Refractory primary and secondary headache disorders that dramatically responded to combined treatment of ultrasound-guided percutaneous suprazygomatic pterygopalatine ganglion blocks and non-invasive vagus nerve stimulation: a case series

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ABSTRACT

In 1981, Devoghel achieved an 85.6% success rate in treating patients with treatment-refractory cluster headaches with alcoholization of the pterygopalatine ganglion (PPG) via the percutaneous suprazygomatic approach. Devoghel’s study led to the theory that interrupting the parasympathetic pathway by blocking its transduction at the PPG could prevent or treat symptoms related to primary headache disorders (PHDs). Furthermore, non-invasive vagus nerve stimulation (nVNS) has proven to treat PHDs and has been approved by national regulatory bodies to treat, among others, cluster headaches and migraines.

In this case series, nine desperate patients who presented with 11 longstanding treatment-refractory primary headache disorders and epidural blood patch–resistant postdural puncture headache (PDPH) received ultrasound-guided percutaneous suprazygomatic pterygopalatine ganglion blocks (PPGB), and seven also received nVNS. The patients were randomly selected and were not part of a research study. They experienced dramatic, immediate, satisfactory, and apparently lasting symptom resolution (at the time of the writing of this report). The report provides the case descriptions, briefly reviews the trigeminalvascular and neurogenic inflammatory theories of the pathophysiology, outlines aspects of these PPGB and nVNS interventions, and argues for adopting this treatment regime as a first-line or second-line treatment rather than desperate last-line treatment of PDPH and PHDs.

BACKGROUND

Devoghel developed a treatment regime based on results published in 1933 to treat patients with longstanding treatment-refractory cluster headaches. He unsuccessfully treated the patients over at least 4 years with antihistamines, phenothiazines, H1-antagonists, methysergide, indomethacin, prednisone, propanolol, and lithium carbonate before the pterygopalatine ganglion (PPG) alcoholizations. Similar to more recent studies, Devoghel found that the percutaneous suprazygomatic approach to the PPG is the simplest and safest technique, and he achieved a remarkable success rate of 85.8% of patients who went into apparent permanent remission.

While the etiopathogenesis of most secondary headaches are generally well understood, that of primary headache disorders (PHDs) still eludes us. However, regarding the pathophysiology of the pain associated with PHDs, the trigeminalvascular theory (TVT), although disputed, has stood the test of time to simplify and comfortably explain
information and experience obtained in research and clinical practice. According to the TVT, pain associated with PHD involves a vicious cycle of parasympathetically induced vasodilation and inflammation caused by inflammatory mediators in the cerebral extraparenchymal blood vessels and the meninges. It is reasonable to argue that interrupting this pathway with a conduction block could prevent vasodilatation and inflammation (whichever phenomenon causes the other) and, thus, nociception of the PHDs and, theoretically, that of postdural puncture headaches. Blocking the PPG is also theorized to be effective in treating ipsilateral autonomic symptoms classically associated with trigeminal autonomic cephalalgias, which follow similar anatomical pathways.

Transcutaneous cervical vagus nerve stimulation (GammaCore, ElectroCore, Rockaway, New Jersey, USA) has been approved for episodic cluster headaches since 2017. A comprehensive update on the mechanism of action of non-invasive vagus nerve stimulation (nVNS) for PHD has recently been published by Silverstein and colleagues, in which they provide an in-depth review of the relationship between the vagus nerve and the trigeminal autonomic reflex. These and the potent anti-inflammatory actions via the cholinergic anti-inflammatory process of nVNS are briefly discussed in the Discussion section.

This communication presents nine case studies of desperate patients with severe treatment-refractory and long-standing suffering with PHDs who responded dramatically to percutaneous suprayzgomatic pterygopalatine ganglion blocks (PPGB) and transcutaneous auricular vagus nerve stimulation (taVNS) (Parasym, London, UK) and briefly discusses the pathophysiology as it is currently understood as well as aspects and rationale of these treatment regimes.

CASE DESCRIPTIONS

The patients in this case series included five patients with PHD (epicrania fugax, chronic paroxysmal hemicrania, new daily persistent headache, episodic cluster headache, and menstrual migraine without aura), one patient with two types of PHDs (menstrual followed by chronic retinal migraine), one with primary and secondary headache disorders (tension-type headache and medication overuse headache), and two patients with secondary headache disorders (postdural puncture headache) (table 1). The patients in this case series were randomly selected as they presented to individual practitioners and did not form part of a research project. They were all treated with PPGB (the video ‘Ultrasound Guided Sphenopalatine Ganglion Block’ on the Regional Anesthesia and Acute Pain Medicine YouTube channel details this approach), and seven of the nine also received taVNS. These were offered as desperate attempts to manage their conditions. All cases (except for patients #8 and #9) suffered for many years from debilitating, severe refractory headaches and presented to individual practitioners who had vast experience with PPGB procedures and taVNS. These practitioners had abandoned epidural blood patch (EBP) to treat PDPH and replaced it with PPGB with excellent results for the previous 7 years. They had also gained extensive experience with PPGB for various persistent PHD disorders and postoperative pain management for conditions such as adult and pediatric tonsillectomy, pediatric cleft palate repair, functional endoscopic sinus surgery, and others. As with Devogel’s cases, all of the patients (except #2 and #6, who presented to seek alternative non-pharmacological treatments because of unwanted adverse effects) failed to respond to all known and locally available therapies (table 1) and were desperate for relief.

All the patients were Caucasian and provided written consent to publish their case studies. Patients were managed in different private practice out-of-hospital settings, thus precluding institutional review board approval for publication of the case reports.

The PPGBs were all performed with 4 mL of 0.5% ropivacaine and 3 mg (1 mL) of betamethasone per side via a 22-gage B-bevel needle after thorough numbing of the skin and subcutaneous tissue with 1%–2% lidocaine via a 27-gage needle. All the patients also received mild conscious sedation with low-dose propofol and midazolam as required. taVNS, applied to the tragi or conchae of the patients’ ears at a frequency of 30 Hz and pulse width of 250 μs for at least 60 min per day (but typically for longer and up to 180 min), was added to try to minimize any further exacerbations.

DISCUSSION

This case series presents nine patients with 11 treatment-resistant and longstanding primary (eight) and secondary (three) headache disorders. The patients responded dramatically and potentially (as of the time of writing this report) permanently to PPGB and taVNS.

Despite the variety of disorders, we propose that their pathophysiologies were comparable due to a common anatomical and biochemical pathway and process involved in generating pain, thus yielding similar results.

The etiopathogenesis of PHDs eludes us and that of PDPH is perhaps better understood, while the pathophysiology of these conditions is still being investigated and debated. It is complex, and several theories attempt to explain what causes the pain of PHD. Although the neurogenic inflammatory theory has to a large extent replaced the trigeminovascular theory (TVT) as the current favorite, the TVT still adequately, although perhaps in an oversimplified manner, and comfortably explains why PPGB, by blocking the parasympathetic pathway, is successful in treating PHD and PDPH, both characterized by meningeal cerebral extraparenchymal blood vessel dilatation and meningeal inflammation, whichever is first and of whatever thus far unknown other mechanism or cause(s) (please see figure 1 for an abbreviated explanation of the TVT).

On the other hand, according to the neurogenic inflammatory theory, inflammatory mediators—among others, substance-P, acetylcholine, and calcitonin gene-related peptides—are released by the trigeminal autonomic reflex from the trigeminal system and cause the extraparenchymal cerebral vasodilatation, an epipheneomenon that, according to this theory, does not per se cause the headache.

Nociceptive impulses originate from the inflamed meningeal areas and pass through the trigeminal ganglion, which comprises trigeminal pseudounipolar neurons, to the trigeminal nerve’s principal sensory, mesencephalic, and spinal nuclei. Additional inflammation and nociceptive impulses are generated in and around these nuclei and join those from the meninges to spread to other brain areas where the impulses are interpreted as pain. These other brain areas may include, but are not limited to, the superior salivatory nucleus and the trigeminal nerve and its branches, the spinal nucleus of the trigeminal nerve and the cervical nerves and muscles, the parabrachial nucleus, the periaqueductal gray matter, the hypothalamus, and the thalamus.

The etiopathogenesis of PDPH is, likewise, still not completely understood, but better than that of PHDs. In a 2003 porcine study, Boezaart demonstrated a loss of approximately 0.3 mL of CSF per kg body weight of these animals (around 23–25 kg) aspirated from a cisterna magna needle puncture caused an
**Table 1** Case series of primary and secondary headache disorders

<table>
<thead>
<tr>
<th>Case #</th>
<th>Diagnosis*</th>
<th>ICHD-3 classification†</th>
<th>Sex and age</th>
<th>Headache quality and frequency</th>
<th>Triggers</th>
<th>HD duration pretreatment</th>
<th>Related symptoms</th>
<th>Location</th>
<th>Successful therapies</th>
<th>Unsuccessful therapies</th>
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<tbody>
<tr>
<td>1</td>
<td>Epicrania fugax⁴¹⁻⁴⁴</td>
<td>ICHD-3 Appendix class A4.11</td>
<td>F in mid-60s</td>
<td>Stabbing</td>
<td>Sudden neck movements</td>
<td>30 years</td>
<td>Redness and tearing of right eye</td>
<td>Strictly right-sided, unilateral</td>
<td>1st PPGB—51 weeks (figure 2)</td>
<td>3x ONB</td>
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<td></td>
<td>Electric</td>
<td>Vibrations</td>
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<td></td>
<td>2nd PPGB at 52 weeks; treatment included taVNS—7 months to WOR</td>
<td>3x cervical spine fusions</td>
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<td>10–15s</td>
<td>Light touch to occipital area</td>
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<td>Indomethacin</td>
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<td>3–5 attacks per month</td>
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<td>Valproic acid</td>
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<td>Topiramate</td>
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<td>2</td>
<td>Chronic paroxysmal hemisindrome⁴⁵</td>
<td>ICHD-3 class 3.2.2</td>
<td>F in mid-40s</td>
<td>Severe, stabbing sensation</td>
<td>Spontaneous</td>
<td>20 years</td>
<td>Left-sided tearing</td>
<td>Indomethacin—treatment discontinued due to gastric symptoms</td>
<td>Indomethacin</td>
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<td>&gt;5 attacks lasting 2–30min per day</td>
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<td>PPGB, treatment included taVNS—15 months to WOR</td>
<td>Verapamil</td>
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<td>Remission &lt;3 months per year</td>
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<td>Topiramate</td>
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<td>3</td>
<td>New daily persistent headache⁴⁶</td>
<td>ICHD-3 class 4.10</td>
<td>F in late 30s</td>
<td>Severe, pulsating, bitemporal, and behind eyes</td>
<td>Spontaneous</td>
<td>4 years</td>
<td>Nausea and vomiting</td>
<td>Partial relief with acupuncture</td>
<td>OTC</td>
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<td></td>
<td>Predominantly to the right side</td>
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<td>Light and sound sensitivity</td>
<td>Sodium valproate</td>
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<td>Clearly remembered onset date, time, and environment</td>
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<td>No autonomic symptoms</td>
<td>Amitriptyline</td>
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<td>Predicates HA medication usage</td>
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<td>&gt;15 days per month</td>
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<td>Dicyclomine</td>
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<td>Lignocaine</td>
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<td>4</td>
<td>Chronic tension-type headache medication overuse headache</td>
<td>ICHD-3 classes 2.3 and 8.3.1–5</td>
<td>F in early 40s</td>
<td>Pressing and band-like</td>
<td>Not exacerbated by physical activity</td>
<td>10 years</td>
<td>Photophobia</td>
<td>PPGB and taVNS—1 year to WOR</td>
<td>Naproxen</td>
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<td>Moderate to severe pain</td>
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<td>Phonophobia</td>
<td>Ergotamine</td>
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<td>Physical activity, once per month</td>
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<td>Lasting a few hours to a few days</td>
<td>Rizatriptan</td>
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<td>Lasting 4–24 hours</td>
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<td>&gt;15 days per month</td>
<td>Taminol</td>
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<td>5</td>
<td>Menstrual migraine followed by chronic retinal migraine</td>
<td>ICHD-3 classes 1.2.1 and 1.2.4</td>
<td>F in mid-60s</td>
<td>Pre-TAH: pulsating, moderate to severe, aggravated by physical activity, once per month, pre-TAH and post-TAH lasting 4–24 hours, CRM more than 15 attacks per month</td>
<td>Pre-TAH: visual aura; After TAH headaches were spontaneous, with no specific triggers</td>
<td>24 years for MM 30 years for CRM</td>
<td>Photophobia</td>
<td>Strictly left-sided unilateral</td>
<td>PPGB and taVNS—2 years to WOR</td>
<td>OTC</td>
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<td>Trigeminal neuralgia</td>
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<td>Phonophobia</td>
<td>Diclofenac sodium and free acid</td>
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<td>Right-sided monocular vision loss</td>
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<td>Severe nausea and vomiting</td>
<td>Topiramate</td>
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<td>Transient visual aura</td>
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<td>Negative ophthalmological evaluation</td>
<td>Gabapentin</td>
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<td>Trigeminal neuralgia</td>
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<td>Propranolol</td>
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<td>Post-TAH visual aura</td>
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<td>Amitriptyline</td>
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<td>After TAH left-sided gradual monocular vision loss (white-out) over 5 min resolving with onset of headache</td>
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<td>Cannabidiol</td>
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<td>After TAH left-sided gradual monocular vision loss (white-out) over 5 min resolving with onset of headache</td>
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<td>Acupuncture</td>
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<td>Right-sided monocular vision loss</td>
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<td>Botulinum toxin type A</td>
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<td>Right-sided monocular vision loss</td>
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<td>Partial relief with rizatriptan and metoclopramide</td>
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</table>

*Case 1: Epicrania fugax*<sup>[41-44]</sup> ICHD-3 Appendix class A4.11 F in mid-60s

1. Stabbing
2. Electric
3. 10–15s
4. 3–5 attacks per month

Triggers:
- Sudden neck movements
- Vibrations
- Light touch to occipital area

HD duration pretreatment: 30 years

Related symptoms:
- Redness and tearing of right eye
- Right eye ptosis
- Right eyelid swelling
- Right-sided rhinorhea (<figure 1A>)

Location: Strictly right-sided, unilateral

Successful therapies: 1st PPGB—51 weeks

Unsuccessful therapies: 2nd PPGB at 52 weeks; treatment included taVNS—7 months to WOR

*Case 2: Chronic paroxysmal hemisindrome*<sup>[45]</sup> ICHD-3 class 3.2.2 F in mid-40s

1. Severe, stabbing sensation
2. Predominantly to the right side
3. Predicates HA medication usage
4. >15 days per month

HD duration pretreatment: 20 years

Related symptoms:
- Left-sided tearing
- Conjunctival injection
- Eyelid edema
- Facial sweating
- Phosis
- Agitation

Location: Indomethacin—treatment discontinued due to gastric symptoms

Successful therapies: PPGB, treatment included taVNS—15 months to WOR

Unsuccessful therapies: Indomethacin

*Case 3: New daily persistent headache*<sup>[46]</sup> ICHD-3 class 4.10 F in late 30s

1. Severe, pulsating, bitemporal, and behind eyes
2. Predominantly to the right side
3. Predicates HA medication usage
4. >15 days per month

HD duration pretreatment: 4 years

Related symptoms:
- Nausea and vomiting
- Light and sound sensitivity
- No autonomic symptoms

Location: Partial relief with acupuncture

Successful therapies: PPGB and taVNS—treatment—6 months to WOR

Unsuccessful therapies: OTC

*Case 4: Chronic tension-type headache medication overuse headache* ICHD-3 classes 2.3 and 8.3.1–5 F in early 40s

1. Pressing and band-like
2. Predicates HA medication usage
3. Post-TAH: pulsating, moderate to severe pain
4. >15 days per month

HD duration pretreatment: 10 years

Related symptoms:
- Photophobia
- Phonophobia

Location: Bilateral

Successful therapies: PPGB and taVNS—1 year to WOR

Unsuccessful therapies: Naproxen

*Case 5: Menstrual migraine followed by chronic retinal migraine* ICHD-3 classes 1.2.1 and 1.2.4 F in mid-60s

1. Pre-TAH: pulsating, moderate to severe, aggravated by physical activity, once per month, pre-TAH and post-TAH lasting 4–24 hours, CRM more than 15 attacks per month
2. Pre-TAH visual aura; After TAH headaches were spontaneous, with no specific triggers
3. Trigeminal neuralgia

HD duration pretreatment: 24 years for MM 30 years for CRM

Related symptoms:
- Photophobia
- Phonophobia
- Severe nausea and vomiting
- Negative ophthalmological evaluation

Location: Strictly left-sided unilateral

Successful therapies: PPGB and taVNS—2 years to WOR

Unsuccessful therapies: OTC

*Continued*
<table>
<thead>
<tr>
<th>Case #</th>
<th>Diagnosis*</th>
<th>Headache quality and frequency</th>
<th>Triggers</th>
<th>HD duration pretreatment</th>
<th>Related symptoms</th>
<th>Location</th>
<th>Successful therapies</th>
<th>Unsuccessful therapies</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>Episodic cluster headache</td>
<td>Severe and stabbing, lasting 15–180 min</td>
<td>Alcohol (especially red wine)</td>
<td>25 years</td>
<td>Restlessness</td>
<td>Strictly right-sided unilateral</td>
<td>1st BSGB—4 year remission</td>
<td>Inhaled O2, Nasal and parenteral triptans</td>
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<td></td>
<td>ICHD-3 class 3.1.1</td>
<td>Up to eight times per day</td>
<td>Exercise</td>
<td></td>
<td>Agitation</td>
<td>Right orbital area</td>
<td>2nd BSGB 10 year remission</td>
<td>Calcium channel blockers</td>
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<td></td>
<td>M in mid-50s</td>
<td>Attacks come in series lasting up to 3 months</td>
<td>Warm temperatures</td>
<td></td>
<td>Conjunctival injection</td>
<td></td>
<td>PPGB and taVNS—4 years to WOR</td>
<td>Anticonvulsants</td>
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<td>Warm drinks like tea or coffee</td>
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<td>Lacrimation</td>
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<td>3rd BSGB (note: absent Horner’s with 3rd BSGB)</td>
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<td>7</td>
<td>Menstrual migraine without aura</td>
<td>Moderate to severe throbbing</td>
<td>No aura</td>
<td>35 years</td>
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<td>Strictly right-sided unilateral</td>
<td>Paracetamol and codeine combination</td>
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<td></td>
<td>ICHD-3 class 1.1</td>
<td>Starts 3 days prior to menstrual cycle</td>
<td>Nausea and vomiting</td>
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<td>Photophobia</td>
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<td>Dihydroergotamine</td>
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<td></td>
<td>F in mid-40s</td>
<td>Lasts 3 days per month</td>
<td>Photophobia</td>
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<td>Phosphophoria</td>
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<td>PPBG and taVNS—16 months to WOR</td>
<td>Online supplemental video, published with the patient’s written permission</td>
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<td>8</td>
<td>Postdural puncture headache</td>
<td>Severe throbbing</td>
<td>Photophobia</td>
<td>4 months</td>
<td>Stiff neck</td>
<td></td>
<td>Bilateral occipital and behind eyes</td>
<td>Epidural blood patch with 10 mL autologous blood</td>
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<td></td>
<td>ICHD-3 class 7.1.2</td>
<td>Strictly positional on sitting or standing, relieved on lying down</td>
<td>Severe nausea</td>
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<td>M in mid-50s</td>
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<td>Vomiting</td>
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<td>9</td>
<td>Postdural puncture headache</td>
<td>Severe throbbing</td>
<td>Photophobia</td>
<td>7 months</td>
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<td>5x epidural blood patch</td>
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<td>Strictly positional on sitting or standing, relieved on lying down</td>
<td>Severe nausea</td>
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<td>M in late 40s</td>
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<td>Vomiting</td>
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<td>Caffeine</td>
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<td>Stiff neck</td>
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*Diagnosis as per Lumina Primary Headache Diagnostic Aid: https://tools.lumina-pain.com/forms/primary-headache?enant=trial.
†As per https://ihd-3.org/classification-outline.*
BSGB, bilateral sphenopalatine ganglion block; CRM, chronic retinal migraine; F, female patient; HA, headache; HD, headache disorder (primary and secondary); ICHD-3, International Classification of Headache Disorders, third edition; M, male patient; MM, menstrual migraine; MOH, medication overuse headache; NV&MS, nausea, vomiting, and motion sickness; ONB, occipital nerve block; OTC, over the counter; PPGB, bilateral percutaneous ultrasound-guided sphenopalatine ganglion block; TAH, total abdominal hysterectomy; taVNS, transcutaneous auricular vagus nerve stimulation; WOR, the time of writing of this report.
immediate and significant increase in cerebral cortical blood flow. This, in turn, was immediately reversed by distant lumbar EBP—iatrogenic peridural hematoma—which is known as an early and potent stimulus for cerebral vasoconstriction. While vasodilation (in the case of PDPH, based on the Monro-Kellie hypothesis), and inflammation, most likely due to the cortical vasodilatation or some trigeminal reflex, are probably shared features in some PHDs and PDPH, we recognize that these conditions’ specific etiology, triggers, and pathophysiological mechanisms differ.

Despite the theoretical mechanistic differences and poorly understood pathophysiology, treating both PHD and PDPH with PPGB may share similar reasons to be effective. These may include the disruption of parasympathetic-activated vasodilatation or inflammation at the PPG and the modulation of inflammatory neurotransmitters. Finally, it may have the potential to interrupt trigeminal activation and thus the transmission of pain signals during PHDs and PDPHs. By blocking conduction through the PPG, the transmission of parasympathetic vasodilatory or inflammatory signals from the superior salivatory ganglion and trigeminal nerve causing the release of further inflammatory mediators to spread to other areas of the brain and be interpreted as pain (reproduced with the kind permission of Mary K. Bryson and Lumina Health). PHD, primary headache disorder; TVT, trigeminovascular theory.

There are several approaches to blocking the PPG. However, suprazygomatic seems the safest percutaneous approach. We have, over a 7-year period, not encountered any serious side effects in using PPGB on hundreds of patients for various indications (see Background section) other than transient numbness of the upper jaw and teeth and rarely lower jaw and tongue for as long as the local anesthetic agent is active, and postprocedure short-lived cheek tenderness and swelling. These could easily be treated by patient reassurance and with non-steroidal anti-inflammatory agents. Other extremely rare complications may be encountered, such as puncturing of the maxillary artery, hematoma formation, and intravascular injection. However, to date, we have not met these side effects, nor to the best of our knowledge, has anyone reported them.
knowledge have they been reported in literature. Patient discomfort during the procedure is limited to an absolute minimum if a fine needle is used for skin and subcutaneous local anesthetic lignocaine infiltration (or for the PPGB) combined with mild levels of conscious sedation as indicated.

In the experience of the authors and as argued by Narouze, among others, the transnasal sphenopalatine ganglion block (SGB) yields inconsistent results. It may block the autonomic nerve fibers in the nasal cavity and interrupt some of the autonomic symptoms associated with PHD. Still, due to its unreliable results, we do not support its use. It may be argued that it is the safest approach to blocking the PPG (SGB). We concur with Narouze that the transnasal approach most likely does not reach the PPG. If it does, it does so unreliably and with ineffective, minimal dosages of local anesthetic agents.

We cannot explain why short-acting local anesthetic agents combined with relatively short-acting (~3 months) steroids could have such lasting effects. Breaking the vicious cycles of vasodilatation and inflammation may partially explain it. However, the long-term effects may also be explained by our patients’ compliant use of taVNS postprocedure. This long-lasting effect was especially apparent in the patient described as case #6 (CH, who experienced years of remission after single-injection superior cervical (stellate) ganglion blocks). Since remission recurred on three occasions after autonomic blocks in this patient, it is unlikely to be purely coincidental or a placebo effect. However, the patients with PPDH (cases #8 and #9), in whom the PBGB could not possibly have stopped the CSF leaks and whose leaks could arguably still have been active in the form of fistulae at the time of the blocks, were not treated with nVNS. This finding should be further debated and ultimately clarified by ongoing research. The answer to this question may pave the way for radiofrequency ablation or other destructive techniques such as alcoholization or PPG electrical stimulation. The immediate effects on the patient with epiconia fugax (case #1, figure 2) can be partially explained by the blocking of the autonomic nerve fibers that run with the ophthalmic (V1) and maxillary (V2) nerves.

The precise mechanisms underlying the therapeutic effects of nVNS in PHD are still being investigated, and additional research is needed for a comprehensive understanding. Evidence suggests that nVNS interacts with multiple aspects of headache pathophysiology. These include short-term and long-term neurotransmitter modulation and thus a lower frequency of attacks, autonomic regulation leading to a decreased firing of trigeminal neurons, and hence acute relief of parasympathetic nervous system symptoms. nVNS furthermore causes nociceptive modulation, mitigating increased nociception and acute pain relief, decreased susceptibility to cortical spreading depression initiation and frequency, and thus acute attack (aura) resolution and reduced attack risk. Finally, nVNS has potent anti-inflammatory effects through its effect on the cholinergic anti-inflammatory process. This all ultimately leads to symptom relief and improved headache management with nVNS.

CONCLUSIONS

The conclusive clinical benefit of PPGB and nVNS, separately or combined for treating PHDs and, to a lesser extent, that of PDPH remains to be determined. Further research is required to compare this treatment strategy prospectively to other newer pharmacologic therapies. Because of the simplicity, relative safety, and cost-effectiveness of PPGB and nVNS, these treatment modalities should be offered early on to patients with therapy-refractive or therapy-resistant PHDs and early on to patients with PDPH not responding to simple conservative non-invasive measures to eliminate yet another epidural injection (EBP). For the same reasons, we strongly advocate that it should be offered to patients as first-line or second-line treatment after failed simple pharmacological treatment with OTCs, triptans, etc., rather than desperate last-resort treatments—especially in middle-to-low-income developing countries where newer, expensive therapy modalities and super-specialized services and treatments are not readily available.

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REFERENCES


