Peripheral nerve blocks (PNBs) have long been employed in the treatment of various primary and secondary headache disorders (1), are increasingly used in general neurological practice (2) and may be utilized by up to 69% of practitioners with expertise in the treatment of headache disorders (3).

The mechanism for PNBs in the treatment of headache disorders is not known. Clearly, the treatment effect is not based on a pure peripheral action. This principle is best demonstrated by the highest quality of evidence for PNBs in the treatment of cluster headache. A single (4,5) or repeated (6) injection with corticosteroid in the occipital or suboccipital region, targeting the greater occipital nerve (GON), derived largely from the C2 spinal level, effectively treats cluster headache, which is a trigeminal autonomic cephalalgia featuring pain in the ophthalmic division of the trigeminal nerve. In addition, pain relief from PNBs may not depend on the presence or duration of a pure local anesthetic effect (5), also evident by their reduction in allodynia contralateral to the side of injection (7) as well as photophobia (8). Presumably, GON blocks and other PNBs reduce nociceptive input into the trigeminocervical complex and lead to central descending inhibitory, secondary effects (8) in aborting an acute headache attack or shortening an acute cluster period.

There is a wealth of clinical experience and a heterogeneous evidence base suggesting PNBs as a safe and effective therapy in headache medicine, particularly cluster headache (1,3,9). However, for migraine the evidence is less certain (1,9), most notably featuring a single randomized controlled comparative trial that assessed the benefit of a corticosteroid added to a local anesthetic agent in patients with transformed migraine (10).

In this issue of *Cephalalgia*, Dilli and colleagues fill this gap, addressing GON blockade with corticosteroid for the treatment of migraine in a randomized, double-blind, placebo-controlled trial (11). They included patients at a single center, 18–75 years of age with episodic or chronic migraine who had at least one weekly attack but without continuous headache, recent initiation of evidence-based prophylaxis, frequent opioid use, substance abuse, allergy to injection ingredients, major psychiatric disorder or other contemporaneous headache disorders.

Patients were randomized to injections in the GON region with either the active therapy: 2.5 ml 0.5% bupivacaine plus 0.5 ml 20 mg methylprednisolone or what they termed their placebo: 2.75 ml normal saline plus 0.25 ml 1% lidocaine without epinephrine. Injections were performed unilaterally or bilaterally, depending on the location of the patient’s head pain. Various baseline predictive data points were captured that are novel in this setting, including pain directionality and graded GON region tenderness. Prospective diary completion in the 4 weeks before and after GON blockade was another major strength. Reasonably based on their clinical experience, the primary endpoint was defined as a 50% or more reduction in the frequency of moderate or severe headache days in the active versus placebo group at 4 weeks compared to a 4 week pre-injection baseline period.

Ultimately the authors analyzed 33 patients in the active group and 30 patients in the placebo group, who were mostly women, usually featured an occipital location of head pain and had a mean baseline headache frequency of 13 days during the 4-week baseline period. Over 75% of patients in both groups received bilateral injections.

The study failed to meet its primary endpoint, as the 50% reduction in the frequency of moderate or severe migraine headache days at 4 weeks was 30% for both groups. The study also failed to meet any secondary endpoints. The study failed to meet its primary endpoint, as the 50% reduction in the frequency of moderate or severe migraine headache days at 4 weeks was 30% for both groups. The study also failed to meet any secondary endpoints.
endpoints. A response rate did not correlate with other variables, including pain directionality, acute medication use or high baseline frequency of moderate to severe headache days. Adverse events occurred similarly in both groups and were uncommon, with injection site pain occurring in 12% of the active group and 6% of the placebo group. Only one serious adverse event was reported in the placebo group, where idiopathic intracranial hypertension was diagnosed 6 days after injection, which presumably was a pre-existing condition.

The authors reasonably conclude that a unilateral or bilateral single GON injection with corticosteroid and local anesthetic does not provide a short-term preventive effect at 4 weeks. There are methodological points worthy of commentary. Patients injected but lost to follow-up, potentially from an ineffective treatment, were more frequent in the placebo group (5/35, 14.3%) in comparison to the active treatment group (1/34, 2.9%), though the authors attempted to correct for this in their analysis. Though the number of total headache days in the 4-week baseline period was captured, the proportion of patients diagnosed with episodic and chronic migraine was not described. This may be important because other injection therapies acting on peripher al targets, such as onabotulinumtoxin A, are effective for the prophylaxis of chronic migraine but not episodic migraine (12). The degree of immediate post-injection pain reduction was not captured, which may be helpful in confirming an anatomically successful block and could predict responsiveness.

Most importantly, it is not clear if a solution containing 0.25 ml of 1% lidocaine should be considered a placebo. Though this is a small local anesthetic dose in comparison to the dose used in the active group, it is a dose commonly used for supraorbital and supratrochlear PNBs (9). Presumably, this dose was conceptualized as one that would be potent enough to cause numbness in the dermalonal distribution of the GON, but small enough to not have an active impact on headache reduction. However, rates of immediate post-injection numbness were not reported. Even true placebo (normal saline) injections in clinical trials for chronic migraine prophylaxis have high response rates (12), which may indicate that an important component of improvement may not be related simply to the specific agent used, but from the impact of the needle and inert ingredients used via a diffuse noxious inhibitory control mechanism (7).

Finally, the appropriate duration of a treatment effect for PNBs in migraine is not clear and as Dilli and colleagues suggest may be less than 4 weeks, their primary endpoint time. Another study examining treatment response times to GON injections revealed a mean duration of complete response of 9 days (median 6 days) and partial response of 61 days (median 30 days) in patients with migraine. A preliminary report of a large, prospective, multicenter, observational study in the USA enrolling 164 subjects showed that relief after PNBs was in the order of weeks, but more specific response times have not yet been reported (13). Future studies may consider utilizing response at 2 weeks as the appropriate time to assess a primary endpoint.

Where do we place PNBs in the armamentarium of headache medicine therapy? For cluster headache, recent well-designed, high-quality studies have demonstrated efficacy and safety of a single occipital nerve injection with corticosteroid for short-term prophylaxis, providing a therapeutic and likely safer alternative to oral corticosteroids (14). However, despite expert opinion (9), the current study places a degree of uncertainty for the role of PNBs in migraine therapy and future studies will need to refine the study population, injectate used and outcome measures. It is not known whether PNBs should be performed unilaterally or bilaterally, or in cervical and/or trigeminal branches in all patients regardless of pain location, as theoretically a cumulative dose–response relationship may exist. It also is unclear if for prophylaxis, serial PNBs would yield a higher therapeutic gain, akin to onabotulinumtoxin A. The role of injected corticosteroid for migraine remains unsettled and, at this point, with the perspective of previous work (10), its addition may not be useful. One may speculate that the duration of response suggests PNBs are more appropriate for the treatment of status migrainosus or short-term prophylaxis to enable reduction of medication overuse and serve as a bridge while a contemporaneous long-term prophylactic treatment is added. In the interim, because of the impressive work by Dilli and colleagues we can counsel our patients with migraine to not expect a long duration of response for GON block with corticosteroid.

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References


