OPEN ACCESS

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

Andre P Boezaart ,[1,2] Cameron R Smith,[1] Yury Zasimovich,[1] Rene Przkora ,[1] Sanjeev Kumar ,[1] Olga C Nin,[1] Louis C Boezaart,[3] Daniel AJ Botha,[4] André Leonard,[5] Miguel A Reina ,[1,6] Juan A Pareja[7]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rapm-2023-104967).

For numbered affiliations see end of article.

Correspondence to
Andre P Boezaart, Anesthesiology, University of Florida College of Medicine, Gainesville, FL 32610, USA; ABoezaart@anest.ufl.edu

Some of the cases (1-5) have been presented as abstracts and poster presentations at the American Academy of Pain Medicine Annual Meeting on March 23, 2023, in Florida, USA.

Received 21 September 2023
Accepted 6 November 2023
Published Online First 20 November 2023

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 trigeminovascular 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Primary headache disorders (PHDs) are challenging to treat effectively because the precise mechanisms that trigger attacks or episodes are unknown, and they are particularly refractory. Furthermore, postdural puncture headache (PDPH) treatment is mostly effective with an epidural blood patch (EBP), but it requires another epidural injection.

WHAT THIS STUDY ADDS

⇒ Percutaneous suprazygomatic pterygopalatine ganglion blocks (PPGB) and non-invasive vagus nerve stimulation (nVNS) can provide immediate and long-lasting relief of the pain and other symptoms associated with primary and some secondary headache disorders and prevent further attacks. Repeated EBP failed to provide relief to our patients with PDPH.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Research into the impulses that trigger the mechanisms that cause the pain associated with PHDs will help further demystify these disorders' elusive etiopathogenesis and pathophysiology. This case series argues for adopting PPGB and nVNS as first-line and second-line treatments rather than desperate last-line treatment modalities for PHDs and PDPHs and to compare standardized versions of them to modern drug therapies prospectively.

BACKGROUND

Devoghel[1] developed a treatment regime based on results published in 1933[2] to treat patients with longstanding treatment-refractory cluster headaches.[1] He unsuccessfully treated the patients over at least 4 years with antihistamines, phenothiazines, H1-antagonists, methysergide, indomethacin, prednisone, propranolol, and lithium carbonate before the pterygopalatine ganglion (PPG) alcoholizations. Similar to more recent studies,[3 4] 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.[1]

While the etiopathogeneses of most secondary headaches are generally well understood,[5] that of primary headache disorders (PHDs) still eludes us.[6–9] However, regarding the pathophysiology of the pain associated with PHDs, the trigeminovascular theory (TVT), although disputed, has stood the test of time to simplify and comfortably explain

Check for updates

© American Society of Regional Anesthesia & Pain Medicine 2024. Re-use permitted under CC BY-NC. No commercial re-use. Published by BMJ.

To cite: Boezaart AP, Smith CR, Zasimovich Y, *et al*. *Reg Anesth Pain Med* 2024;**49**:144–150.

Reg Anesth Pain Med: first published as 10.1136/rapm-2023-104967 on 20 November 2023. Downloaded from http://rapm.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

information and experience obtained in research and clinical practice.[10–14] 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.[15 16] 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.[17]

Transcutaneous cervical vagus nerve stimulation (GammaCore, ElectroCore, Rockway, New Jersey, USA) has been approved for episodic cluster headaches since 2017.[18] A comprehensive update on the mechanism of action of non-invasive vagus nerve stimulation (nVNS) for PHD has recently been published by Silberstein and colleagues, in which they provide an in-depth review of the relationship between the vagus nerve and the trigeminal autonomic reflex.[19] These and the potent anti-inflammatory actions via the cholinergic anti-inflammatory process of nVNS are briefly discussed in the Discussion section.[20 21]

This communication presents nine case studies of desperate patients with severe treatment-refractory and long-standing suffering with PHDs who responded dramatically to percutaneous suprazygomatic 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 Anesthesiology and Acute Pain Medicine YouTube channel details this approach),[1 3 4 22–25] and seven of the nine also received taVNS.[26–28] 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 Devoghel's cases,[1] 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 tragii 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.[6–10 15 29] Although the neurogenic inflammatory theory[29] 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)[10–14] (please see figure 1 for an abbreviated explanation of the TVT).

On the other hand, according to the neurogenic inflammatory theory,[29] 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 epiphenomenon 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[30] 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

Reg Anesth Pain Med: first published as 10.1136/rapm-2023-104967 on 20 November 2023. Downloaded from http://rapm.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Table 1 Case series of primary and secondary headache disorders

Case #	Diagnosis* ICHD-3 classification† [5] Sex and age	Headache quality and frequency	Triggers	HD duration pretreatment	Related symptoms	Location	Successful therapies	Unsuccessful therapies
1	*Epicrania fugax* [41–44] ICHD-3 Appendix class A4.11 F in mid-60s	► Stabbing ► Electric ► 10–15 s ► 3–5 attacks per month	► Sudden neck movements ► Vibrations ► Light touch to occipital area	30 years	► Redness and tearing of right eye ► Right eye ptosis ► Right eyelid swelling ► Right-sided rhinorrhea (figure 1A)	► Strictly right-side, unilateral ► Right occiput pain that spreads epicranially linearly to ipsilateral nares or maxilla	► 1st PPGB—51 weeks (figure 2) ► 2nd PPGB at 52 weeks, treatment included taVNS—7 months to WOR	► 3x ONB ► 3x cervical spine fusions ► OTC ► Indomethacin ► Valproic acid ► Topiramate ► Gabapentin ► Pregabalin ► Amitriptyline ► Opioids ► Acupuncture ► Physical therapy ► Chiropractic therapy
2	*Chronic paroxysmal hemicrania* [45] ICHD-3 class 3.2.2 F in mid-40s	► Severe, stabbing sensation ► Predictable daily rhythm ► >5 attacks lasting 2–30 min per day ► Remission <3 months per year	► Spontaneous	20 years	► Left-sided tearing ► Conjunctival injection ► Eyelid edema ► Facial sweating ► Ptosis ► Agitation	► Strictly unilateral ► Left parietal ridge, temple, eye, cheek, and ear	► Indomethacin—treatment discontinued due to gastric symptoms ► PPGB, treatment included taVNS –15 months to WOR	► Indomethacin ► OTC ► Verapamil ► Topiramate ► ONB ► Acupuncture
3	*New daily persistent headache* [46] ICHD-3 class 4.10 F in late 30s	► Severe, pulsating, bitemporal, and behind eyes ► Clearly remembered onset date, time, and environment ► Predates HA medication usage ► >15 days per month	► Spontaneous	4 years	► Nausea and vomiting ► Light and sound sensitivity ► No autonomic symptoms	► Bilateral	► Partial relief with acupuncture ► PGBB and taVNS treatment—6 months to WOR	► OTC ► Methylprednisolone ► Sodium valproate ► Amitriptyline ► ONB ► Doxycycline ► Lignocaine
4	*Chronic tension-type headache medication overuse headache* ICHD-3 classes 2.3 and 8.3.1–5 F in early 40s	► Pressing and band-like ► Moderate to severe pain ► Pericranial muscle tenderness ► Lasting a few hours to a few days ► >15 days per month	► Not exacerbated by physical activity	10 years	► Photophobia ► Phonophobia	► Bilateral	► PPGB and taVNS—1 year to WOR	► Naproxen ► Ergotamine ► Rizatriptan ► Tramadol ► OTC > 10 days per month (partially successful: resulted in MOH) ► Amitriptyline ► Acupuncture ► Exercise therapy ► Sedatives ► ONB
5	*Menstrual migraine followed by chronic retinal migraine* ICHD-3 classes 1.2.1 and 1.2.4 F in mid-60s	► 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	► Triggered by menstruation ► After TAH headaches were spontaneous, with no specific triggers	24 years for MM 30 years for CRM	► Pre-TAH: visual auras ► After TAH left-sided gradual monocular vision loss (white-outs) over 5 min resolving with onset of headache ► Photophobia ► Phonophobia ► Severe nausea and vomiting ► Negative ophthalmological evaluation	► Strictly left-sided unilateral ► Temporal and left eye	► PPGB and taVNS—2 years to WOR	► OTC ► Diclofenac sodium and free acid ► Topiramate ► Gabapentin ► Propranolol ► Amitriptyline ► Cannabidiol ► Acupuncture ► Botox ► Partial relief with rizatriptan and metoclopramide

Continued

Reg Anesth Pain Med: first published as 10.1136/rapm-2023-104967 on 20 November 2023. Downloaded from http://rapm.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Table 1 Continued

Case #	Diagnosis* ICHD-3 classification†[5] Sex and age	Headache quality and frequency	Triggers	HD duration pretreatment	Related symptoms	Location	Successful therapies	Unsuccessful therapies
6	*Episodic cluster headache* ICHD-3 class 3.1.1 M in mid-50s	► Severe and stabbing, lasting 15–180 min ► Up to eight times per day ► Attacks come in series lasting up to 3 months	► Alcohol (especially red wine) ► Exercise ► Warm temperatures ► Warm drinks like tea or coffee	25 years	► Restlessness ► Agitation ► Conjunctival injection ► Lacrimation ► Stuffy nose ► Eyelid edema ► Ptosis	► Strictly right-sided unilateral ► Right orbital area	► 1st BSGB—8 year remission ► 2nd BSGB 10 year remission ► PPGB and taVNS—4 years to WOR	► Inhaled O_2 ► Nasal and parenteral triptans ► Calcium channel blockers ► Anticonvulsants ► 3rd BSGB (note: absent Horner's with 3rd BSGB)
7	*Menstrual migraine without aura* ICHD-3 class 1.1 F in mid-40s	► Moderate to severe throbbing ► Starts 3 days prior to menstrual cycle ► Lasts 3 days per month	► Monthly premenstruation	35 years	► No aura ► Nausea and vomiting ► Photophobia ► Phonophobia ► Aggravated by physical activity ► No autonomic symptoms	► Strictly right-sided unilateral	► Paracetamol and codeine combination ► Doxylamine ► PPBG and taVNS −16 months to WOR (online supplemental video, published with the patient's written permission)	
8	*Postdural puncture headache* ICHD-3 class 7.1.2 M in mid-50s	► Severe throbbing	► Strictly positional on sitting or standing, relieved on lying down	4 months	► Photophobia ► Phonophobia ► Mild nausea ► New-onset tinnitus ► Stiff neck	► Bilateral occipital and behind eyes	► PPGB—7 months to WOR	► Epidural blood patch with 10 mL autologous blood
9	*Postdural puncture headache* ICHD-3 class 7.1.2 M in late 40s	► Severe throbbing	► Strictly positional on sitting or standing, relieved on lying down	7 months	► Photophobia ► Phonophobia ► Severe nausea ► Vomiting ► Motion sickness ► Weight loss ► Stiff neck	► Bilateral occipital and behind eyes	► 1st PPGB to WOR—nausea, vomiting, and severe motion sickness persisted ► 2nd–5th monthly PPGB after monthly nausea, vomiting, and motion sickness (NV&MS) return ► 6th PPGB—resolved NV&MS for 5 years to WOR after 6th PPGB	► 5x epidural blood patch ► OTC ► Caffeine ► Hydration ► Bedrest ► ONB

*Diagnosis as per Lumina Primary Headache Diagnostic Aid: https://tools.lumina-pain.com/forms/primary-headache?tenant=trial.
†As per https://ichd-3.org/classification-outline/.
BSGB, bilateral stellate 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 suprazygomatic pterygopalatine ganglion block; TAH, total abdominal hysterectomy; taVNS, transcutaneous auricular vagus nerve stimulation; WOR, the time of writing of this report.

Reg Anesth Pain Med: first published as 10.1136/rapm-2023-104967 on 20 November 2023. Downloaded from http://rapm.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

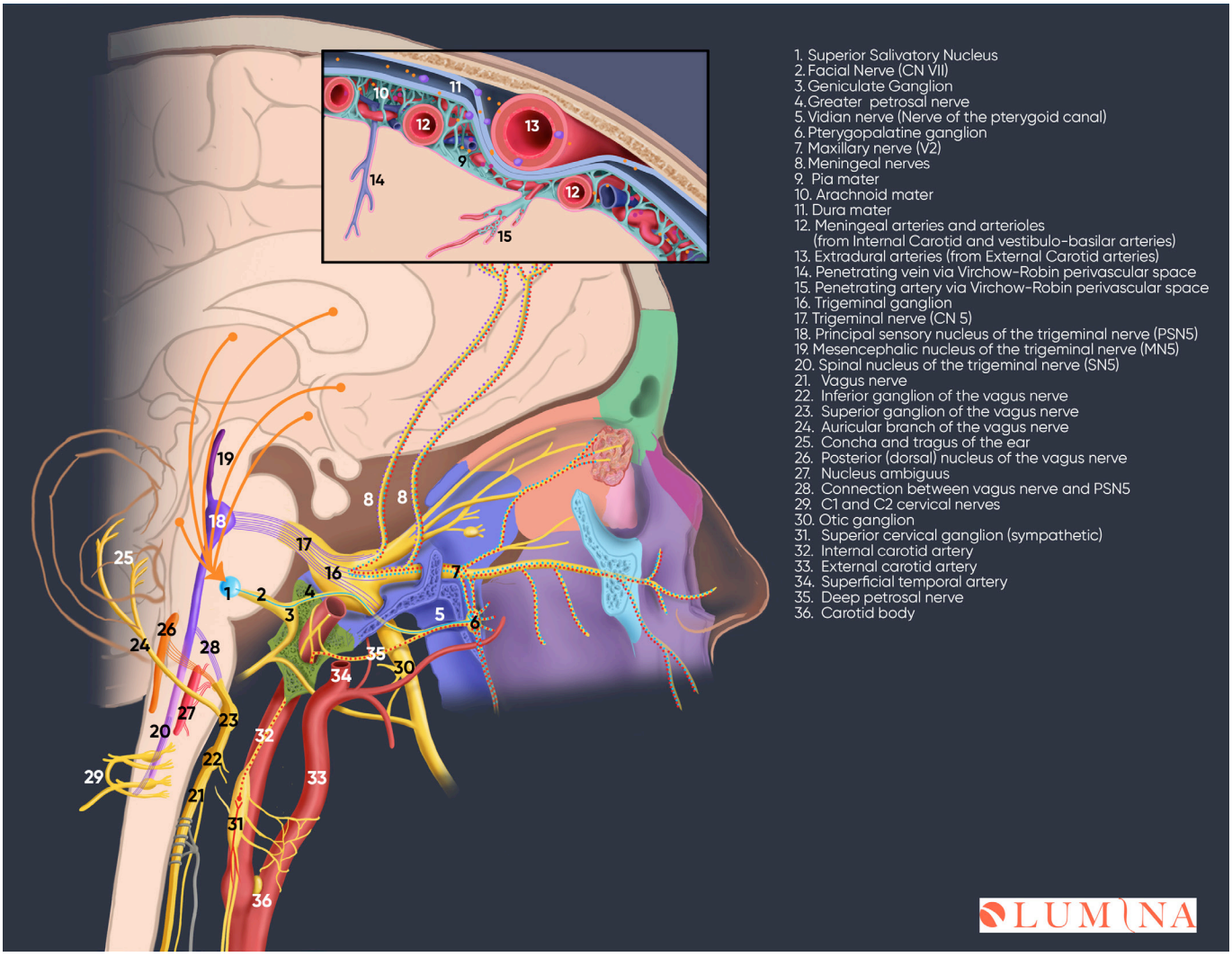

Figure 1 Pathophysiology of PHD according to TVT. Impulses generated from different brain areas (orange arrows) travel to the salivatory nucleus (1) from where parasympathetic impulses travel via the facial nerve (2), geniculate ganglion (3), greater petrosal nerve (4), and Vidian nerve (5) to synapse in pterygopalatine ganglion (6). From here, postsynaptic parasympathetic impulses travel via the maxillary nerve (7) and meningeal nerves (8) to reach the meninges (10, 11) and extraparenchymal meningeal blood vessels (12), which are dilated and inflammatory mediators are released. Either the vasodilatation or the inflammation or both cause nociception, and the nociception impulses travel via the trigeminal ganglion (16) and trigeminal nerve (17) to the principal (18), mesencephalic (19), and spinal (20) nuclei of the 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.

immediate and significant increase in cerebral cortical blood flow. This, in turn, was immediately reversed by distant lumbar EBP—iatrogenic peridural hematoma[31] —which is known as an early and potent stimulus for cerebral vasoconstriction.[32] While vasodilation (in the case of PDPH, based on the Monro-Kellie hypothesis[33]), 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.[34]

Despite the theoretical mechanistic differences and poorly understood pathophysiologies, treating both PHD and PDPH with PPGB may share similar reasons to be effective.[35] 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 (figure 1) and pain signals from the trigeminal nerve to the central nervous system are disrupted, relieving headache symptoms.

There are several approaches to blocking the PPG.[36] However, suprazygomatic seems the safest percutaneous approach.[3 4] 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

Reg Anesth Pain Med: first published as 10.1136/rapm-2023-104967 on 20 November 2023. Downloaded from http://rapm.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

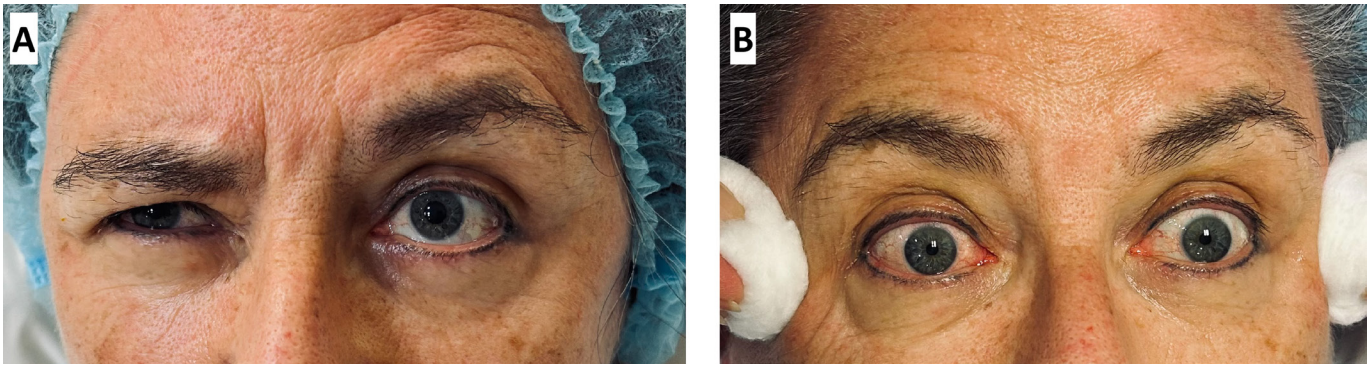

Figure 2 (A) Before and (B) immediately after images of the patient with epicrania fugax (#1) undergoing a percutaneous suprazygomatic pterygopalatine ganglion block (photographs published with patient's kind permission).

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[4 36] and as argued by Narouze,[37] 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[37] 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[38] or other destructive techniques such as alcoholization[1] or PPG electrical stimulation.[39] The immediate effects on the patient with epicrania 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.[8] Evidence suggests that nVNS interacts with multiple aspects of headache pathophysiology.[19] 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.[19] 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.[19] Finally, nVNS has potent anti-inflammatory effects through its effect on the cholinergic anti-inflammatory process.[20 40] 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.

Author affiliations
[1]Anesthesiology, University of Florida College of Medicine, Gainesville, Florida, USA
[2]Lumina Health, Surrey, UK
[3]Private Ophthalmology Practice, Cape Town, South Africa
[4]Private Family Practice, Still Bay, South Africa
[5]Private Neurology Practice, Mossel Bay, South Africa
[6]Anesthesiology, CEU San Pablo University Faculty of Medicine, Madrid, Spain
[7]Neurology, Hospital Universitario Quirón Madrid, Madrid, Spain

Acknowledgements The authors express their deepest gratitude to the patients for permitting them to publish their case reports. They also sincerely thank Dr Natasha Beukes (PhD), Waldi du Toit, Gareth Coetzee, and Kirsten Holman of Lumina Health, and Bryan Penberthy (MFA) of the University of Florida for their valuable contributions to editing and preparing the manuscript.

Contributors All authors contribute to project development, data collection and management, and manuscript writing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Reg Anesth Pain Med: first published as 10.1136/rapm-2023-104967 on 20 November 2023. Downloaded from http://rapm.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Ethics approval This study involves human participants. The cases described in this case series were all managed in the offices of various private practitioners who are not attached or affiliated to nor associated with any institution. Institutional review boards or ethical review boards are therefore not applicable as the practitioners, who own their practices and who are the coauthors, have complete authority over their private practices. To comply with this, they would in fact have to give themselves approval, which would not make any sense. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, an indication of whether changes were made, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Andre P Boezaart http://orcid.org/0000-0002-1221-1214
Rene Przkora http://orcid.org/0000-0002-3517-7450
Sanjeev Kumar http://orcid.org/0000-0001-9078-1020
Miguel A Reina http://orcid.org/0000-0001-9078-1020

REFERENCES

1 Devoghel JC. Cluster headache and sphenopalatine block. *Acta Anaesthesiol Belg* 1981;32:101–7.
2 Alajuanine T, Thurel R. Les Traitements des Algies Faciales. *J Méd Franç* 1933;22:202.
3 Jerman A, Umek N, Cvetko E, *et al*. Comparison of the feasibility and safety of Infrazygomatic and suprazygomatic approaches to pterygopalatine fossa using virtual reality. *Reg Anesth Pain Med* 2023;48:359–64.
4 Smith CR, Dickinson KJ, Carrazana G, *et al*. Ultrasound-guided suprazygomatic nerve blocks to the pterygopalatine fossa: a safe procedure. *Pain Med* 2022;23:1366–75.
5 Headache classification committee of the International headache society (IHS) the International classification of headache disorders. *Cephalalgia* 2018;38:1–211.
6 Goadsby PJ, Holland PR. An update: pathophysiology of migraine. *Neurol Clin* 2019;37:651–71.
7 Silvestro M, Tessitore A, Orologio I, *et al*. Cluster headache pathophysiology: what we have learned from advanced neuroimaging. *Headache* 2022;62:436–52.
8 Wei DY, Goadsby PJ. Cluster headache pathophysiology - insights from current and emerging treatments. *Nat Rev Neurol* 2021;17:308–24.
9 Burish M. Cluster headache and other trigeminal autonomic cephalalgias. *Continuum (Minneap Minn)* 2018;24:1137–56.
10 Moskowitz MA, Reinhard JF, Romero J, *et al*. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine *Lancet* 1979;2:883–5.
11 Moskowitz MA. The Neurobiology of vascular head pain. *Ann Neurol* 1984;16:157–68.
12 Moskowitz MA. Defining a pathway to discovery from bench to bedside: the trigeminovascular system and sensitization. *Headache* 2008;48:688–90.
13 Moskowitz MA. Pathophysiology of headache--past and present. *Headache* 2007;47 Suppl 1:S58–63.
14 Samarasekera U. Michael Moskowitz: solving the puzzle of migraine. *Lancet Neurol* 2021;20:790.
15 Dodick DW. A phase-by-phase review of migraine pathophysiology. *Headache* 2018;58 Suppl 1:4–16.
16 Iser C, Arca K. Headache and autonomic dysfunction: a review. *Curr Neurol Neurosci Rep* 2022;22:625–34.
17 Piagkou M, Demesticha T, Troupis T, *et al*. The pterygopalatine ganglion and its role in various pain syndromes: from anatomy to clinical practice. *Pain Pract* 2012;12:399–412.
18 Urits I, Schwartz R, Smoots D, *et al*. Peripheral neuromodulation for the management of headache. *Anesth Pain Med* 2020;10:e110515.
19 Silberstein SD, Yuan H, Najib U, *et al*. Non-invasive Vagus nerve stimulation for primary headache: A clinical update. *Cephalalgia* 2020;40:1370–84.
20 Yuan H, Silberstein SD. Vagus nerve and Vagus nerve stimulation, a comprehensive review: part III. *Headache* 2016;56:259–66.
21 Doshi TL, Staats PS. fMRI in Vagus nerve stimulation for migraine: a biomarker-based approach to pain research. *Reg Anesth Pain Med* 2021;46:467–8.
22 Jespersen MS, Jaeger P, Ægidius KL, *et al*. Sphenopalatine ganglion block for the treatment of postdural puncture headache: a randomised, blinded, clinical trial. *Br J Anaesth* 2020;124:739–47.
23 Nader A, Kendall MC, De Oliveria GS, *et al*. Ultrasound-guided trigeminal nerve block via the pterygopalatine Fossa: an effective treatment for trigeminal neuralgia and atypical facial pain. *Pain Physician* 2013;16:E537–45.
24 Smith CR, Fox WC, Robinson CP, *et al*. Narcotic-sparing treatment for headache in patients with spontaneous subarachnoid hemorrhage. *Neurocrit Care* 2021;35:241–8.
25 Mireault D, Cawthorn TR, Todd AR, *et al*. Suprazygomatic maxillary nerve block: an ultrasound and cadaveric study to identify correct sonoanatomical landmarks. *J Anesth* 2021;35:150–3.
26 Lai YH, Huang YC, Huang LT, *et al*. Cervical noninvasive Vagus nerve stimulation for migraine and cluster headache: a systematic review and meta-analysis. *Neuromodulation* 2020;23:721–31.
27 Diener H-C, Goadsby PJ, Ashina M, *et al*. Non-invasive Vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: the multicentre, double-blind, randomised, sham-controlled PREMIUM trial. *Cephalalgia* 2019;39:1475–87.
28 Villar-Martinez MD, Goadsby PJ. Non-invasive neuromodulation of the Cervical Vagus nerve in rare primary headaches. *Front Pain Res* 2023;4:1062892.
29 Ferrari MD, Klever RR, Terwindt GM, *et al*. Migraine pathophysiology: lessons from mouse models and human genetics. *Lancet Neurol* 2015;14:65–80.
30 Boezaart AP. Effects of cerebrospinal fluid loss and epidural blood patch on cerebral blood flow in swine. *Reg Anesth Pain Med* 2001;26:401–6.
31 Narouze S. Epidural blood patch is an iatrogenic epidural hematoma: asymptomatic or symptomatic? This is the question. *Reg Anesth Pain Med* 2020;45:1–4.
32 Salvant JB, Muizelaar JP. Changes in cerebral blood flow and metabolism related to the presence of subdural hematoma. *Neurosurgery* 1993;33:387–93;
33 Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology* 2001;56:1746–8.
34 Koep JL, Taylor CE, Coombes JS, *et al*. Autonomic control of cerebral blood flow: fundamental comparisons between peripheral and cerebrovascular Circulations in humans. *J Physiol* 2022;600:15–39.
35 Katz D, Beilin Y. Review of the alternatives to epidural blood patch for treatment of Postdural puncture headache in the parturient. *Anesth Analg* 2017;124:1219–28.
36 Anthony Cometa M, Zasimovich Y, Smith CR. Percutaneous sphenopalatine ganglion block: an alternative to the transnasal approach. *Int J Obstet Anesth* 2021;45:163–4.
37 Narouze S. Intranasal local anesthetic application: possible mechanisms of action. *Reg Anesth Pain Med* 2022;47:75–6.
38 Narouze SN. Role of sphenopalatine ganglion neuroablation in the management of cluster headache. *Curr Pain Headache Rep* 2010;14:160–3.
39 Fontaine D, Santucci S, Lanteri-Minet M. Managing cluster headache with sphenopalatine ganglion stimulation: a review. *J Pain Res* 2018;11:375–81.
40 Tracey KJ. The inflammatory reflex. *Nature* 2002;420:853–9.
41 A4-11-Epicrania-Fugax. n.d. Available: https://ichd-3.org/appendix/a4-other-primary-headache-disorders/a4-11-epicrania-fugax/
42 Pareja JA, Cuadrado ML, Fernández-de-las-Peñas C, *et al*. Epicrania fugax: an ultra-brief paroxysmal epicranial pain. *Cephalalgia* 2008;28:257–63.
43 Cuadrado ML, Guerrero AL, Pareja JA. Epicrania Fugax. *Curr Pain Headache Rep* 2016;20:1–7.
44 Alberola-Amores FJ, Moral-Rubio J. Drug-resistant epicrania fugax: responding to onabotulinumtoxinA. *Headache* 2023;63:839–42.
45 Villar-Martínez MD, Moreno-Ajona D, Chan C, *et al*. Indomethacin-responsive headaches: a narrative review. *Headache* 2021;61:700–14.
46 Peng KP, Wang SJ. Update of new daily persistent headache. *Curr Pain Headache Rep* 2022;26:79–84.

Reg Anesth Pain Med: first published as 10.1136/rapm-2023-104967 on 20 November 2023. Downloaded from http://rapm.bmj.com/ on April 18, 2024 by guest. Protected by copyright.