A Thin Treatment Landscape

To date, no large placebo-controlled studies on the treatment of PTH exist. All current evidence is based on small, prospective/retrospective studies and case reports. These studies have looked at various abortive treatments, including dihydroergotamine, injectable sumatriptan, and topical ketoprofen, and all have demonstrated efficacy. In particular, the dihydroergotamine study demonstrated a good/excellent response in 85 percent of the patients treated. Also, indomethacin has been shown to successfully treat patients with post-traumatic hemicrania.

Other studies have looked at the use of preventive medications, including valproic acid as well as amitriptyline, both alone and in combination with propranolol, with results ranging from no improvement to variable improvement, to a modest reduction in headache frequency. In perhaps the most comprehensive study to date, investigators examined 100 soldiers undergoing treatment for chronic PTH. Headache frequency and Migraine Disability Assessment scores were determined at the initial clinic visit and then again by phone three months after starting headache prophylactic medication. Investigators determined response rates of headache abortive medications and compared treatment outcomes between individuals with blast-related PTH and non-blast PTH. Medications included topiramate, low-dose tricyclic antidepressants, and sumatriptan. Results demonstrated that sumatriptan was usually effective for aborting headaches in military troops with chronic PTH attributed to a concussion due to a blast injury or non-blast injury. Topiramate was suggested to be an effective headache prophylactic therapy in military troops with chronic PTH, whereas low doses of tricyclic antidepressants appeared to have little efficacy. An interesting finding was that chronic PTH triggered by a blast injury was less responsive to commonly prescribed prophylactic headache medications when compared to non-blast PTH.

PRACTICAL POINTER

Although treatment options specifically indicated for post-traumatic headache are few, ongoing research has elucidated acute, subacute, and possible preventive interventions that may have some benefit. Importantly, more studies are needed to verify the viability of many of these therapies.
Current consensus suggests treatment based on headache phenotype. As with other primary headache disorders, treatment involves abortive and prophylactic therapy. Abortive treatment should be instituted when the pain is mild, and headache should be treated completely. Given that most PTH meets International Headache Society criteria for migraine or probable migraine, standard migraine treatments are often employed. It is also important to account for the subtype of trauma, i.e., concussion, mild traumatic brain injury (TBI), or TBI. However, the lack of standard or even consensus definitions for the aforementioned sub-types presents significant challenges. Most definitions take into account duration, imaging findings, and physiology. For discussion purposes, concussion will be defined as a transient physiological process involving disruption of cerebral metabolism, neurotransmission, and blood flow, usually lasting 10 to 14 days, but not longer than three months, with no structural abnormalities on standard imaging (i.e., conventional MRI or CT). Mild TBI will be defined as a permanent disruption of neurotransmission and possibly metabolism beginning at least three months after the initial head trauma with no structural abnormalities on standard imaging. TBI will be defined as a permanent disruption of brain neurotransmission and possibly metabolism with structural abnormalities on standard imaging (i.e., diffuse axonal injury and shear, subdural hematoma, epidural hematoma, subarachnoid hemorrhage, and blast-related structural changes). It is also important to consider patient age, mechanism, and circumstances surrounding the head trauma. For example, individuals with sports-related concussion and even blast-related TBI are more likely to underreport symptoms in order to return to play or duty, whereas those with motor vehicle accidents, work accidents, and even falls are likely to overreport and experience more prolonged symptoms as a result of possible secondary gain.

Acute Treatment

When treating individuals with acute post-concussive headache, a transitional approach (similar to what is used in the treatment of cluster headache) is often most appropriate when the physiology involves a transient process. A transition approach factors for physical and cognitive activity, tolerance with short-acting medications, and even interventional procedures such as nerve blocks and physical medicine.

Some patients may do well with over-the-counter (OTC) medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or diphenhydramine. Due to risk of medication overuse headache, it is best to avoid combination medications such as acetaminophen/aspirin/caffeine, which often need to be taken multiple times per day until the concussion resolves. It is also worth considering that patients have likely tried several OTC medications before arriving at the neurologist’s office. Preventive medications are usually not required, because a majority of the headaches resolve within a month. Moreover, these types of medicines often take weeks to show effect and may have significant side effects.

For patients who do not respond to OTC medications, triptan medications—either oral, nasal, or via injection—or NSAIDs are the next logical choice. A study presented at the 2017 American Headache Society Annual Meeting suggested that prescription NSAIDs (e.g., diclofenac, ketorolac, indomethacin, and meloxicam) may be more effective than triptans and ergots in aborting PTH. If the patient does not respond consistently to the previously mentioned medications, a triptan may be combined with an OTC NSAID, such as naproxen. Dihydroergotamines (e.g., DHE-45, Migranal) are excellent alternatives for triptan non-responders. Prescription NSAIDs can be added to a triptan or DHE-45, or used alone in patients who have contraindications to the use of the previously mentioned medications. As in the case with any headache type, narcotics and butalbital- or caffeine-containing compounds should never be used, because they have minimal effects on the hypothesized neurovascular process of migraine and are the main culprits in triggering medication overuse headache.

Another approach is to use NSAIDs or corticosteroids, either alone or in combination with a long-acting triptan (naratriptan or frovatriptan) as transitional medications for the first seven to 10 days after an initial head injury. Of note, NSAIDs should not be started until after the first three days due to the risk of delayed bleeds (e.g., subdural, epidural, and subarachnoid).

For those patients who prefer not to take medications or for whom these medications are not effective, peripheral nerve blocks provide a treatment option and are widely used to treat PTH. Common sites include the greater occipital nerve (GON), lesser occipital nerve, auriculotemporal nerve, supraorbital nerve, supratrochlear nerve, and

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sphenopalatine ganglion. Interventions include blocking a single nerve unilaterally or bilaterally or blocking multiple nerves (usually bilaterally). The supraorbital nerve, supratrochlear nerve, and auriculotemporal are branches of the trigeminal nerve, whereas the GON and lesser occipital nerve are derived from the dorsal and ventral rami of C2-4.11-14 Typical anesthetics include bupivacaine (0.25% to 0.75%) or lidocaine (2%), with volumes ranging from 0.5 to 2cc per site. Local anesthetics inhibit conduction through nerve fibers by reversibly inhibiting sodium channels and can act on the unmyelinated C-fibers and the thinly myelinated A delta fibers that mediate pain.15 Local anesthetics can be given alone, combined with each other and/or with a steroid, usually triamcinolone.

The addition of steroids in nerve blocks for non-cluster headaches has never been shown to be efficacious.16 However, steroids should never be used in the forehead area due to the risk of tissue necrosis and unwanted adverse cosmetic side effects. Numerous injection techniques are currently being utilized, including ultrasound-guided occipital nerve blocks, which have been shown to be effective in a single case report.17 Another possible target in treating PTH is the sphenopalatine ganglion block. Recent advances in equipment have allowed for the intranasal blockade of the sphenopalatine ganglion. These blocks are easy to administer and are preferred to conventional nerve blocks by patients who have significant fear of needles as well as children. Of note, one drawback with the use of nerve blocks in general is they are not paid for by most insurance carriers.

Despite the variety of management options, the most important treatment for acute PTH is physical and cognitive activity to tolerance, with the institution of light non-aerobic exercise at approximately day five. Patients who over-exert themselves cognitively and/or physically will likely experience worsening symptoms, including headache. There are no medications or other available treatment options to counteract or speed up recovery from the metabolic and blood flow abnormalities seen with concussion.

Subacute Treatment and Preventive Medications

Patients who continue to experience PTH for more than a month with a frequency of more than eight headaches per month may benefit from prophylactic treatment. Unlike migraine prophylaxis, preventive treatment options for patients who suffer head trauma are somewhat limited, because many standard preventive measures can worsen associated symptoms. The best option may be tricyclic antidepressants (TCAs), though amitriptyline should be avoided due to anticholinergic effects that can worsen cognitive symptoms. Antiepileptic medications (AEDs), which are the mainstay of preventive migraine treatment for most neurologists, are not good options in patients with concussion and especially patients with mild TBI and TBI in whom neurocognitive deficits are common. Not only can these medications worsen neurocognitive symptoms, but they can also cause sedation (which patients with concussion and some individuals with mild TBI and TBI already experience), and require prolonged titration and weaning schedules. These schedules can prolong return to play or to the battlefield for athletes and those in the military. One of the worst offenders is topiramate, a widely prescribed preventive migraine medication that can cause unwanted weight loss and worsen psychomotor retardation. These recommendations contradict findings showing that topiramate was felt to be an effective headache prophylactic therapy in military troops with chronic PTH, whereas low doses of tricyclic antidepressants appeared to have little efficacy.10 Importantly, the study in question did not examine side effects, and the benefit was modest (i.e., a 23 percent reduction in headache frequency). It was also not controlled and did not involve the use of headache diaries.

Another medication that should be used with caution or avoided altogether is valproic acid, which can also cause psychomotor retardation, birth defects, as well as weight gain, and hair loss. Beta-blockers and calcium channel blockers can lower pulse and blood pressure, which could worsen underlying autonomic dysfunction that individuals with concussion often experience. Beta-blockers are also sedating. If considering using an AED, zonisimide (Zonegran, Eisai), 50mg to 100mg twice daily may be the best option. This medication has a similar mechanism as topiramate but without the cognitive side effects. Other options include leukotriene receptor antagonists such as montelukast (Singulair, Merck) and zafirlukast (Accolate, AstreZeneca), which are hypothesized to inhibit the neurovascular inflammatory response (i.e., mast cell activation and overactivity). They are each associated with minimal side effects and have a proven safety record in children, however, their efficacy has not been demonstrated in class I trials.

Another interesting possibility is memantine, which has been shown in retrospective studies as an effective migraine prophylactic.18 It is an NMDA receptor antagonist and appears to inhibit cortical spreading and depression—seen both in concussion and migraine. It may also be protective and improve associated concussion and TBI symptoms. Finally, class I evidence indicates that certain vitamins, including magnesium oxide 200mg to 400mg per day, whole leaf feverfew, riboflavin, and petasites root, alone or in combination, are effective in preventing migraine. Given their low side effect profile and ease of use,
these agents would be excellent initial options to consider. In addition to oral medications, patients may benefit from cognitive behavioral therapy using modalities such as biofeedback and meditation. Nerve blocks continue to play a role in management and have shown to be effective in preventing PTH in a number of studies.\textsuperscript{19,20}

Importantly, the possibility that headaches are triggered by the cervical spine should not be overlooked. A good musculoskeletal exam looking for trigger points, tenderness over the spinous processes, and decreased range of motion should be part of the initial evaluation. In patients with significant musculoskeletal dysfunction, a combination of physical medicine and trigger point injections may help to lower the patient’s headache frequency. Trigger points of the head and neck are often associated with various headache disorders.\textsuperscript{21} Therefore, in theory, amelioration of trigger points in the head and neck should result in a decrease in headache. As is the case with peripheral nerve blocks, trigger point injections can be performed with lidocaine and/or bupivacaine, and steroids are also often used.

Other methods to alleviate trigger points include dry needling (i.e., no medication is injected) and the use of manual therapy and transcutaneous electrical nerve stimulation. Unfortunately, there are no studies looking at the treatment of trigger points in post-traumatic headache. There are, however, studies examining the treatment of trigger points in cervicogenic headache (CGH). A retrospective analysis of 147 patients found improvements in headache (57 percent), neck pain (52 percent), and dizziness (46 percent), after receiving combined GON blocks and cervical trigger point injections.\textsuperscript{22} There are also very few studies that specifically look at physical therapy, massage therapy, spinal manipulation and mobilization as a treatment for PTH.

Numerous studies have assessed the aforementioned modalities in CGH and include patients with mild TBI and TBI. Anecdotal evidence from thousands of patients from our clinic (most of whom have episodic and chronic PTH secondary to mild TBI/concussion) who were treated with neuromuscular/physiotherapy (i.e., massage, myofascial release, traction, ultrasound, electrical stimulation, heat, ice, and therapeutic exercise) in conjunction with medications and other interventional techniques, shows a significant improvement in PTH in patients who undergo adjunctive neuromuscular and physiotherapy compared to those who do not. It is also our experience that most if not all patients with PTH have pain and/or spasm in the cervical muscles, suboccipital muscles, and over the temporalis region, which when palpated can reproduce headache symptoms. These findings are also consistent with the observations of other headache specialists. A few small studies are also supportive.\textsuperscript{23-25}

Two other modalities that have received considerable study (especially with respect to chronic PTH) are spinal manipulation and mobilization. Cervical spinal manipulation is a technique often used by chiropractors and involves high-velocity low-amplitude localized force directed at cervical joint segments, whereas spinal mobilization involves low-velocity, low-amplitude movements with the patients range of motion and is often used by osteopathic physicians and physical therapists.\textsuperscript{26} When addressing the cervical spine, mobilization techniques are safer than manipulation techniques, which can be associated with adverse effects (i.e., disc herniation and arterial dissection). Moreover, in individuals with concussion, the high-velocity forces used in manipulation can actually reproduce the angular and rotational forces that result in concussion, thus potentially resulting in a second concussion.

Despite these potential issues, a number of studies examined cervical manipulation as a modality to treat primary headache disorders. A majority are prospective or retrospective case analyses.\textsuperscript{27,28} Another article identified six studies employing spinal manipulative therapy to treat CGH.\textsuperscript{27} There were numerous methodological flaws in all of the studies ranging from participants experiencing intermittent headaches, lack of treatment in the control group, small numbers of participants and a lack of serial treatments. The authors conclude the spinal manipulation may be an effective treatment for CGH, however better studies are needed.

Conversely there are few studies looking at manipulation. One article comparing the efficacy of spinal mobilization with that of massage therapy found that those in the mobilization group experienced statistically significant reductions in all variables when compared to the massage group.\textsuperscript{26}

**Treatment of Chronic PTH**

Approximately 15 percent of patients will go on to develop persistent PTH attributed to mild or moderate
to severe head injury. These patients have headaches for more than three months and are out of the physiological window for concussion, with most having normal neurological exam results. Many also meet the International Headache Society criteria for chronic migraine (CM). It is difficult to determine whether these cases represent a continuation of the concussion, if the patient developed chronic post-traumatic migraine, or if it is another primary headache disorder.

Assuming these patients have tried most if not all of the treatment modalities already discussed and are experiencing more than 15 headache days per month, the best option for these patients is onabotulinumtoxinA (Botox, Allergan), which is the only FDA-approved treatment for chronic migraine. Some case reports have shown efficacy in the treatment of chronic post-traumatic headache with onabotulinumtoxinA.29-32

The most extensive study to date retrospectively looked at the charts of 63 servicemen between 20 and 50 years old with chronic PTH.29 Of those, 36 patients (56.3 percent) had more than one type of headache, 10 (15.6 percent) had more than two headaches, and 48 (75 percent) had continuous headache. Individuals were injected using the current FDA-approved protocol of 31 fixed-site injections (five units per site), with additional injections being placed in a fixed dose to follow the pain paradigm. Some patients had a combined diagnosis of cervical dystonia and chronic PTH and underwent injections to follow the pain FTP pattern. The mean number of injection cycles was 3.3, with 30 patients receiving only one set of injections. Notably, 41 patients (64 percent) reported that they were “better” after treatment, 18 were unchanged, two were worse, and three were lost to follow-up. In addition, 18 (29 percent) continued to undergo treatment, while 26 (43 percent) discontinued therapy due to lack of efficacy. About half of the patients continued on active duty or were redeployed and the other half either retired or were discharged (all but one for medical reasons). The most significant variable for lack of efficacy appeared to be the presence of continuous headache prior to treatment.

Finally, the authors suggested that the discrepancy in efficacy when compared to the Phase 3 FDA studies may be the result of issues with secondary gain in the treatment population.29

Finally, some patients with PTH may also have suffered concomitant trauma to their cervical spine, whereby the underlying cervical pathology may be a “trigger” for their headaches. These patients may benefit from interventional procedures such as trigger point injections, epidural injections and facet blocks. Finally, a small number of patients will become refractory, and these individuals are excellent candidates for peripheral nerve stimulation.

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