN/A is too large to pass through fascia. Most or all of the fibres of the levator palpebrae are generally behind the orbital septum and the corrugators are within their own fascial compartment as one can see in the illustration of the dissection during a surgical brow lift. I keep the angle of injection at 20-30deg to the skin, directing the needle centrally along the length of the corrugator and injecting 10U (0.25ml) at each point.

Lid ptosis in aesthetic procedures is uncommon. It is usually due to poor injection technique, and the same is true for the increased doses injected for migraines. If you see scars around the eyebrows it is good practice to take a history of the extent of the injury, which may have happened in childhood, for rarely this may be enough to have caused disruption of the fascial compartments. I have never had a case of lid ptosis.

OUTCOME
You must explain at the consultation that botulinum toxin does not work for everybody and in my experience about one in 10 does not respond or are unhappy with the outcome, though usually you will have a fair idea from the history. Conversely, 1 in 10 finds their migraines disappear completely while the rest report that they are enormously happy with the response. They may still have migraines but they are shorter, less frequent and less severe, and the autonomic symptoms are less. Most of all, they find they are free of the continuous feeling that they are about to have another migraine. There will be a small group who need further injections in the neck. This requires a specific technique which can be learnt later.

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Dr Chris Blatchley MB BCHir has been working in aesthetics since 2007, and is passionate about exploring the clinical experiences across specialities to improve treatments to the patient. He has been studying migraine treatments since 2009 and has presented to specialist neurologists at the Oxford Headache Symposium. He is also researching on optimal preparation of PRP without using expensive kits, as well as combining HRT into aesthetic practice since many of our patients are peri/post-menopausal.