THE DORSAL ROOT GANGLION: Target for Neuromodulation in the Treatment of Chronic Pain

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DISCLOSURES

- Medtronic
- Spinal Modulation
TARGETS FOR NEUROMODULATION

Brain Stimulation

Spinal Cord Stimulation
- Stimulation of the Dorsal Column
- Stimulation of the Intraspinal Nerve Roots
- Stimulation of the Dorsal Root Ganglion

Peripheral Nerve Stimulation

PNFS Stimulation

DORSAL ROOT GANGLION: DESCRIPTION OF THE NEURAL TARGET

The DRG is a critical structure in pain transmission and also in transduction and modulation
- Houses soma from primary sensory neurons involved in pain transmission
- Over 15,000 neurons per DRG at segmental levels where major plexus innervate the limbs
- Location is predictable: lateral epidural space within the spinal foramen which makes it easy to target with the right tools

Axial cryomicrotome section through C5/6 intervertebral foramen

“That uninhibited state, however, can last too long, leaving DRG cells hypersensitized and causing them to fire pain messages without an external stimulus. This situation is the primary cause of neuropathic pain.”

PATHOLOGICAL CASCADE LEADING TO NEUROPATHIC PAIN

- Increased neuronal discharge from primary sensory neurons
- Increase EAA release
- Increased ATP, NO release
- Increased neural peptide release

- Activate surrounding glia
- Release proinflammatory cytokines
- Ultimately stimulates neurons
- Increased membrane excitability
THE PREDICTABILITY OF THE LOCATION OF THE DRG

- In the epidural space
- Within the neural foramen
- Between the medial and lateral aspects of the pedicle


NEUROMODULATION OF THE DORSAL ROOT GANGLION

- Therapies result in short-term pain relief to treat radicular pain
  - Drug Delivery
    - Local anesthetics
    - Corticosteroids
  - Radiofrequency
    - Pulsed
    - Non-pulsed
    - Repeat treatment is often necessary
- Key takeaways from these techniques
  - Procedures are safe
  - The DRG is an attractive, robust target

Neuromodulation of the dorsal root ganglion has been utilized safely for many years
**POWER REQUIREMENTS FOR STIMULATION OF THE DRG**

- Predictability of target allows for placement directly next to target neural tissue
- Minimal CSF near neural target results in less energy lost to extraneous tissue

**DRG Stimulation uses 92.5% less power than Dorsal Column Stimulation**

<table>
<thead>
<tr>
<th>Power (nW)</th>
<th>Intraspinal DRG Stimulation</th>
<th>Dorsal Column Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>5</td>
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</tbody>
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*Based on clinically relevant settings*

1 Abejon, Pain Physician, 2007.
2 A Prospective Trial to Assess the Safety and Efficacy of the Spinal Modulation Neurostimulator System in the Treatment of Chronic Pain

**Caution – The Spinal Modulation Neurostimulator System is not approved for use or sale in the United States.**

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**DRG: SUBDERMATOMAL SPECIFICITY**

- Nerve fibers are roughly somatotopically arranged
- Potential for different activation thresholds for different neuronal populations
- Theoretically, we may be able to specify the target within a single DRG

Green = Digit 4
Blue = Digit 5

1. An *in vitro* model for recording neuronal membrane events during field stimulation of the Dorsal Root Ganglion was developed.

**Essential Findings**

1. Stimulation reduces cell excitability which may contribute to pain reduction seen clinically.
2. Stimulation effects a specific region in the cell bodies located in the DRG that filters propagation of pain signals.
3. Continue to conduct *in vitro* and *in vivo* experiments.

Koopmeiners et al., NANS, 2011.
MULTISEGMENTAL INNERVATION PATTERNS: CROSS-DERMATOMAL COVERAGE

Multi-Segmental Input to Similar Spinal Synaptic Locations

Multi-Segmental Input to Divergent Spinal Synaptic Locations

Convergence and Divergence


PAIN COVERAGE IMPLICATIONS

Individual Lead Activation And Stimulation
A PROSPECTIVE STUDY EVALUATING THE SAFETY AND EFFICACY OF DRG STIMULATION

- Safety and Efficacy Endpoints: 50% pain reduction endpoint
- 7 sites enrolled in Europe and Australia
- Trials may either be permanent or percutaneous temporary lead placements depending on clinical practice
- Multiple ON/OFF periods evaluated
- Presenting n=24 subjects with monitored data
KEY INCLUSION/EXCLUSION CRITERIA

► Inclusion Criteria
  › Pain in the thoracic, lumbar, or sacral distributions
  › Refractory to prior treatment options for at least 6 months
  › Stable neurologic function and medication for at least 30 days
  › Spinal Cord Stimulation inclusion criteria

► Exclusion Criteria
  › Subject with foraminal stenosis with nerve root compression at target level
  › Currently has active, implantable device
  › Failed psychological screening
  › Participation in prior clinical trial within last 30 days

SUMMARY OF SUBJECTS ENROLLED TO DATE

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Subjects Implanted</th>
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<tbody>
<tr>
<td>Failed Back Surgery</td>
<td>9</td>
</tr>
<tr>
<td>CRPS</td>
<td>4</td>
</tr>
<tr>
<td>Other neuropathic pain conditions</td>
<td>11</td>
</tr>
</tbody>
</table>

► Previous back surgeries included laminectomies, multilevel fusion, and discectomy
► All patients with a diagnosis of CRPS had primarily foot pain
► Other neuropathic pain conditions included post-surgical neuralgias (lower limbs, thorax), radicular leg pain without surgery, and post-amputation neuralgia (stump pain)
STUDY OUTCOMES

► Primary Outcomes:
  › Device safety: passed all safety performance criteria
  › Device performance:
    • 63% of subjects with >50% pain reduction

<table>
<thead>
<tr>
<th>% of subjects with &gt;50% pain reduction</th>
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<tbody>
<tr>
<td>Back Pain</td>
</tr>
<tr>
<td>Leg Pain</td>
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<tr>
<td>Foot Pain</td>
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► Secondary Outcomes:
  › Quality of Life (EQ-5D): 32% improvement
  › Physical Functioning (BPI): 40% improvement
  › Psychological disposition (POMS): 70% improvement
  › Positional effects on paresthesia: No need to change settings due to postural changes
OVERALL PAIN REDUCTION

- 53% pain reduction at latest follow-up

Baseline | Week 1 | Week 4 | Week 8 | Month 3 | Month 6
---|---|---|---|---|---

The 8-week follow-up is only performed in the European protocol.

DURING STIMULATION OFF PERIODS, PATIENTS EXPERIENCE REBOUND PAIN

- >28mm increase in pain after ~1 week of no therapy

End of temporary stimulation period ~ 7 days

Subjects experience rebound pain during stimulation off.
Leg Pain Reduction

72% pain relief at 3-months (p<0.01)

Foot Pain Reduction

55% pain relief at 3-months (p<0.05)
MINIMAL POSTURAL EFFECTS ON PARESTHESIA

- Changes in paresthesia intensity was evaluated in 16 subjects
- These subjects were asked to rate the intensity of paresthesia while:
  - Standing
  - Lying down
- Stimulation parameters were not changed while rating intensity

**Outcomes**
- Subjects did not experience an uncomfortable change in paresthesia

CASE STUDY – CRPS

**Subject History**
- 59-year-old male with CRPS Type I of feet
  - Primary area: Left leg and foot
  - Pain duration: 2 years
  - Prior treatment: vasodilation, oxygen free radical scavengers

**DRG Stimulation**
- Lead placed at Left L5
- Stimulation ongoing for >1 month

**Results**
- 100% pain relief
- Decrease in foot swelling and discoloration

**Findings**
- DRG stimulation may treat sympathetically mediated conditions
Somatosympathetic Reflexes and DRG Stimulation

- Somatic sensory neurons in the DRG have connections to key autonomic regions.
- Stimulation of afferent neurons can cause reduction in segmented sympathetic outflow.
- These decreases in sympathetic outflow may have significant impact on sympathetically mediated and maintained pain, and also may have an impact on swelling in the periphery.

SUMMARY

- Prior clinical work indicates that the DRG is a robust target.
- Predictable location allows for the long-term neuromodulation with a system designed for stimulation of the DRG.
- Hypersensitization of the DRG may lead to preferential stimulation within a given anatomy.
- Potential to steer stimulation within a single dermatome (i.e. top of foot, side of the calf).
- Cross-dermatomal innervation allows for flexibility in targeting painful areas.
- Potential to treat a wide variety of intractable pain conditions with the correct tools.