Refractory migraine: a cerebrovascular disease?

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DEFINITION, PREVALENCE, AND COSTS
Migraine is a common and disabling neurological disorder that is estimated to affect nearly 40 million people in the USA and 10% of people worldwide.1 The cost of migraine is extraordinary. The estimated annual US healthcare costs in 2010 for migraine were associated with outpatient visits ($3.2 billion), ER visits ($700 million), and inpatient hospitalizations ($375 million), and have continued to increase yearly since then.2

The term ‘refractory migraine’ is typically used to describe migraine that persists despite treatment.3 This can be most rigorously defined as patients who have failed to respond to two of the available preventative medication classes plus either onabotulinumtoxinA (Botox; Abbvie, Chicago, IL), calcitonin gene-related peptide (CGRP) receptor antagonists (gepants, e.g., ubrogepant, atogepant, rimegepant), or CGRP monoclonal antibodies; and suffer from at least eight debilitating headache days per month for at least 6 consecutive months. Status migrainosus describes an unremitting migraine attack that does not respond to medications, lasting 72 hours or more.4

The prevalence of refractory migraine varies widely in different epidemiological studies, but is estimated to affect between 5–30% of migraine sufferers5—translating to between 2 and 12 million patients in the USA per year. The incidence of migraine and refractory migraine far outstrips the incidence of any diseases we commonly see in practice as cerebrovascular physicians.

EVIDENCE FOR A NEUROVASCULAR ETIOLOGY
The role of the neurovasculature in migraine remains a controversial and complex area fraught with inconsistent and conflicting observations.6 The effectiveness of vasoconstricting ergotamines, one of the original and primary treatments for migraine, formed the basis for the notion that vasodilation plays a role in migraine pathogenesis.7,8 Similarly, the ability of vasoconstrictive medications to reliably induce migraines in susceptible patients further substantiated this hypothesis.9,10

The middle meningeal artery (MMA) has specifically been a focus of many of these investigations. Migraines, whether spontaneous or medically induced, have been reported to be associated with dilation of the MMA ipsilateral to the side of the headache.11–14 Correspondingly, the resolution of headache after treatment has been, in some studies, reported to correlate to a normalization in the caliber of the MMA. However, several additional studies examining the dilation or constriction of the MMA in migraine have either failed to corroborate these findings or have contradicted them.15

More recently, some have argued that vasodilation is an epiphenomenon which does not directly contribute to migraine. The vasoactive molecules, like CGRP and nitric oxide, which induce migraines also cause subsequent vasodilation.16 Other substances which induce vasodilation without neurogenic inflammation, such as vasoactive intestinal peptide, do not induce migraine.17 As such, inflammation of the meninges and meningeal vessels, rather than only their caliber, may be the key inciting mechanism.18 The dura is a well-vascularized structure, which is densely innervated by pain fibers.19 Some investigators have invoked a theory which incorporates both phenomena, suggesting that the dilation of dural vessels activates perivascular nerve fibers to release inflammatory factors. These factors not only activate local nociceptors, but incite further regional vasodilation and the release of additional inflammatory factors, inducing a positive feedback cycle.20

Thus, despite many studies performed to delineate a neurovascular basis for migraine, no consistent hypothesis has been established.21 While the failure to identify a consistent vascular mechanism underlying migraine is vexing, it is not surprising. ‘Migraine’ may be a final common non-specific symptom resulting from a myriad of different pathophysiologies. As such, it is likely that while a subset of migraine patients may have an underlying disorder of neurovascular regulation, it may not be generalizable across all patients with the diagnosis.

USE OF LIDOCAINE TO TREAT MIGRAINE
Lidocaine, first introduced in the 1940s, is one of the oldest and most widely used anesthetic and analgesic agents in medicine. There are multifold applications of lidocaine, most commonly to achieve local anesthesia and as a cardiac antiarrhythmic.22 Lidocaine has been administered by nearly every known route of administration—as topical, subcutaneous, epidural, intravenous (IV), and intra-arterial (IA) injections, in addition to oral, nasal, and aerosolized respiratory preparations. The mechanisms of action, drug interactions, side effects, toxicity, and maximal doses are well understood. The use of IV lidocaine for the treatment of pain has been well documented and is believed to be primarily related to its ability to block voltage-gated sodium channels, a synergistic effect with opioids, as well as various other potential activities inhibiting additional mechanisms of pain transmission.23–25

IV lidocaine has been used with some success for the treatment of chronic daily headache, severe refractory migraine, and status migrainosus. In some centers, lidocaine can be offered as a continuous infusion over several days to achieve headache relief.26,27 These types of infusions require in-patient hospitalization and close observation as the doses administered may approach or exceed the average toxicity threshold for lidocaine, which is reported to be approximately 4.5 mg/kg. Chronic
daily headache patients treated with continuous IV lidocaine infusions (ranging between 1–4 mg per min) for a week or more have shown remarkably high rates of symptomatic relief in several series. For example, Williams et al reported improvement in 90% at discharge. However, more striking than the acute response, 70% of patients in their series still reported symptomatic improvement at 6 months. Schwenk et al described 609 inpatients undergoing IV lidocaine infusion therapy for refractory migraine. They reported a 90% acute response rate, with a sustained response at 1 month in 43%. Lidocaine is rapidly metabolized in the liver with an average terminal elimination half-life of 1.5–2 hours (slightly longer for prolonged infusions), indicating that its mechanism of action in headache is related to an effect that persists far beyond the original receptor interaction. In general, the prolonged effect of IV infusion therapy has been attributed to lidocaine ‘breaking the cycle’ of chronic pain.

**INFUSION OF LIDOCAINE INTO THE MMA TO TREAT MIGRAINE**

Considering that the ‘vasocentric’ theories of migraine have focused on the MMA and dural pain receptors, the concept of a direct infusion of lidocaine into the MMA is certainly attractive. Such a route of administration achieves a substantially higher local concentration of lidocaine directly at the proposed site of primary pathology, potentially achieving better effectiveness while avoiding the potential systemic toxicity, time, and cost associated with continuous IV infusion therapy during prolonged inpatient admissions.

The IA administration of lidocaine into dural-meningeal arteries during neurointerventional procedures has been reported, typically to ameliorate the dimethyl sulfoxide-induced pain response and/or to avoid the trigeminocardiac reflex encountered during Onyx infusions.

Qureshi et al were the first to report on the effectiveness of bilateral intra-arterial lidocaine infusions into the MMA for patients with intractable headache. In these two small, but innovative, case series (reporting on two and four patients, respectively), all of the six treated patients experienced a substantial reduction in their headaches after the infusions. Similar to the responses observed with IV lidocaine, headache relief persisted well beyond the expected half-life of the lidocaine. Migraine Disability Assessment (MIDAS) scores were available for two of these patients 3 months after the IA infusions and were decreased in both.

The procedure is technically straightforward and can be performed under local anesthesia and often through a radial access. Following placement of a 5 French radial sheath, a Simmons-2 glide catheter is manipulated into the external carotid artery, and diagnostic angiography is performed to document the anatomy of the MMA. A microcatheter (0.017 inch or 0.021 inch internal diameter) is then manipulated into the main trunk of the MMA, proximal to the bifurcation of the anterior and posterior divisions, and superselective angiography is performed (figure 1). Next, 30 mg of cardiac preservative-free lidocaine (1 mg per mL normal saline) is slowly infused over 5–10 min into the MMA. The patient is awake and conversant and can easily be continuously neurologically monitored for ocular or facial nerve symptoms throughout the infusion. The infusions are performed bilaterally if possible.

A retrospective review (Stony Brook IRB2023-00498) of prospectively maintained databases at two institutions (Stony Brook Medicine, Stony Brook, NY, and University of Tennessee Health Sciences Center/Semmes-Murphey Clinic, Memphis, TN) identified a series of 14 patients with refractory headache who had undergone lidocaine infusions. All cases were performed under local anesthetic only, 12 of 14 were completed via radial access, and bilateral infusions were possible in 13 of 14 cases. Improvement in headache symptoms was observed in 10 with the duration of relief persisting for more than 1 month in all responders. Of the responders, nine experienced a gradual recrudescence of their headaches after 1 month, with only one patient reporting a maintained improvement in headache severity and frequency after

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**Figure 1** Lateral superselective angiograms of the right (A) and left (B) middle meningeal arteries demonstrate a conventional anterior and posterior branch pattern. No direct communication with the ophthalmic artery is noted on either side. The microcatheter was positioned distal to the foramen spinosum on each side; 50 mg of intra-arterial lidocaine was sequentially infused from each of these microcatheter positions over 10 min. Throughout the injection the patient was conversant and experienced no neurological symptoms. During the month before the injection, the patient reported debilitating migraines (rated 10 of 10) 25 out of 30 days and was not able to work. The first month after the infusions she reported her headache days were reduced to 15 of 30 days and the severity had significantly decreased. The second month, she reported 8 headache days and the third month, 3 headache days. She was able to discontinue rimegepant, gabapentin and onabotulinumtoxinA (Botox; Allergan) injections by the end of the third month. After the third month the patient was able to return to work.
3 months (figure 1). In one patient, the injection could only be performed unilaterally due to an ophthalmic origin of the MMA on one side. This patient was one of the four ‘non-responders’.

POTENTIAL FOR MMA EMBOLIZATION TO TREAT MIGRAINE

Experience with MMA-based interventions has rapidly escalated as MMA embolization with liquid embolics for the treatment of chronic subdural hematoma (cSDH) has become increasingly prevalent.32

One prominent observation among operators performing this procedure has been that headache and ‘head pressure’, frequent presenting symptoms in patients with cSDH, consistently resolve very early after MMA embolization, typically far before any evidence of radiographic resolution of the cSDH. Interestingly, Catapano et al reported on the effect of MMA embolization (MMAE) in patients with migraine or chronic severe headache.36

The authors examined their database of patients who underwent MMAE for cSDH and identified nine patients who, for at least 2 years before their presentation with cSDH, had suffered from chronic headaches. After MMAE with a liquid embolic, eight of the nine patients reported improvement in their headaches. Seven reported complete resolution. In six of the seven patients experiencing complete resolution, bilateral MMAE was performed. Of the eight patients with headache resolution, six reported sustained complete relief and one noted a continued decrease in headache frequency and severity at long-term follow-up (average follow-up 46 months, range 41–52 months, median 45 months). One patient had died from non-neurological causes before longer-term follow-up could be obtained.

A robust response to superselective MMA lidocaine infusion may be useful as a provocative tool to identify those patients whose headache syndromes are attributable to a primary pathology of the MMA and regional dura. If disordered regulation of the MMA is primarily responsible for inciting and/or maintaining these headache syndromes, these patients may ultimately benefit from permanent MMAE.

CONCLUSION

Migraine is a common, disabling, and costly disorder. The myriad of ‘migraine’ and ‘chronic refractory headache’ syndromes are possibly a final common pathway of a variety of different pathophysiological mechanisms. Existing data suggest that these headache syndromes may be related to a primary neurovascular disorder affecting the MMA and regional dural pain receptors in some patients. It is possible that this subset of patients (as opposed to those whose headaches are related to other mechanisms) would be more likely to demonstrate a favorable response to superselective lidocaine infusion into the MMAs. The procedure is technically straightforward, safe, and largely familiar to practicing neurointerventionalists, and is not substantially more invasive or costly than other treatments offered to this patient population. If validated in robust, prospective trials, it is feasible that selective MMA lidocaine infusion could represent an important addition to the armamentarium of techniques employed to manage patients with severe, refractory headaches and status migrainosus. If even just a fraction of the estimated 2–12 million US patients with refractory migraine were to achieve significant relief from these MMA procedures, it would profoundly expand the spectrum of patients who could benefit from neuroendovascular interventions.

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REFERENCES

2. Insinga RP, Ng-Mak DS, Hanson ME. Costs associated with outpatient, emergency room and inpatient care for migraine in the USA. Cephalalgia 2011;31:1570–5.