Peripheral Nervous System Targets: Therapeutic Targets of the Future

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Disclosures

- None

Overview

- Pathophysiology and rationale for Peripheral Nervous System (PNS) Targets
- Nerve blocks/Nerve ablations
  - Occipital nerve blocks
- Neuromodulation
  - Transcutaneous nerve stimulator
  - Vagus nerve stimulator
- Cervical nerve targets
Pathophysiology and Rationale

- Input through peripheral afferents may modulate trigeminal nociceptive signaling through convergence on the trigeminal nucleus caudalis (TNC) in the trigeminocervical complex.
- Benefits of PNS targets:
  - Nonpharmacologic
  - May reduce abortive use
  - Fewer systemic side effects
  - Fewer medical contraindications
  - New mechanism for nonresponders

How do we target the PNS?

Modalities
- Nerve blocks
- Nerve ablations
- Neuromodulation

Targets for Nerve Blocks and Lesioning

Nerve Blocks
- Trigeminal Nerve
  - Branches of V1: Supratrochlear, Supraorbital
  - Branches of V2: Infraorbital
  - Branches of V3: Auriculotemporal
  - Sphenopalatine Ganglion
  - Transnasal injection
- Occipital Nerve
- Greater Occipital Nerve (GON)
- Lesser Occipital Nerve (LON)

Nerve Lesioning
- Trigeminal Nerve (V2, V3)
  - Radiofrequency ablation (RFA)
- Sphenopalatine Ganglion
  - RFA
- Occipital Nerves
  - RFA
Occipital Nerve Blocks

- 65% - 76% adult neurologists perform nerve blocks.\(^{1,2}\)
- 63% pediatric neurologists perform nerve blocks.\(^3\)
- Not included in treatment guidelines for migraine by AHS, AAN, IHS, EFNS, or CHS.
- Observational studies often with conflicting or weakly positive data.
- Seven randomized, controlled studies.
  - Six show GON benefit.

Updates to the Literature

  - Repeated GON block with bupivacaine decreased headache days and pain scores at 1, 2 and 3 months.
  - Decrease in medium-severe headache days in week after block.
  - Increase in pressure pain thresholds in trigeminal area.

Updates to the Literature, cont.

  - 87% of patients had a 30% reduction in pain.
  - 58% of patients had a 50% reduction in pain.
  - Correlation between ≥ 2 GON blocks and reduction in pain score.
  - 36.2% decrease in pain intensity and 18.3% in analgesic use.
RCTs on GON Blocks in Migraine

GON BLOCK EFFECTIVE FOR ACUTE AND CHRONIC MIGRAINE MANAGEMENT

Final Thoughts on Occipital Nerve Blocks

- Effective, safe, well-tolerated, rapid, inexpensive
- Insurance considerations
- Questions remaining:
  - Ideal treatment frequency
  - Ideal injectate combination
  - Acute, preventive or both?

Neuromodulation

- Botulinum toxin
- Implantable nerve stimulator: (Occipital, SPG, Vagus)
- Transcutaneous nerve stimulator
- Cefaly: external trigeminal nerve stimulation (eTNS)
- Vagus Nerve Stimulator
- gammaCore: Noninvasive vagus nerve stimulation (nVNS)
- Calmar: Vascular Stimulator
- Remote Nonpainful Electrical Upper Arm Skin Stimulation
eTNS: Cefaly

- May involve modulation of central pain processing centers
- Increase in metabolism of orbitofrontal cortex and rostral anterior cingulate cortex in migraineurs after 3 months of Cefaly use
- Approved for acute migraine treatment in 2017

ACME trial

- Primary endpoint: Mean change in pain score after 1h
- Secondary endpoints: Mean change in pain intensity 2h and 24h
  - Percentage not using rescue meds 2h and 24h
  - Met primary endpoint
  - Pain intensity reduced by 59% vs. 30%
- Secondary endpoints:
  - Pain intensity reduced at 2h and 24h
  - No difference in use of pain meds at 24h

Cefaly

- Safe, well-tolerated
- Considerations: cost
- Use in special populations
nVNS: gammaCore

- Mechanism of action may involve:
  - Inhibition of nociceptive pathways that converge on TNC
  - Decreased CSDs
  - Inhibition of dural evoked trigemino-cervical nociceptive firing
  - Approved for acute migraine treatment in 2018

PRESTO trial

- Primary endpoint:
  - Pain freedom at 2h
- Secondary endpoints:
  - Pain relief at 2h
  - ≥ 50% responder rate
- Did not meet primary endpoint
  - 30.4% vs 19.7% (P=0.067)
- Met secondary endpoints
  - 40.0% vs 27.6% had pain relief
  - 47.6% of patients had relief for ≥50% of all treated attacks

gammaCore

- Safe, relatively well tolerated
- Considerations: cost
- Use in special populations

Gammacore.com


Tassorelli et al. 2018, Image used with permission from Eric Liebler
Cervical Targets of Headache

- No sensory dermatomal or cutaneous branches of C1 have been described.
- C1 spinal nerve present in 100% of cadaveric specimens.
- C1 dorsal roots in 46.6%.
- C1 DRG in 28.5%.
- 100% of C1 DRGs have neuronal cell bodies and sensory neurons.
- C1 structures never examined in living individuals.

C1 Referral Patterns

- Stimulation of C1 spinal nerve evokes periorbital and frontal pain in migraineurs versus occipital or cervical pain in nonmigraine controls.

UCLA Cervical Nerve Imaging Study

- Specialized craniovertebral junction MRI.
- Migraine with and without pain.
- Cluster headache patients.
- Controls with no headache disorder.
- Research questions:
  - Difference in incidence of C1 in primary headache disorder vs. controls?
  - Laterality of structure compared with pain?
  - Variations in anatomy of C1 and surrounding structures.
The innervation of the scalp: A comprehensive review including anatomy, pathology, and neurosurgical correlates. Surgery of


M et al; on behalf of the PRESTO Study Group. The

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