Procedural Treatment of Migraine

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Disclosures

• Honoraria for educational activities
  – Medlink neurology
  – American Headache Society
  – American Academy of Neurology
  – Springer

• Book royalties - Wiley

• Treatments discussed herein are off-label except SpringTMS, Cefaly, and onabotulinumtoxinA
Procedural Treatment of Migraine

1. Case and overview
2. Neurostimulation
3. OnabotulinumtoxinA
4. Peripheral nerve blocks
5. Trigger point injections
6. Sphenopalatine ganglion blocks
7. Training
8. Summary
Example case

• Bronx woman of Ecuadorian descent
• Migraine onset age 18 after mild head injury
• Gradual evolution to chronic migraine by age 40
• Severe depression
• DM, HTN, hyperlipidemia, sleep apnea
• Obese, but exam unrevealing
• Previous MRI, CSF normal
• Completely disabled
Example case

- Prophylactic drug trials: >30 agents
- Acute drug trials: numerous, including indomethacin
- Detoxification from all acute drugs: unchanged
- Peripheral nerve blocks: transient benefit
- Admission for IV therapies: transient benefit
- 10-20 ED visits per year
- Divalproex 1250mg/day
- OnabotulinumtoxinA → 20-25 HA days/month
- Referred for occipital nerve stimulation
Why are new therapies needed?

- Chronic migraine prevalent (1%), burdensome
- Remission rate low (26% over 2 years)
- Single FDA approval – OnabotulinumtoxinA
  - Ineffective in many
  - Therapeutic gain not large in absolute terms
- Oral prophylaxis
  - Effective in minority
  - Combination therapies – evidence poor
  - Adherence poor – 26-29% at 6 months

Buse DC et al, Headache 2012
Manack A et al, Neurology 2011
Aurora SK et al, Headache 2011
Silberstein SD et al, Neurology 2012
Hepp Z et al, Cephalalgia 2014
Neurostimulation for CM

<table>
<thead>
<tr>
<th>Anatomic target</th>
<th>Stimulation</th>
<th>Invasive</th>
<th>Treatment concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater occipital nerve</td>
<td>Electrical</td>
<td>Yes</td>
<td>Prevention</td>
</tr>
<tr>
<td>Supraorbital nerve</td>
<td>Electrical</td>
<td>Yes and no</td>
<td>Prevention</td>
</tr>
<tr>
<td>Vagus nerve</td>
<td>Electrical</td>
<td>No</td>
<td>Acute and Prevention</td>
</tr>
<tr>
<td>Sphenopalatine ganglion</td>
<td>Electrical</td>
<td>Yes</td>
<td>Acute and Prevention</td>
</tr>
<tr>
<td>Cervical cord</td>
<td>Electrical</td>
<td>Yes</td>
<td>Prevention</td>
</tr>
<tr>
<td>Cortex</td>
<td>Electrical, Magnetic</td>
<td>Yes and no</td>
<td>Acute and Prevention</td>
</tr>
</tbody>
</table>

FDA approved
- Cefaly
- SpringTMS
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Headache Disorders</th>
<th>Indication</th>
<th>Injection Series</th>
<th>Best evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum toxin A</td>
<td>Chronic migraine</td>
<td>NDPH</td>
<td>Prophylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nummular headache</td>
<td></td>
<td>Repetitive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trigeminal neuralgia</td>
<td></td>
<td>3 month intervals</td>
<td></td>
</tr>
<tr>
<td>Peripheral nerve blocks</td>
<td>Cluster Migraine</td>
<td>Hemicrania continua</td>
<td>Single or repetitive</td>
<td>Best evidence</td>
</tr>
<tr>
<td></td>
<td>Post-dural puncture headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trigger point injections</td>
<td>ETTH, CTTH</td>
<td>Migraine</td>
<td>Acute treatment or short-term prophylaxis</td>
<td>Single or repetitive</td>
</tr>
</tbody>
</table>
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“In spite of a growing field…further controlled studies to validate, strengthen and disseminate the use of neurostimulation are clearly warranted. Consequently, until these data are available any neurostimulation device should only be used in patients with medically intractable syndromes from tertiary headache centers either as part of a valid study or have shown to be effective in such controlled studies with an acceptable side effect profile.”
Neurostimulation: Mechanism

• Effect on periphery
  – Melzack-Wall gate-control theory
    • Large fiber stimulation $\rightarrow$ suppression of small fiber nociceptive input $\rightarrow$ pain threshold elevation

• Effect on CNS
  – Increased metabolic activity at TCC
  – Alterations in thalamic activity (PET studies)
  – Decreased GABA levels in PAG $\rightarrow$ engaged pain inhibitory mechanisms

Schwedt TJ, Curr Neurol Neurosci Rep 2009
Bartsch T et al, Curr Opin Neurol 2009
Neurostimulation: Targets

Adapted from Bartsch T et al, Curr Opin Neurol 2009
Central neuromodulation: PET study
Chronic migraine, occipital neurostimulation, n=8

- Pain correlation
  - dorsal rostral pons
  - ACC
  - cuneus

- Paresthesia correlation
  - ACC
  - pulvinar

Matharu MS et al, Brain 2004
### Randomized Sham-Controlled Studies Occipital Nerve Stimulation for CM

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Medication overuse</th>
<th>Therapeutic Response Requirement</th>
<th>Control</th>
<th>Primary Endpoint</th>
<th>Other endpoints? Subgroups?</th>
<th>Adverse Events (%)</th>
</tr>
</thead>
</table>
| **ONSTIM (Medtronic) N=60**  | Refractory chronic migraine             | Excluded (>15 days/month) | Occipital nerve block  
Intraoperative testing for adequate paresthesia | 1. Preset stimulation  
1 min/day  
2. Medically managed | None (feasibility study) | • 39% for active stimulation  
• 6% for preset stimulation  
• 0% for medically managed | Lead migration  
Infection  
Pain/numbness | 24  
18  
2 |
| **St. Jude N=157**           | Refractory chronic migraine             | Not excluded       | Temporary implanted stimulation trial, those with ≥50% pain relief enrolled | No stimulation         | ≥50% ↓mean daily pain score at week 12  
*not met* | • Pain intensity  
• Headache days  
• Disability | Pain/numbness  
Lead migration  
Infection | 22  
19  
7 |
| **PRISM (Boston Scientific) N=139** | Refractory episodic or chronic migraine  
(≥6 migraine days/28 day period) | Excluded opioid use >15 days/month | Percutaneous stimulation trial, 5-10 days active and placebo | 1 second on / 90 minutes off | ↓Migraine days/month at week 12  
*not met* | • Trend towards better improvement with no medication overuse  
• Secondary endpoints positive at 52 weeks | Implant site pain  
Sensory  
Infection  
Lead migration | 25  
18  
15  
8 |
ONS: 52-week follow-up (n=157)
12 weeks randomized, 40 weeks open-label

• Efficacy
  – Monthly headache days ↓ 6.7-7.7 (p < 0.001)
  – 50% reduction in headache days and/or pain intensity: 47.8%
  – 2/3 of patients satisfied

• Adverse effects: 70%
  – 8.6% required hospitalization
  – 40.7% required surgical intervention
Combined peripheral neurostimulation in CM

• Initial case series (n=7) in 2011
  – 6/7 headache freedom ("prompt")
  – 3/7 revisions (infection, migration, allergy)

• Preliminary report (163/188 surveyed) in 2014
  – Variable leads: SON, ON, temple, parietal, infraorbital, mandibular, vertex, cervical
  – Mean 14 month F/U
  – ≥50% dec. in HA freq. and/or severity = 85%
  – "Virtually complete headache resolution" = 50%

Reed K et al, Cephalalgia 2010
Linder S, AHS 2011
Reed K et al, AAN 2014
Supraorbital transcutaneous stimulation: Cefaly®

- Double-blind, sham-controlled trial, n=67
- Stimulation 250 µs, 60 Hz, 16 mA, 20 min / day

<table>
<thead>
<tr>
<th>3 months</th>
<th>Verum</th>
<th>Sham</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in mean migraine days</td>
<td>6.94 → 4.88</td>
<td>6.54 → 6.22</td>
<td>Verum 0.023*, Sham 0.608</td>
</tr>
<tr>
<td>50% responder rate</td>
<td>38.1%</td>
<td>12.1%</td>
<td>0.023*</td>
</tr>
</tbody>
</table>

Schoenen J *et al*, Neurology 2013
### Supraorbital transcutaneous stimulation

<table>
<thead>
<tr>
<th>AEs Reported by &gt;1 Patient (40-day trial period)</th>
<th>Patients (N)</th>
<th>AEs (%)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not like the feeling and want to discontinue use</td>
<td>29</td>
<td>29.29</td>
<td>1.25</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>12</td>
<td>12.12</td>
<td>0.52</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>12.12</td>
<td>0.52</td>
</tr>
<tr>
<td>Reversible forehead skin irritation</td>
<td>5</td>
<td>5.05</td>
<td>0.22</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>4.04</td>
<td>0.17</td>
</tr>
<tr>
<td>Feeling of fatigue</td>
<td>3</td>
<td>3.03</td>
<td>0.13</td>
</tr>
<tr>
<td>Forehead paresthesia for several minutes post-session</td>
<td>3</td>
<td>3.03</td>
<td>0.13</td>
</tr>
<tr>
<td>Feeling of stress during the session</td>
<td>3</td>
<td>3.03</td>
<td>0.09</td>
</tr>
<tr>
<td>Allergic skin reaction</td>
<td>2</td>
<td>2.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Dental pain during the session or at the beginning</td>
<td>2</td>
<td>2.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Inability to keep eyes open during sessions</td>
<td>2</td>
<td>2.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Feeling of contusion on the forehead during a few days</td>
<td>2</td>
<td>2.02</td>
<td>0.09</td>
</tr>
</tbody>
</table>

2,313 renters  
Mean 58.2 day rental  
46.6% unsatisfied, returned device

Magis D et al, J Headache Pain. 2013
Supraorbital transcutaneous stimulation

FDA NEWS RELEASE

For Immediate Release: March 11, 2014

FDA allows marketing of first medical device to prevent migraine headaches

Today, the U.S. Food and Drug Administration allowed marketing of the first device as a preventative treatment for migraine headaches. This is also the first transcutaneous electrical nerve stimulation (TENS) device specifically authorized for use prior to the onset of pain.

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm388765.htm
http://www.cefaly.us/en/cefaly-shop
Noninvasive vagus nerve stimulation
Open label acute migraine treatment

- 27 patients treating 80 attacks
- 90 sec doses x2, 15 min intervals to right cervical branch
- Efficacy (2 hours):
  - 21% pain free
  - 47% pain relief
- Adverse events:
  - Stiff neck (n=5)
  - Polyuria (n=4)

Goadsby PJ et al, Cephalalgia 2014
nVNS Chronic Migraine Prevention EVENT Study

- Sham-controlled for 8 weeks; n=59
- Stimulation 90 sec doses x2, 15 min intervals, 3x per day to right cervical branch

<table>
<thead>
<tr>
<th>Over 28 days</th>
<th>nVNS</th>
<th>Sham</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HA day reduction</td>
<td>-1.90</td>
<td>+0.20</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;50% reduction of HA days</td>
<td>11.5%</td>
<td>0%</td>
<td>NR</td>
</tr>
</tbody>
</table>

- Adverse events:
  - Infection
  - Facial twitching
  - Local pain, swelling, rash

Silberstein S et al, AHS 2014
Sphenopalatine Ganglion Stimulation
ATI Neurostimulation System

Schoenen J *et al.*, *Cephalalgia* 2013
Sphenopalatine ganglion stimulation
Chronic cluster headache treatment

- Acute treatment (n=28)
  - Pain relief in 67.1% (active) vs 7.4% (sham) (p< 0.0001)
  - 81% V2 numbness
- Prophylaxis (n=18, interim)
  - 28.4 → 17.3 mean attacks / week overall
  - 22.3 → 2.1 mean attacks / week in 9 “frequency responders”

Ansarinia M et al, Headache 2010
Schoenen J et al, Cephalalgia 2013
Jurgens TP et al, EHMTIC 2014
SPG stimulation for migraine

- N=11, open label
- Results:
  - 2: pain-free within 3 minutes of stimulation
  - 3: pain reduction
  - 5: no response
  - 1: not stimulated
- Lack of relief:
  - suboptimal lead placement,
  - poor physiologic sensory response
  - MOH
- Well-tolerated

Tepper SJ et al, Headache 2009
Cervical cord neurostimulation

• Used in neuropathic pain, failed back, CRPS, postherpetic neuralgia, angina, PVD, cluster
• N=17, median F/U 15 months (2–48)
• Outcomes:
  – Pain intensity ↓60% ($p < 0.0001$), 71% ↓≥50%
  – Median migraine days: 28 (12–28) $\rightarrow$ 9.0 (0–28) ($p = 0.0313$)
  – Quality of life, not working capacity improved
• Complications:
  – infection (13.0%)
  – lead dislocations (17.6%)

De Agostino R et al, Neuromodulation 2014
Transcranial magnetic stimulation
Rationale

- sTMS inhibits CSD in animal models
- Modulates cortico-thalamic activation; no clear affect in the TCC
- May lead to persistent changes in brain excitability and modulate neurotransmitter levels
- Traditional TMS devices: hospital, clinic, or office-based settings

Lipton RB, et al, Neurotherapeutics 2010
Goadsby P, Scottsdale Headache Symposium 2014
sTMS: migraine with aura
Multicenter, sham-controlled trial, n=201

- ≥30% of attacks: with aura
- ≥90% of attacks: aura followed by headache
- Device to occiput: 2 sTMS impulses x 30 sec
- Pain freedom rates:

<table>
<thead>
<tr>
<th></th>
<th>2 hours</th>
<th>24 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>sham</td>
<td>22%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>sTMS</td>
<td>39%</td>
<td>29%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Lipton RB et al, Lancet Neurol 2010
sTMS for migraine
post-market pilot program in UK

- Episodic (n=59) and chronic (n=131) migraine
- Pulses: single, double or multiple; some daily
- No serious or unanticipated adverse events
- 3 patients treated in pregnancy

### Monthly Headache Days

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Episodic</strong></td>
<td>12 (median, 8–13 IQ range)</td>
<td>9 (4–12)</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td>24 (median, 16–30 IQ range)</td>
<td>16 (10–30)</td>
</tr>
</tbody>
</table>

Bhola R et al, J Headache Pain 2015
TMS for migraine: safety

• Seizure risk
  – Mainly with medically-intractable epilepsy
    • sTMS: 0.0% to 2.8%
    • rTMS: 0.0% to 3.6%

• No adverse consequences on:
  – Brain tissue
  – Prolactin, cortisol
  – Cognition
  – BP, HR
  – Hearing

Dodick DW et al, Headache 2010
Schrader LM et al, Clin Neurophysiol 2004
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Botulinum toxin: molecular action

• Therapeutic neurotoxin derived from *Clostridium botulinum*; secretes 7 serotypes (A-G)

• Blocks neurotransmitter release (exocytosis) at peripheral nerve terminals

• Cleavage target is SNAP-25 (t-snare), which attaches to syntaxin & the presynaptic membrane
Botulinum toxin: chronic migraine

1. Peripheral sensory effect
2. Transcranial afferent effect
3. Trigeminal-autonomic reflex effect
4. Direct central inhibition of trigeminovascular neurons

Kosaras *et al*, *J Comp Neurol* 2009
OnabotulinumtoxinA: Mechanism

- reduces peripheral sensitization
- reduces central sensitization
- inhibits release of several neuronal signaling markers
- reduces c-fos gene expression in dorsal horn, trigeminal nucleus caudalis

Aoki KR, Headache 2003
OnabotulinumtoxinA: Mechanism?

Extracranial projections of meningeal afferents form functional connections between extra and intracranial tissues.
Injection Technique

• Needle size
  – 30-gauge with 1cc tuberculin syringe

• Patient position
  – Sitting for posterior injections
  – Lying for frontal and temporalis injections

• Dilution
  – 200 U (4ml NS) x1
  – 100 U (2ml NS) x2

• Dose range
  – 155 to 195 U
Fixed-Site, Fixed-Dose Injection

Corrugator 10U

Procerus 5U

Frontalis 20U
Fixed-Site, Fixed-Dose Injection

- Temporalis 20U (each side)
- Occipitalis 30U
- Cervical Paraspinal 20U
- Trapezius 30U
Follow the pain

Temporalsis 5U/site (≤2 additional sites)

Occipitalis 5U/site (≤2 additional sites)

Trapezius 5U/site (≤4 additional sites)
OnabotulinumtoxinA for chronic migraine

versus other agents: similar efficacy, better tolerated

Dodick DW et al, Headache 2010
Blumenfeld A et al, Headache 2008
Mathew NT et al, Headache 2009
Safety in chronic migraine

- Neck pain 5.9-7.5%
- Muscle weakness 5.2-5.9%
- Extreme caution in patients with neuromuscular junction disorders
- Avoid in those who take medications that affect neuromuscular transmission
- One fatal case in use for pain (reconstituted in lidocaine)

Aurora S et al, Cephalalgia 2010
Diener HC et al, Cephalalgia 2010
Li M et al, J Forensic Sci 2005
Response prediction: pain directionality

Jakubowski M et al, Pain 2006
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Peripheral nerve blocks

Blumenfeld A et al, Headache 2013
Peripheral nerve blocks

- Decreasing afferent input to TNC
  - Decreased activation of central structures involved in pain perception

- Mechanism
  - Unrelated to reducing local pain
  - Example: response to cluster headache V1 pain in GON injection
  - Aborts aura, treats photophobia, distant allodynia
Table 1.—Potential Indications for Peripheral Nerve Blocks in the Treatment of Headache Disorders

<table>
<thead>
<tr>
<th>Headache Disorder</th>
<th>Nerve(s) Blocked</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary headache disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>GON, STN, SON</td>
<td>Retrospective$^{23,25}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective, noncontrolled$^{12,26}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case series$^4,13$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open label$^{14}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retrospective$^{15}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Double blind, placebo controlled$^{7,8}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case series$^4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open label$^{27}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective, noncontrolled$^{28}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective, randomized controlled$^{20}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case series$^4,18$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case series$^4,29$</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>GON</td>
<td></td>
</tr>
<tr>
<td>Chronic daily headache</td>
<td>GON</td>
<td></td>
</tr>
<tr>
<td>Hemicrania continua</td>
<td>GON, SON</td>
<td>Case series$^{40,31}$</td>
</tr>
<tr>
<td>New daily persistent headache</td>
<td>GON</td>
<td>Retropective$^{25}$</td>
</tr>
<tr>
<td>Secondary headache disorders</td>
<td></td>
<td>Prospective, noncontrolled$^{32}$</td>
</tr>
<tr>
<td>Cervicogenic headache</td>
<td>GON, LON, SON</td>
<td>Prospective, comparative$^{33}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Double blind, placebo controlled$^{34}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retrospective$^{35}$</td>
</tr>
<tr>
<td>Post-traumatic headache</td>
<td>GON</td>
<td>Prospective, comparative$^{36}$</td>
</tr>
<tr>
<td>Post-dural puncture headache</td>
<td>GON, LON</td>
<td></td>
</tr>
<tr>
<td>Cranial neuralgias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraorbital neuralgia</td>
<td>SON</td>
<td>Case series$^{37,39}$</td>
</tr>
<tr>
<td>Auriculotemporal neuralgia</td>
<td>ATN</td>
<td>Case series$^{40}$</td>
</tr>
</tbody>
</table>
Local Anesthetics

• Preferentially block sensory nerve fibers
  – Block pain fibers (Aδ, C)
  – Spare motor fibers (Aα)

• Basis of selective blockade—myelin sheath thickness affects drug penetration

• Bind to sodium channels, producing reversible conduction blockade—axons differ in sodium channel density
Local Anesthetics

- Duration of nerve blockade depends on dose and pharmacokinetic properties of local anesthetic.
- Longer than expected duration of analgesic (vs anesthetic) effect of nerve block is common.
- Mechanism of prolonged analgesic effect incompletely understood.

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical concentration</td>
<td>1-2% (10-20 mg/mL)</td>
<td>0.25%-0.5% (2.5-5 mg/mL)</td>
</tr>
<tr>
<td>Duration of effect</td>
<td>1-3 hours</td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>300 mg</td>
<td>175 mg</td>
</tr>
</tbody>
</table>
Nerve blocks with steroids

- Migraine: no benefit versus anesthetic alone
- Cluster: should be used in GON injections
  - 2 RCTs
- Adverse effects
  - Systemic if repetitive
  - Local if dose high

Blumenfeld A et al, Headache 2013
Ashkenazi A et al, J Neurol Neurosurg Psychiatry 2008
Ambrosini A et al, Pain 2005
Leroux E et al, Lancet Neurol 2011
Shields KG et al, Neurology 2004
Injection Technique Considerations

- **Needle size**
  - 25-30 gauge needle
  - 1-10 mL syringe: depends on number of nerve injections and if targeting trigger points

- **Patient position**: depends on nerve being injected
  - Sitting vs lying down

- **Injectate**
  - 1-2% lidocaine and/or bupivacaine 0.25-0.5%; 1:1 volume ratio
  - Add triamcinolone (5-40mg), methylprednisolone (20-80mg), dexamethasone (4-8mg) for cluster
  - Volume 0.2-4mL

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Blumenfeld A et al, Headache 2013
Peripheral nerve blocks

Blumenfeld A et al, Headache 2013
Peripheral nerve blocks

Blumenfeld A et al, Headache 2013
Table 2.—Potential Precautions and Contraindications for Peripheral Nerve Blocks in the Treatment of Headache Disorders

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Concern</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthesia allergy</td>
<td>Allergic reaction, including anaphylaxis</td>
<td>PNB with local anesthetic contraindicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use corticosteroids only&lt;sup&gt;19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Elderly</td>
<td>Hypotension</td>
<td>Reduce concentration of anesthetic (avoid lidocaine 5%)&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Limit number of nerves to be blocked in a single session</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restrict PNB to unilateral GON injection if possible</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Teratogenicity</td>
<td>Use lidocaine (FDA Category B) over bupivacaine (FDA Category C)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid betamethasone and dexamethasone (accelerate fetal lung development)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caution is warranted in the use of any corticosteroids in the pregnant population</td>
</tr>
<tr>
<td>Prior vasovagal attacks</td>
<td>Vasovagal reaction</td>
<td>Perform PNB in supine position, where feasible</td>
</tr>
<tr>
<td>Prior syncopal attacks</td>
<td>Presyncope or syncope</td>
<td>Use bupivacaine instead of lidocaine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce concentration of anesthetic agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allow for extra time in the supine position after the procedure as a precaution</td>
</tr>
<tr>
<td>Open skull defect</td>
<td>Intracranial diffusion of anesthetic agent</td>
<td>PNB contraindicated&lt;sup&gt;42,43&lt;/sup&gt;</td>
</tr>
<tr>
<td>Craniotomy</td>
<td></td>
<td>Extra attention to palpate for (and avoid) neighboring arteries (occipital, temporal)</td>
</tr>
<tr>
<td>Anticoagulation therapy</td>
<td>Hematoma</td>
<td>Compress at each PNB site for 5-10 minutes</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td>Avoid corticosteroids</td>
</tr>
<tr>
<td>Cosmetic concerns</td>
<td>Alopecia</td>
<td>If methylprednisolone must be used, dose &lt;80 mg in GON region&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Occipital nerve block with steroid: short-term migraine prophylaxis

- Adults (18–75 years old) with episodic or chronic migraine
- Double-blind, placebo-controlled
- Primary endpoint: ≥50% frequency reduction mod-severe headache days at 4 weeks
- Treatments: unilateral or bilateral GON injection
  - Active: 2.5 ml 0.5% bupivacaine + 0.5 ml 20mg methylprednisolone (n=34)
  - Placebo: 0.25 ml 1% lidocaine + 2.75 NS (n=35)
- 30% of patients in both groups met the primary endpoint (Δ0.00, 95% CI -0.22 to 0.23)
- Injection site pain (4 active, 2 placebo)

Dilli E et al, Cephalalgia 2015
Repetitive Occipital Nerve Blocks for Chronic Migraine

- Double-blind, placebo-controlled, multicenter
- Treatments: weekly unilateral or bilateral GON injections
  - Active: 1.5 ml 0.5% bupivacaine + 1 ml NS (n=39)
  - Placebo: 2.5 ml saline (n=33)
- After 1 month of treatment:

<table>
<thead>
<tr>
<th>1° Endpoint</th>
<th>Active</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache days</td>
<td>18.1 ± 5.3 to 8.8 ± 4.8</td>
<td>16.9 ± 5.7 to 13.2 ± 6.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Headache duration (hours)</td>
<td>25.9 ± 16.3 to 19.3 ± 11.5</td>
<td>24.2 ± 13.7 to 21.2 ± 13.4</td>
<td>0.767</td>
</tr>
<tr>
<td>Pain score</td>
<td>8.4 ± 1.5 to 5.3 ± 2.1</td>
<td>8.1 ± 0.9 to 6.7 ± 1.6</td>
<td>0.004</td>
</tr>
</tbody>
</table>

- AEs: local pain, vertigo, nausea

Other patient populations

Outcomes of Greater Occipital Nerve Injections in Pediatric Patients With Chronic Primary Headache Disorders

Amy A. Gelfand MD a,b,* , Amanda C. Reider MD c , Peter J. Goadsby MD, PhD a

Peripheral Nerve Blocks in the Treatment of Migraine in Pregnancy

Shravya Govindappagari, MD, Tracy B. Grossman, MD, MSc, Ashlesha K. Dayal, MD, Brian M. Grosberg, MD, Sarah Vollbracht, MD, and Matthew S. Robbins, MD
Peripheral nerve blocks: pregnancy

- 27 PNBs in 13 pregnant women
- Single (n=6) or multiple (n=7) injection series
- All migraine, 38.5% chronic migraine
- Indications:
  - status migrainosus 51.8%
  - short-term prophylaxis 48.1%
- All failed PO meds, most failed IV meds

Peripheral nerve blocks: pregnancy

• Pain reduction
  – status migrainosus
    • -4.0 (±2.6), p<.001 immediately postprocedure
    • -4.0 (±4.4), p=.007 24h postprocedure
  – short-term prophylaxis
    • -3.0 (±2.1) immediately postprocedure

• Safety
  – No serious, procedurally related adverse events
  – 1 brief vasovagal attack
  – 2 patients with no acute pain reduction ultimately developed preeclampsia → postpartum resolution

Expert consensus statement

Review Article

Expert Consensus Recommendations for the Performance of Peripheral Nerve Blocks for Headaches – A Narrative Review

Andrew Blumenfeld, MD; Avi Ashkenazi, MD; Uri Napchan, MD; Steven D. Bender, DDS; Brad C. Klein, MD; Randall Berliner, MD; Jessica Ailani, MD; Jack Schim, MD; Deborah I. Friedman, MD, MPH; Larry Charleston IV, MD; William B. Young, MD; Carrie E. Robertson, MD; David W. Dodick, MD; Stephen D. Silberstein, MD; Matthew S. Robbins, MD
Procedural Treatment of Migraine

1. Case and overview
2. Neurostimulation
3. OnabotulinumtoxinA
4. Peripheral nerve blocks
5. Trigger point injections
6. Sphenopalatine ganglion blocks
7. Training
8. Summary
What are trigger points?

- Hyperirritable focus within muscle or fascia
- Tender, taut band
- “Twitch response”
- Stereotyped pain referral to distant structures
- Identified on physical exam
- Active TPs found more often in headache disorders

Simons DG et al, Trigger Point Manual 1999
Fernandez-de-Las-Penas C et al, Headache 2006
Robbins MS et al, Headache 2014
Trigger point pathophysiology poorly understood

- Abnormal endplate potentials
- Excessive Ach release in NMJ
- Taut band in muscle
- Peripheral sensitization
- Local ischemia, hypoxia, algogenic substances
- Central sensitization
- Hyperalgesia, allodynia

Simons DG et al, Trigger Point Manual 1999
Robbins MS et al, Headache 2014
Injection technique

- Seated or recumbent position
- 22-30 gauge, 1.5-inch needle
- Hold overlying skin and stabilize between thumb and index finger
- Insert 1-1.5 cm away from the TP, advance at 30°
- Local anesthetics
  - 0.1–0.3 cc of 1% lidocaine or 0.5% bupivacaine
  - 1-4 mL per site

Robbins MS et al, Headache 2014
Trigger point injections: 3 most common muscles

Robbins MS et al, Headache 2014
<table>
<thead>
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<th>Patient Population</th>
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<tbody>
<tr>
<td>Local anesthesia allergy</td>
<td>Allergic reaction, including anaphylaxis</td>
<td>Local anesthetic contraindicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use saline, corticosteroids, or other agents only</td>
</tr>
<tr>
<td>Vulnerability to neurally-mediated syncope or hypotension</td>
<td>Near syncope Syncope</td>
<td>Reduce concentration of anesthetic (^{64})</td>
</tr>
<tr>
<td>• First TPI series</td>
<td></td>
<td>Limit number of total TPIs in a single session</td>
</tr>
<tr>
<td>• Pregnancy</td>
<td></td>
<td>Perform TPIs in supine or prone position, where feasible</td>
</tr>
<tr>
<td>• Elderly</td>
<td></td>
<td>Allow for extra time in the supine position after the procedure as a precaution</td>
</tr>
<tr>
<td>• History of vasovagal events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dehydration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Protracted headache attack with nausea and/or vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Teratogenicity</td>
<td>Local anesthetics may be preferable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use lidocaine (FDA Category B) over bupivacaine (FDA Category C)</td>
</tr>
<tr>
<td>Open skull defect</td>
<td>Intracranial diffusion of anesthetic agent</td>
<td>TPI may be contraindicated, but if benefits &gt; risks inject at a distance or contralateral from defect</td>
</tr>
<tr>
<td>Craniotomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local or systemic infection</td>
<td>Abscess, cellulitis, myositis</td>
<td>Avoid TPI</td>
</tr>
<tr>
<td>Immunocompromise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulation therapy</td>
<td>Hematoma</td>
<td>Recent INR should be available if taking warfarin, and avoid TPI if &gt;3.0</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td>Extra attention to palpate for (and avoid) neighboring arteries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimize total number of injection sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only perform TPI in superficial and easily compressible sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compress at each TPI site for 5-10 minutes</td>
</tr>
<tr>
<td>Cosmetic concerns</td>
<td>Cutaneous or muscle atrophy Alopecia</td>
<td>Avoid corticosteroids</td>
</tr>
<tr>
<td>Obesity or thin body habitus</td>
<td>Pneumothorax</td>
<td>Avoid TPI in those regions, especially trapezius</td>
</tr>
<tr>
<td>Unclear anatomical landmarks</td>
<td></td>
<td>Use a smaller needle (27 gauge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use EMG or sonographic guidance</td>
</tr>
</tbody>
</table>
Expert consensus statement

Review Articles

Trigger Point Injections for Headache Disorders: Expert Consensus Methodology and Narrative Review

Matthew S. Robbins, MD; Deena Kuruvilla, MD; Andrew Blumenfeld, MD; Larry Charleston IV, MD; Michael Sorrell, MD; Carrie E. Robertson, MD; Brian M. Grosberg, MD; Steven D. Bender, DDS; Uri Napchan, MD; Avi Ashkenazi, MD
Procedural Treatment of Migraine

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Vinny Barbarino technique

Up your nose with a rubber hose.
Sphenopalatine ganglion blocks

SphenoCath®

Allevio™

Tx360®
**SPG Blockade**

**Chronic migraine** (N=38)
- B/L SPG blocks twice per week for 6 weeks
- Sig. pain reductions vs placebo at 15m, 30m, 24h post-treatment
- HIT-6 scores significantly decreased from before treatment to the final treatment ($P=0.005$) vs NSD in the placebo group
- No significant or lasting adverse events (abnormal taste $\rightarrow$ blinding?)
- $2^\circ$ endpoints: Decreased headache days at 1 month, HIT-6 scores at 1 and 6 months, and medication usage; trends but NSD vs placebo

**Emergency department**: acute headache
- 50% pain reduction: 48.8% bupivacaine vs 41.3% placebo (No SD)
- 24-hour headache-free: 24.7% difference (95% CI 2.6%–43.6%)
- 24-hour nausea free: 16.9% difference (95% CI 0.8% to 32.5%)

Cady R *et al*, *Headache* 2015
Cady R *et al*, *Headache* 2015
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Headache procedures: training

- Clinic-based procedures have assumed a more prominent role in neurology practice, especially headache.
- Relying solely on fellowship-trained headache neurologists cannot match the population eligible for treatments.
- Need for general neurologists to develop procedural expertise to accommodate patients in their practice.
- Residency curriculum does not include the development of expertise nor a mechanism for credentialing interested trainees.

Robbins MS et al, Headache 2015
Headache procedures: training

- Web-based, 17 question survey of US neurology residency PDs
- Collaboration between AHS procedural, AAN headache SIS
- OnabotulinumtoxinA (onabotA), peripheral nerve blocks (PNBs), trigger point injections (TPIs)

55 PDs (42.6%) completed the survey; vs non-completers:
  - Program class size 6.1 vs 5.3, p=0.18
  - Headache division 56.4% vs 41.9%, p=0.10
  - Headache fellowships 38.2% vs 10.8%, p=0.0002

Robbins MS et al, Headache 2015
Headache procedures: training

• Exposure
  – Rates: onabotA=90.9%, PNBs=80.0%, TPIs=70.9%
  – Type: hands-on patient instruction (66.2%), lectures (55.7%)
• Residents perform procedures?
  – Rates: onabotA=65.5%, PNBs=60.0%, TPIs=52.7%
  – Venue: continuity clinic (60.0%), headache elective (50.9%)
  – Supervisors: headache (69.1%) or general neurology (32.7%) faculty
• Formal credentialing
  – Uncommon (16.4-18.2%)
  – Mechanism: documenting supervised procedures (25.5%)
• Permission for independent performance 27.3% of programs
• PD views – importance?
  – Procedural exposure: 80.0-90.9%
  – Procedural competence: 50.9-56.4%
Procedural Treatment of Migraine

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Example case

- B/L ONS (Boston Scientific) implanted
- After 1 month headache frequency 5-10 days per month → stable >3 years
- OnabotulinumtoxinA dose reduced (leads)
- Divalproex <1000mg/day lead to HA worsening
- Father died (pancreatic cancer) → did not worsen
- Finished coursework and able to go back to work
What else is coming?

- 4 CGRP-related mAbs
- 5HT$_{1F}$-agonist – Lasmitidan phase 3 trials
- Occipital Cefaly
- OnabotulinumtoxinA vs topiramate
- Oxytocin INH
- “Migraine surgery” – will we get a multicenter RCT?
Take home points

1. Emerging therapies are in need because currently available treatments are few, insufficient, and feature low adherence.

2. Neurostimulation leads to CNS modulation based on PNS or direct CNS targets.

3. Approved therapies include supraorbital TNS for migraine prevention and sTMS for migraine with aura.
Take home points

4. Implantable occipital nerve stimulation has been extensively studied, but efficacy is not clear and lead migration is a common complication.

5. Invasive and noninvasive stimulation designed for acute therapies may also have beneficial longer term prophylactic effects.
Take home points

6. Therapeutic injections for headache can be performed effectively, safely, and efficiently after gaining a basic understanding of the literature and anatomic landmarks.

7. Onabotulinumtoxin A is indicated for chronic migraine, and is effective, safe and with few contraindications.

8. Peripheral nerve blocks have the best evidence for cluster headache, but are useful for many headache disorders.
Take home points

9. Adding a steroid to an occipital nerve block may be particularly effective for cluster headache but is of uncertain benefit for migraine.

10. Trigger point injections have the least amount of evidence but may be effective in tension-type headache and migraine, are identified by physical examination, and should be restricted to local anesthetics only.

11. Training mechanisms are desired but lacking.