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General

Review of Interventional Therapies for Refractory Pediatric Migraine

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This is a review of the latest and seminal evidence in pediatric migraine. It covers the etiology and pathophysiology known today, and then will review treatment options, efficacy and safety, quality of data and indications. Though migraine is usually regarded as an infliction in adults, it is not uncommon in the pediatric population and affects up to 8% of children. Children may experience migraine differently than adults, and present not only with headache but also frequent gastrointestinal symptoms. They are frequently shorter in duration than in adults. Traditional migraine treatment in adults is less effective in children. In this population, adjunct therapies – such as interventional techniques – should be considered when traditional treatment fails, including Botulinum Toxin A (BTA) injections, peripheral nerve and ganglion blocks. BTA injections are FDA approved for migraine prophylaxis in adults, but currently not in children; however, recent evidence shows efficacy and safety in pediatric migraine management. Nerve blocks stop nociceptive afferent fibers through injection of local anesthetics, and it may be associated with the local injection of corticosteroids. Although more common in adults, recent data suggests they are safe and effective in children and adolescents. Blocking the sphenopalatine ganglion can be achieved through nasal approach, and achieves a similar action by blocking the entire ganglion. Interventional techniques may provide a key component in the alleviation of this otherwise debilitating chronic migraine pain. Though most studies have been performed in adults, new studies provide encouraging results for treatment in children.

INTRODUCTION

Chronic migraines can be devastating for children. Migraine can affect schoolwork, group participation, interpersonal relationships, and may impact the child's mental health.[1] Chronic migraine is defined as a headache for more than 15 days per month over at least three months, with a minimum of eight days with classic migraine symptoms of aura, nausea, vomiting, photophobia, or phonophobia.[1] Headaches are frequent among pediatric patients. Migraines affect approximately 8% of children and are even more frequent during adolescence.[2] Pediatric migraine symptoms may be similar to those of adult migraines. However, young children may have difficulty identifying or explaining the symptoms of their migraine and may present instead with predominantly gastrointestinal symptoms, in-

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cluding abdominal pain, nausea, and vomiting.[2] Pediatric migraines are also commonly shorter in duration than adult migraines, and this may cause difficulty with treatment or even dismissal of the child's pain.

First-line treatment of migraine headaches among adults includes non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, triptans, and antiemetics. Few medications show evidence-based superiority over placebo in children, however, and chronic use of these medications may include significant side effects including medication overuse headache. Furthermore, oral medication may be inadequate to control the child's symptoms.[3,4] When symptoms are refractory to medical management, interventional therapies may be considered as an adjunct or alternative. Here we review the emerging scientific evidence for the use of interventional procedures in the management of chronic pediatric migraines.

BOTULINUM TOXIN A

OnabotulinumtoxinA is the only Botulinum toxin derivative approved for chronic migraine treatment in adults by the Food and Drug Administration (FDA). Botulinum toxin A affects the SNAP-25 protein in the SNARE complex at the pre-synaptic neural cleft.[5] The disruption of SNARE, in turn, inhibits vesicle fusion and release of acetylcholine, resulting in flaccid paralysis of the targeted muscles.[5] Also, there is some evidence that the botulinum toxin also affects the release of proinflammatory neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P, in peripheral sensory neurons.[5] CGRP and substance P are thought to contribute to migraine initiation and central sensitization.[6]

Botulinum toxin is generally well tolerated when used in the treatment of chronic migraine. Adverse effects are generally transient and mild in most patients. The most common adverse effects include weakness or pain in muscles around the injection site, headache, and injection-site hemorrhage.[7] In the analysis of the COMPEL study, only one serious treatment-related adverse event, a generalized rash, was found in patients treated with botulinum toxin.[8] Ptosis, neck pain, and stiffness were also reported as adverse effects.[8]

In the limited evaluation of botulinum toxin in pediatric patients, the side effect profile appears comparable to adults. Flu-like symptoms and arm paresthesia were the two most common adverse effects reported in the study conducted by Ahmed et al.[9] In the retrospective review conducted by Kabbouche et al., only 8 of 131 pediatric patients experienced any side effects.[10] Of the eight, pain at the injection site, eyelid inflammation and pain, and neck and shoulder myalgia were the reported adverse events. Contraindications to use include hypersensitivity reaction to OnabotulinumtoxinA or active infection in any of the injection sites.[11]

BOTULINUM TOXIN IN ADULTS

The most updated definition of chronic migraine is a headache present for at least 15 days each month, for more than three months.[12] In addition, at least 8 of these 15 headache days must classify as a migraine headache for greater than three months.[12] In contrast, episodic migraine is defined as 14 or fewer days of headaches in a month.[12] Most of the research concerning the use of botulinum toxin A in migraine treatment has been conducted in the adult population.

Botulinum toxin type A was first approved for use in chronic migraine based on the results from the PREEMPT 1 and 2 trials.[13,14] In both trials, there were significant improvements in headache days per month compared to baseline, and participants experienced relatively few side effects.[13,14] Following FDA approval, the COMPEL study was undertaken to gather further data on the efficacy of OnabotulinumtoxinA.[8] Since then, many different studies have been conducted to evaluate the efficacy of botulinum toxin A in adults with chronic migraine.

The most recent Cochrane systematic review evaluating the efficacy of botulinum toxin treatment in chronic and episodic migraine included 90 articles involving 26 total trials.[6] The data from this review highlighted a 2-headache-day reduction per month for patients with chronic migraine, which was supported with a high quality of evidence.[6] In contrast, due to the low quality and volume of evidence for the use of botulinum toxin type A in patients with episodic migraine, authors were unable to draw any conclusions for the efficacy in this patient population.[6]

Currently, NICE recommendations for botulinum toxin type A are to use it for prophylaxis in chronic migraine patients who have failed three or more migraine prophylaxis medications and do not have medication overuse.[15]

BOTOX IN CHILDREN

Few studies investigate the use of botulinum toxin type A in children. Currently, there is no FDA approval for the use of botulinum toxin type A in the pediatric population for migraines. However, some retrospective studies have shown promise for this treatment option in refractory pediatric migraines.

Recently, Ali et al. published a retrospective analysis involving 30 pediatric patients with chronic migraines who were treated with botulinum toxin type A injections.[16] Each patient received a standard regimen of 31 injections with five units of Botox in each, plus an additional six injections if myofascial pain was elicited, for a total of 185 units of OnabotulinumtoxinA.[16] Investigators found a statistically significant reduction in both headache frequency and headache severity after an average of 2.47 Botox cycles.[16] Headache frequency decreased from 24.4 ± 7.49 to 14.8 ± 12.52 painful days per month.[12] Headache severity was measured on a visual analog scale and decreased from 7.47 ± 1.89 to 4.34 ±3.02.[16] One patient developed post-injection nausea; the treatment was otherwise well tolerated in all patients.[16] It is important to note that in this trial, the sample size was limited and there was no control group

with placebo treatment. Still, the results of this study are promising, with significant decreases in migraine frequency and severity for children affected by chronic migraine.

Another recent retrospective study demonstrated similar findings. Patients between ages 8-17 with refractory migraine were included in the study, for a total of 10 subjects.[17] OnabotulinumtoxinA injections were based on the PREEMPT protocols, with an increased dose of up to 190-200 units per session, based on each patient's migraine symptoms and pain.[13] For primary outcomes, investigators found a statistically significant decrease in headache frequency from 15.5 migraine days/month pretreatment to 4 days/month post-treatment.[17] In addition, the median migraine duration had a statistically significant decrease from 8 hours to 0.75 hours after treatment.[17] Finally, their third primary outcome measure was the median migraine intensity, which also had a statistically significant decrease from 6 to 4 on a visual analog scale.[17] Looking at the clinical impact of the OnabotulinumtoxinA treatment, between pre and post-treatment, patients had a 2-point decrease in median head pain scores, which translates to a clinically significant improvement in chronic pain.[17] There were few reported adverse events overall, and the most common side effects included injection site pain and tenderness.[17] Both studies suggest that botulinum toxin A injections were effective and well-tolerated in children with refractory migraines.

SUMMARY

In conclusion, while there have been limited studies looking into the efficacy of botulinum toxin in pediatric migraine patients, preliminary findings are promising. The most recent retrospective studies show statistically significant decreases in migraine frequency and severity with Botox therapy in pediatric patients with refractory chronic migraines. In addition, the patients in these studies tolerated the botulinum toxin injections well, with minimal side effects.

This therapy is currently approved for adults with chronic migraines and is typically given after patients have failed conservative treatment. Based on current evidence of the efficacy and the tolerability of this therapy, pediatric patients who have failed more conservative therapy may respond well to botulinum toxin therapy. As there is no FDA approval for its use in children, larger randomized controlled trials need to be conducted to build on current evidence to solidify the role of botulinum toxin type A in the management of refractory chronic migraine in the pediatric population.

OCCIPITAL NERVE BLOCK AND PERIPHERAL NERVE BLOCKS

Peripheral nerve blocks (PNBs) are commonly used in the treatment of headache disorders. These include primary headache disorders such as chronic migraine, status migrainosus, cluster headache, hemicrania continua, and new daily persistent headache (NDPH); or secondary headache disorders such as cervicogenic headache, post-traumatic headache, post-dural puncture headache, and cranial neuralgias.[18–20] Commonly targeted nerves include the greater occipital nerve (GON), lesser occipital nerve (LON), and branches of the trigeminal nerve, such as the auriculotemporal, supraorbital, and supratrochlear nerves.[21] Blocks consist of local anesthetic with or without the use of additives such as corticosteroids. Corticosteroids improve headache remission in cluster headache patients receiving PNBs but have had mixed results in migraine patients and frequent adverse effects such as cutaneous atrophy in PNB of trigeminal branches.[22–25]

The mechanism of PNBs involves modulation of central pain receptors. PNBs disrupt the normal connection that exists between nociceptive meningeal afferent fibers and cervical afferent nerves, such as the GON, at the second-order neuron level.[26] Adverse effects of PNBs include allergic reactions, including anaphylaxis, vasovagal reactions, nerve damage, infection, syncope, hematoma, hypotension or hypertension, alopecia, and cutaneous atrophy. PNBs should be used cautiously in-patient populations that are more susceptible to the AEs, such as the elderly and patients on anticoagulation therapy.[21] Open skull defects or craniotomies are also contraindications for PNBs of the head and neck.[27,28]

EVIDENCE FOR USE IN ADULTS

A recent survey highlighted in a systematic review of PNBs showed that 69% of headache specialists use PNBs in the treatment of their adult patients.[29] A randomized controlled trial (RCT) of 105 adults with triptan-overuse headache found that GON blocks were effective in reducing the number of headache days, the severity of pain, and triptan need. The patients were randomized into three groups: the first group only discontinued their triptan, the second group discontinued their triptan, and received a single GON block, and the third group discontinued their triptan and received a three-stage GON block. Both groups receiving GON block experienced significantly fewer headache-days post-treatment when compared to the pre-treatment period. Patients who received GON block also reported significant decreases in pain severity and reduced triptan use.[30] A prospective study of 44 adults with occipital neuralgia yielded similar results. Patients received either unilateral or bilateral injections in the GON alone or both the LON and GON. At six months post-injection, pain scores, and analgesic medication necessity were significantly decreased.[31] Although these studies focused on the use of PNBs in adults, these results are starting to be applied to the pediatric population.

EVIDENCE FOR USE IN CHILDREN

Though most existing evidence evaluating PNBs for headache disorders stems from adults, new evidence has emerged demonstrating feasibility and efficacy in pediatric populations. In a recent practice pattern survey of 41 pediatric headache specialists, 80% of physicians indicated that they regularly use nerve blocks in their pediatric patients

for more than one headache disorder, with 63% performing nerve blocks themselves. Chronic migraine with status migrainosus was the most common indication for nerve blocks, as expressed by 82% of respondents.[18] Early evidence for the use of PNBs to treat headache disorders in pediatric populations is provided by a case series consisting of three patients (two teenagers and one adult) with occipital neuralgia secondary to a sports-related concussion. After undergoing unilateral GON block, patients achieved 100% relief from all symptoms with duration ranging from eight hours to two months.[32] Similar results were observed in another case series involving 14 teenage patients with post-concussion syndrome and subsequent occipital neuralgia. These patients received GON blocks (bilateral in most) with a lidocaine and triamcinolone solution. Headache frequency was reduced by 50% or more in 64% of patients, and mean headache days per month decreased from 26 to 17. Patients also reported improvements in concussion symptomatology and quality of life. The only adverse event reported was temporary alopecia in one patient.[33] A retrospective case series of 28 adolescents with post-traumatic headaches who were treated with PNBs of the scalp further demonstrated the efficacy of PNBs in headache relief. Immediately post-treatment, 71% of patients reported complete headache resolution with a 94% mean reduction in headache intensity. At 24 hours post-treatment, 93% of patients still experienced headache relief. The procedure was well tolerated, with only three patients reporting minor adverse events, such as injection site swelling. A follow-up survey showed nearly unanimous satisfaction with the treatment, evidenced by 91% of patients indicating that they would recommend PNBs to friends with post-traumatic headaches.[34]

A retrospective chart review of 46 pediatric patients with chronic primary headache disorder (76% having chronic migraines) who received unilateral GON blocks with lidocaine and methylprednisone demonstrated the efficacy of PNBs in treating headache disorders other than post-traumatic headache. There was a mean benefit duration of 4.7 days, with 53% of patients reporting some benefit and 52% reporting significant benefit. In patients with chronic migraines, 56% benefitted, and 62% significantly benefitted. Significant benefit was defined as a decrease in headache frequency, intensity, or duration by at least 33% for at least one month or patient-reported significant or substantial improvement in headache for at least one month. Some benefit was defined as documented improvement in headache symptomatology that does not meet criteria for significant benefit. Adverse events included transient lightheadedness (20%) and brief injection site soreness (10%), with one patient reporting prolonged soreness.[35] An additional retrospective chart review assessed 159 patients who primarily had either chronic migraine (79%), NDPH (14%), or trigeminal autonomic cephalalgia (4%). The patients received GON blocks with lidocaine and methylprednisolone, resulting in headache improvement for a mean duration of 9 weeks and a minimum duration of 3 weeks. Improvement was greatest in migraine patients with 68% reporting relief. Adverse events were reported in 12% of patients and included temporary headache worsening, injection site soreness, and allergic reaction in one patient.[36] A published conference abstract showed similar results in 38 teenage girls with chronic daily headaches secondary to fibromyalgia who received bilateral GON blocks with bupivacaine and methylprednisolone. At two weeks post-treatment, 61% reported some improvement in pain and function. At two months post-treatment, 76% reported some improvement in pain and function.[37]

Additional evidence for the use of PNBs in children with migraines was provided by a study of 17 children who received GON blocks for chronic refractory migraines. The GON block consisted of lidocaine and methylprednisolone and sought to measure the complete or partial resolution of headache at two weeks. Results were encouraging, with 70% of patients reporting complete resolution and 9% reporting partial resolution. Minor adverse events occurred in some patients, including injection site soreness, temporary worsening headache, and transient dizziness.[38] In a retrospective chart review of 137 pediatric patients, PNBs were demonstrated to be moderately effective in reducing headache symptoms at 24 hours, with 53% of patients reporting improvement 24 hours post-treatment and 16% of patients reporting worsening headache or significant adverse events. The study also compared the use of lidocaine alone or in combination with bupivacaine. Combination lidocaine/bupivacaine was significantly less likely to result in headache improvement within 24 hours than lidocaine alone (OR = 0.26).[39]

SUMMARY

PNBs are widely used in the treatment of adult headache disorders and are proven to be an effective treatment. Based on their success in adults, PNBs have cautiously been integrated into the regular treatment regimen for headaches in pediatric patients. Numerous studies have demonstrated that PNBs are effective in reducing headache duration and intensity, particularly in migraine disorders in children. However, most existing studies are case reports and retrospective chart reviews, highlighting the necessity for additional, more conclusive studies. PNB use in pediatric patients has a low risk of adverse events and may serve as prevention and treatment for medication-overuse headaches.

SPHENOPALATINE GANGLION BLOCK

Sphenopalatine ganglion (SPG) blocks are used in the management of refractory migraine headaches among adults. It is also used in the management of additional headache disorders, trigeminal neuralgia, and atypical facial pain. The SPG is an extracranial ganglion that is located within the pterygopalatine fossa and contains autonomic, motor, and sensory neurons.[40] SPG block can be achieved by using one of multiple techniques. These most commonly include passing a cotton-tipped applicator soaked in local anesthetic through the nose or oral cavity to facilitate mucosal absorption of local anesthetic over the sphenopalatine gan-

glion.[41] Local anesthetic can also be delivered using an infratemporal injection or can be applied to mucosa endoscopically using a trans-nasal approach. SPG block is traditionally reserved for adults with migraine refractory to first line abortive treatment or medication overuse headache.

SPHENOPALATINE BLOCK IN ADULTS

Among adults, emerging evidence suggests that SPG may be both safe and effective. In a 2018 prospective study conducted by Binfalah et al., researchers performed SPG block on 55 adult patients with refractory migraine symptoms.[40] Study results indicated that more than 70% of patients were headache-free at 15 minutes, 2 hours, and 24 hours post SPG block. Similarly, in a 2019 retrospective study, the results of eighty-eight consecutive patients undergoing SPG block for refractory migraine were studied.[41] Patients rated their pain a 1-10 Likert scale both pre-procedurally and 30 minutes after SPG block. Results were notable for a 67% reduction in pain scores at 30 minutes post-SBG-block, which correlated to an average of a 5-point reduction on the Likert pain scale.

SPHENOPALATINE GANGLION BLOCK IN CHILDREN

Though SPG block is becoming well established as a treatment modality in adults, little is known about the use of SPG block in children. In a published abstract from the 2017 annual scientific meeting for the Society of International Radiology, the outcomes of 310 SPB blocks in 200 pediatric patients aged 7-18 with refractory chronic migraine is reported.[42,43] Patients again rated their pain on a 1-10 scale both before and after treatment. Headache severity decreased by an average of 2 points at 10-minutes post-treatment. However, while these results are promising, the study remains unpublished, and without a stronger description of methodology and results, the quality of evidence is very low. A quadruple blinded, randomized, placebo-controlled trial is currently in its recruitment phases at Newark Beth Israel Medical Center and may provide a much-needed evaluation of the use of SPG block in pediatric migraine.[44]

SUMMARY

SPG block is an effective treatment for adult chronic migraine that fails abortive therapy. As a minimally invasive therapy that can be applied injection-free via a trans-nasal cotton swab while providing a medication-reducing alternative treatment, SPG blocks may have a role in the future treatment of refractory pediatric migraine. However, presently, high-quality evidence is lacking to support the use of this procedure.

CONCLUSION

While migraines are usually considered an adult infliction, they affect a significant proportion of children and adolescents. In this sensitive population, the effects of chronic headaches can be devastating and include mental health consequences, educational delay, and reduced performance. Though the pathophysiology is believed to be similar, the presentation is more variable and may include gastrointestinal and non-specific symptoms on top of a headache. Traditional therapy used in adults is less effective in children and fails more often. Interventional techniques, such as BTA injections, GON, and SPG blocks, may provide relief where traditional treatments fail. Though these therapies have been investigated mostly in adults, encouraging results displayed both efficacy and safety in the pediatric population.

More research is required to obtain higher quality evidence to support these treatments in children and adolescents and to elucidate their safety profile properly. However, recent results have been positive, and it is likely that we will encounter these treatments in younger patients more often in the near future.

ETHICAL CONSIDERATIONS

HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE)/ IRB manager issued study exemption # 2022-744.

DISCLAIMER

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