ORIGIN AND BACKGROUND

Cryotherapy

- Local or general use of low temperatures in medical therapy
- The application of cold to nerve tissues blocks conduction of pain signals from the pain receptor to the brain
  - similar to the effect of local anesthetics
- When applied to nerves, it is referred to as cryoneurolysis
  - Also known as Cryoanalgesia or Cryoneuromodulation

The History Of Cryotherapy

- 600 – 377 BC: Hippocrates noted analgesic and anti-inflammatory properties
- 1819 – 1879: James Arnott used for palliative tumor treatment
- 1899: Campbell White first to employ refrigerants for medical use
- 1950: Allington used liquid nitrogen
- 1961: Cooper et al. developed device with liquid nitrogen reaching -190°C
- 1967: Amoils used CO₂ or N₂O reaching -70°C
- 1976: Lloyd et al. found cryoanalgesia superior to other methods of peripheral nerve destruction

MECHANISM OF ACTION

Nerve Anatomy

- A nerve is an enclosed, cable-like bundle of axons (the long, slender projections of neurons) in the peripheral nervous system

• Endoneurium - layer of connective tissue surrounding each axon
• Perineurium - layer of connective tissue surrounding each fascicle (axons are bundled together into fascicles)
• Epineurium - layer of connective tissue ensheathing the entire nerve
Sunderland Nerve Injury Classification

<table>
<thead>
<tr>
<th>Degree</th>
<th>Description</th>
<th>Mechanism</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Neuropraxia – Interruption of conduction; Short recovery time</td>
<td>+10°C to -20°C</td>
<td>Reversible</td>
</tr>
<tr>
<td>2nd</td>
<td>Axonotmesis – Loss of continuity of the axon; Wallerian degeneration; Preservation of endo- peri- and epineurium</td>
<td>-20°C to -100°C</td>
<td>Reversible</td>
</tr>
<tr>
<td>3rd/4th</td>
<td>Neurotmesis – Loss of continuity; Some loss of continuity of epineurium and perineurium</td>
<td>-140°C and colder</td>
<td>Non Reversible</td>
</tr>
<tr>
<td>5th</td>
<td>Transection (Severe Neurotmesis) – Gross loss of continuity</td>
<td>Not possible with iovera°</td>
<td>Non Reversible</td>
</tr>
</tbody>
</table>

The iovera° System

Mechanism of Action

- **TREATMENT**
  - A cold zone is created, lowering the temperature to below -20°C.
- **DEGENERATION**
  - Cold zone causes degeneration of the axon and myelin sheath, temporarily blocking nerve signals.
- **REGENERATION**
  - Post-treatment, the axon regenerates at the rate of about 1mm per day.*
- **REINNERVATION**
  - The axon and myelin sheath are fully regenerated and nerve signaling is restored.


Note: Motor nerve depicted; same Mechanism of Action for sensory nerves.

The iovera° System

Safe and Effective

- Mechanism of action is well understood
  - Nerves reliably degenerate and then regenerate
- Decades of safe clinical experience
  - Used for chronic and post-op pain since the 1970s
  - Similar concept as using a cold pack to numb skin
- 2nd degree nerve injury results in Wallerian degeneration of peripheral nerves:
  - Degeneration of the axons and dedifferentiation of the myelin sheaths
  - Regeneration ensues with proliferation and differentiation of the myelin sheaths, shortly followed by the regeneration of axons
  - The newly regenerated axon will mature to its original state

Traditional Cryo System

- Large
- Complicated
- Tissue ablative
- Invasive procedure

The iovera° System

- Handheld
- Simple + Intuitive
- Precise
- Minimally invasive treatment

Mechanism of Action Video
The iovera® System
Revolutionized cryotherapy platform

Simple percutaneous treatment, using proven cold therapy, designed to relieve pain

- Immediate, safe, effective
- Non-opioid, non-systemic
- Long-lasting nerve block
- Well-established billing code
- Cleared to treat the pain and symptoms of osteoarthritis
- Can target nerve location via nerve stimulation (90mm tip only)

Smart & Sophisticated

Smart Tips

- 3-pronged, 27-gauge needles, 6.9 mm long
- Superficial nerves
  - Branches of the femoral cutaneous and infrapatellar branches of the saphenous nerves around the anterior region of the knee
- 22-gauge needle, 55 mm long
- For deeper nerves
  - Branches of the tibial and common peroneal nerves in the posterior region of the knee
- 20-gauge needle, 90 mm long
- For deep nerves
  - Posterior nerves of the knee
- Trocar tip facilitates easy tissue navigation
- Allows for the attachment of nerve stim for more precise nerve targeting

The iovera® Handpiece
Treatment delivered by a handheld device

With the press of a button, the iovera® device precisely delivers Focused Cold Therapy to target peripheral nerves

- Non-opioid and non-systemic
- Immediate pain relief
- Minimal adverse side effects (consistent with needle insertion)

Precise Dose Control

Visual of 3x6.9mm Smart Tip; other Smart Tips operate with the same cycle phases

Indications for Use
US (FDA)

The Myoscience iovera® system is used to destroy tissue during surgical procedures by applying freezing cold. It can also be used to produce lesions in peripheral nervous tissue by the application of cold to the selected site for the blocking of pain. It is also indicated for the relief of pain and symptoms associated with osteoarthritis of the knee for up to 90 days. The iovera® system is not indicated for treatment of central nervous system tissue.

The iovera® system’s “1x90” Smart Tip configuration (indicating one needle which is 90 mm long) can also facilitate target nerve location by conducting electrical nerve stimulation from a separate nerve stimulator.
EFFECTIVENESS AND SAFETY DATA

Peripheral Nerve Degeneration

The iovera° System

Histological results demonstrate disruption of peripheral nerves as a result of cryanalgesia. Absence of axon post-treatment is responsible for the disruption in nerve signaling, while the intact structural nerve tissues, the epineurium and the perineurium, ensure that the nerve regenerates along the same path.

Axon Regeneration

The iovera° Technology

Axon Density Measurements

Safety: Effect on Adjacent Tissues

• Short intense cooling spares surrounding tissues
• No injury/inflammation observed among hair follicles, sebaceous glands or sweat glands

Safety: Effect on Adjacent Tissues

• At 8-32 weeks post-treatment, blood vessels, fat tissue, and surrounding muscles appeared normal
• Transient injury to muscle fully recovers within 2-3 weeks
• Negligible fat cell necrosis observed, <0.1% volume @ 5mm; no fat cell apoptosis
• Lumens of the small arterioles in proximity to the treatment site remained patent

CLINICAL STUDIES

The iovera° System
iovera° Osteoarthritis Study

Multicenter, Prospective, Sham-Controlled, Double-Blind

- 17 sites across the US
- n = 180 (randomized 2:1)
- Control Group = 59 subjects treated with a sham tip
- Treatment Group = 121 subjects treated with iovera°

Methods:

- Treatment of the ISN only, follow-ups at 30, 60, 90, 120 days.
- Subjects demonstrating effect at 120 and 150 days followed to 150 and 180 days, respectively

Results:

- The iovera° group demonstrated a statistically significant greater change from baseline in the WOMAC Total score than the sham group at Days 30, 60 and 90
- Patients deemed WOMAC pain responders at Day 120 continued to experience a statistically significant effect at Day 150

Pre-TKA iovera° Retrospective Study

Results for the iovera° group:

- Required 45% less opioids during the first 12 weeks after surgery based on prescription requests
- Demonstrated a significantly lower proportion of patients with a LOS of ≥2 days compared to the control group (6% vs. 67%, p<0.0001)
- Reported a statistically significant reduction in symptoms at the six- and 12-week follow-up compared to the control group
- Reported within-group significant reductions in pain intensity and pain interference at two- and six-week follow-up, respectively

Pre-TKA Feasibility Study

Results:

- Subjects who received cryoneurolysis at single surgeon sites with highly standardized practices (perioperative treatment, surgical technique and in-patient pain management) demonstrated:
  - A statistically significant difference in cumulative opioid use with respect to the sham group at 4 weeks post-TKA (p=0.0258)
  - A similar trend in cumulative opioid consumption at 6 weeks (p=0.0520) and 12 weeks (p=0.0565) post-TKA
  - Over the 12 week follow-up period, a 36% reduction in average opioids consumed compared to the sham group
- No significant differences in adverse event report rates or hospital readmit rates between the control and treatment groups for the entire study population
**The iovera® System**

**TREATMENT: KNEE PAIN**

**Patient Preparation**

**Patient Assessment**
- Measure baseline pain levels (VAS, etc.)
- Identify activities limited by pain
  - Deep knee bends, stairs, rising from chair
  - Will be used post treatment to verify treatment success
- Identify locations on knee that are painful upon palpation or movement

**Knee pain in anterior inferior portion of the knee:** consider treating the ISN
**Knee pain in anterior superior portion of the knee:** consider treating the AFCN

**Treatment Marking**

**AFCN: Anterior Femoral Cutaneous Nerve**

**Anterior, superior knee pain**
1. Find and mark the center of the patella
2. Draw a line to the inguinal crease in the thigh; measure the line and calculate 1/3
3. Starting at the center of the patella (1), measure the 1/3 calculation, and mark on the line (2)
4. Draw a dotted line on each side of the patella
5. Draw a solid line between the dotted lines (4), at the 1/3 mark (3)

_This is your treatment line_

**ISN: Infrapatellar Branch of the Saphenous Nerve**

**Anterior, inferior knee pain**
1. Find and mark the lower pole of the patella
2. Draw a line 5 cm medial
3. Find and mark the bottom of the tibial tubercle
4. Draw a line 5 cm medial
5. Draw a straight vertical line between the horizontal lines (2 and 4) on the medial side of the knee

_This is your treatment line_

**Treatment**

- Administer anesthetic
  - E.g. Lidocaine or Marcaine
  - Along identified treatment line
- Insert Smart Tip
- Perform treatment cycle
- Move to adjacent site on treatment line (overlapping one needle)
- May also use ultrasound guidance

**Treatment Technique**

**AFCN**
- Treat from A to B along the treatment line
  - Use dotted lines as boundaries
  - Apply pressure during treatment

- If relief is not achieved:
  - Continue treating towards the inside (medially) of the thigh
  - In some cases, the nerve may be at a depth unreachable by the Smart Tip
**Treatment**

**Treatment Technique**

**ISN**

Treat from A to B along the treatment line

- If relief is not achieved:
  - Continue treating inferior to the treatment line (not exceeding 1cm past B)
  - Exercise caution; other nerves may reside in area
- If relief is still not achieved:
  - Treat superior to the treatment line until relief is achieved (not exceeding the midline patellar)

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