SYMPOSIUM 07: Surgical Treatment of the Painful Nerve

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Faculty: Kyle R. Eberlin, MD, Jonathan E. Isaacs, MD, Bauback Safa, MD, MBA, Ian L. Valerio, MD, MS, MBA

Session Handouts
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Diagnosis and Treatment of Neuroma

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2018

Outline

• Definition and Pathophysiology
• Diagnosis and Decision for Surgical Intervention
• Surgical Options

Neuroma: Definition

• Disorganized growth or tumor of nerve tissue
• Commonly present following trauma (surgery!)
• Classified as stump ("end") neuroma or neuroma in continuity
• "Neuroma" vs. "Symptomatic Neuroma"
Neuroma: Definition

• Disorganized growth or tumor of nerve tissue
• Commonly present following trauma (surgery!)
• Classified as stump (“end”) neuroma or neuroma in continuity
• “Neuroma” vs. “Symptomatic Neuroma”

Incidence of Symptomatic Neuroma

• True incidence of symptomatic neuroma unknown: no gold standard for diagnosis
  • ALL digital amputations develop a “neuroma” (by definition)
  • What percentage of nerve repairs following traumatic injury develop neuroma (in continuity)?
Pathophysiology

- Does not require nerve transection
- May occur following poorly performed neurorrhaphy
  - i.e. fascicular overlap, undue tension, axonal escape
- Cause pain through central and peripheral mechanisms\(^1\)
  - **Peripherally** mediated pain through axonal irritation
  - **Centrally** mediated pain through development of spontaneous activity within dorsal root ganglion and CNS

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Outline

- Definition and Pathophysiology
- **Diagnosis and Decision for Surgical Intervention**
- Surgical Options

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Diagnosis of Symptomatic Neuroma

- There are no accepted diagnostic criteria
- We performed meta-analysis to determine criteria for diagnosis
  - Symptoms
  - Physical Examination Findings
  - Diagnostic Nerve Blocks
  - Imaging
Study Design

Clinical Diagnosis

First: identify the involved nerve

- Sometimes obvious, sometimes not
- Think of the surrounding soft tissue envelope and mechanism of development
- Tinel sign with pain, sensitivity in nerve distribution
- Clinical history is important

Diagnostic Criteria for Neuroma

Must have all 3:

1. Pain with at least 3 of the following characteristics: burning, sharp, shooting, electric, paresthesias, numbness, cold intolerance
2. Symptoms in a defined neural anatomic distribution
3. History of nerve injury or suspected nerve injury

Must have at least 2 out of 4:

1. Positive Tinel sign on examination at/along suspected nerve injury site
2. Tenderness/pain on examination at/along suspected nerve injury site
3. Positive response to local anesthetic injection
4. US or MRI confirmation of neuroma
Clinical Diagnosis

Second: Diagnostic block to confirm amelioration of symptoms with anesthesia

- I use 1% lidocaine/0.5% marcaine with epinephrine, sometimes mixed 1:1 with Kenalog 10mg/cc
- US can be helpful
- Visual analog scale important

Decision for Intervention

- Decision making sometimes easy, sometimes difficult
- Obvious stump neuromas are relatively easy to diagnose, decision making straight-forward
- Neuroma in continuity much more difficult – depends on symptoms and preserved function
- How symptomatic is the patient?
First: Non-Surgical Treatment

- Desensitization and occupational hand therapy
- Neuropathic pain medication (gabapentin, amitriptyline, pregabalin)
- Cognitive behavioral therapy
- Generally tried for 3-6 months

Outline

- Definition and Pathophysiology
- Diagnosis and Decision for Surgical Intervention
  - Surgical Options

Categorization of Surgical Interventions for Neuroma

<table>
<thead>
<tr>
<th>Passive/Ablative</th>
<th>Active/Reconstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excision only or traction neurectomy</td>
<td>Hollow tube reconstruction</td>
</tr>
<tr>
<td>Excision and implantation (muscle, bone)</td>
<td>Allograft or autograft reconstruction</td>
</tr>
<tr>
<td>Centro-central connector assisted neurorrhaphy</td>
<td>&quot;End-to-side&quot; neurorrhaphy</td>
</tr>
<tr>
<td>Nerve Cap</td>
<td>TMR</td>
</tr>
<tr>
<td>Relocation Nerve Grafting</td>
<td>RPNI</td>
</tr>
</tbody>
</table>
Neuroma in Continuity or Stump Neuroma with distal target available

Surgical Options for Stump Neuroma
Submuscular or Interosseous Burying

Resect proximal nerve stump and transpose into:

- **Muscle**
  - Dellon: 82% patients had good/excellent pain relief; poor outcomes: digital neuromas, WC, 3 or more prior surgeries, RSN involvement¹

- **Bone**
  - Mass: 90% effective results following interosseous burying²

- **Veins**
  - Herbert: success in 13/14 patients³


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**Treatment of Neuroma**

- **Centro-central neurorrhaphy**
- **Silicone/Epineural Cap**

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**Nerve Graft Reconstruction**

- If distal target available, use nerve graft to direct fibers from the proximal to the distal stump
- “give the nerve somewhere to go and something to do”
Case: common digital neuroma resection and allograft reconstruction

Location of Pain

Neuroma of Common Digital Nerve
Allograft Reconstruction

Surgical Treatment of Neuroma

- Resection and Burying
- Centro-central neurorrhaphy or nerve cap
- Nerve reconstruction with nerve graft
  - Relocation Nerve Grafting
  - Targeted Muscle Reinnervation

Relocation Nerve Grafting
Relocation Nerve Grafting

• 37 year old man s/p lawnmower injury to hand with distal thumb, index finger, and middle finger amputations
• Significant neuropathic pain in the index finger stump consistent with neuroma
Targeted Muscle Reinnervation

• With more proximal nerve injuries, TMR has become my primary intervention to address symptomatic neuroma...
Conclusions

• The diagnosis of symptomatic neuroma is based on a careful history and physical examination

• There are many operative interventions to treat symptomatic neuroma; an active approach to the nerve end may be preferable

Thank You
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Use of wraps for nerves – what is the science and how to choose what to use?
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  - Cook Biotech, Inc.
- TriMed, Inc
  - Speakers Bureau

Introduction
- Goal of wrapping
  - Modulate the local environment around nerve
  - Decrease scarring
    - Mechanical barrier
    - Inhibit fibrotic reaction
- Post traumatic
- Revision decompression surgery
- Revision nerve repair

Carpal tunnel/Cubital tunnel releases
  - CTS:
    - Failure to relieve symptoms 7-20% of cases(Mackinnon 1991)
    - Reoperation rate around 5%(Cobb and Amadio 1996, Concannon, Brownfield et al. 2000)
  - Cubital Tunnel Syndrome:
    - 7-10% failure rate(Dellon and Coert 2004, Goldfarb, Sutter et al. 2009)
    - 19% revision (simple decomp)(Krogue, Aleem et al. 2015)

Reasons for failure:
- Incomplete release
- Reformation of TCL
- Tenosynovitis
- Persistent subluxation?
- *Fibrosis

Post traumatic cicatrix
- Incidence not clear
- Neurolysis is often “default” surgery
  - Exploration but reconstruction/repair not indicated
- Compression can be observed

Traction neuritis
- Nerve Ischemia related to ROM
  - Fibrosis or “spot weld” adhesions
  - Electric pains with motion

Neuroma in-continuity
- Escaped/misdirected axons
  - Entangled in surrounding scar or soft tissue
  - Generate pain when stimulated
    - Compression or stretch

What about exploratory surgery?
- Relieve ongoing compression/scarring
  - There will be fibrosis
  - Address neuroma prn
  - Retraumatize the tissue→New fibrosis!
- Prevent recurrence!
  - Off the shelf options
  - Biologic
  - Vascularized

The ideal wrap
- Well tolerated
- Block wandering axons
- Allow diffusion of humoral factors/nutrients
- Block scar tissue
- Allow nerve gliding
- Reformed scar tissue should adhere to barrier and not nerve!

Vein wrapping
- Usually use saphenous
  - Need 3-4 x length
  - Split longitudinally
  - Wrap (intimal side down) like candy cane
Reforming scar tissue attaches to outside of vein wrap (scar free interface between nerve and intima)
- Inhibits extrinsic epineural scar formation (Chou, Papadimitriou et al. 2003)
- Improves intrinsic epineural vascularity (Xu, Varitimidis et al. 2000)
- Clinical data suggests improvement (Abzug, Jacoby et al. 2012)
  - 19 patients with recurrent CTS and Cub Tun Syndrome (3.3 previous surgeries)→ all with reduction in pain and sensory improvement (Varitimidis, Riano et al. 2000)
  - 16 repairs with vein wrap improved outcomes vs 10 without
    - Decreased pain (Leuzzi, Armenio et al. 2014)
Vein allograft
- Good results reported (Masear and Colgin 1996)
  - Glutaraldehyde-preservation induced inflammation (Ruch, Spinner et al. 1996)
  - Adheres to nerve (so not the same mechanism of action)
Second look—nice place around nerve (Vardakas, Varitimidis et al. 2001)
Down side
- Second surgical site
- Morbidity
  - "no complications" (pain/discomfort resolved at 4 months; 1 patient with welling x1yr) (Varitimidis, Vardakas et al. 2001)
  - Cellulitis, wound healing problems, persistent swelling
    - Though can use basilic or cephalic vein (thinner and not as much "cushion")
Collagen
- Type I collagen matrix from bovine flexor tendons
  - Biodegradable
  - Semi-porous
    - Blocks fibroblasts (Li, Archibald et al. 1992)
Animal studies
- Decreased perineural scarring (c/w sutures) (did not affect healing) (Kim, Hayes et al. 2010, Mathieu, Adam et al. 2012, Lee, Parisi et al. 2014)
  - No difference in gross fibrosis around repair
Clinical data
- Subjective improvement in revision cts and cub tun syndrome surgeries (15 pts) (Soltani, Allan et al. 2014)
Small intestinal submucosa
- Submucosa extracellular matrix (SEM)
  - Processed porcine small intestine (decellularized)
  - Collagen, fibronectin, growth factors, glycosaminoglycans, proteoglycans, and glycoproteins (Schmidt and Leach 2003)
– Revascularized, incorporated into mesoneurium, and prevented scar in a rabbit model (Kokkalis, Pu et al. 2011)

 Revision cubital tunnel and SEM wrapping with good results (Papatheodorou, Williams et al. 2015)
  – Re-exploration shows good plan
  – 10 patient case series showed no difference between collagen and SIS wrapping of median nerves with recurrent CTS (Kokkalis, Mavrogenis et al. 2016)
    ■ All improved (pain, numbness, two point discrimination)

Allograft (dermal)
  ■ 5 patients with recurrent cub tun release ⇒ improvement (VAS 5 pts) (Puckett, Gaston et al. 2011)

Others
  ■ Polycarprolactone
    – Non toxic
    – No inflammatory response
    – Degradation with less acidic
  ■ Polyvinyl alcohol hydrogel
    – Contains water in similar properties to human tissue
    – permanent

Amnion
  ■ Fetal membrane
  ■ multiple layers (Fairbairn, Randolph et al. 2014)
    – Between “spongy layer and chorion” ⇒ natural nonadherent plane
    – Epithelial cells ⇒ vasoactive peptides, growth factors, cytokines

  ■ Probably not immunogenic
  ■ Mesenchymal hyaluronic acid may inhibit TGF-β
    – Related to fibrosis
  ■ Contains interleukin 10
    – down regulates inflammatory response (Hao, Ma et al. 2000)
      ▪ ↓cytokines
      ▪ ↓TNF
      ▪ Etc.
  ■ Contains neurotransmitters, neurotrophic factors, and neuropeptides

Results
  – Improved axon growth at early time points (no difference at 12 weeks)- rat model (Meng, Li et al. 2011)
    ▪ Less adhesions and scar tissue
  – 8 patients recurrent cub tun syndrome (Gaspar, Abdelfattah et al. 2016)
    ▪ Avg 2 prev surgeries
    ▪ Improved pain, disability, grip strength
No complications

Conclusions

- Any interposed material can act as a scar barrier
  - Can still scar on either side of wrap
- No superiority demonstrated in any
  - Though vein is the only one that has been shown to decrease pain
  - My observation is that vein works best (but has morbidity)
- My algorithm
  - Mild scarring or for prophylaxis
    - Off the shelf barrier
    - Collagen or SIS
  - Severe scarring
    - Vein graft
  - Amnion
    - Intriguing... but no recommendation yet


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Background on Amputations

- 2 million amputees currently in U.S.
- 185,000 amputations performed each year

Two Main Issues

1. Function
2. Pain
Amputee pain

• Residual limb pain—up to 76%
• Phantom limb pain—up to 85%

• 2 million amputees in the US
• >185,000 amputations performed in US annually
GOAL: Intuitive Control of Prosthetics

New Muscle Signals

Pattern Recognition

Prosthetic Control

Thumb Abduction
Thumb Adduction
Wrist Supination
Outcomes

Function
An Interesting Observation…

Patients began to report improved pain.

What happened to the neuroma?

Cut nerve endings
Destined to form neuromas

### Table. Effects of Targeted Reinnervation (TR) on Neuroma Pain.

<table>
<thead>
<tr>
<th>Amputation level</th>
<th>No. of Patients</th>
<th>Pre-TR neuroma pain</th>
<th>Post-TR neuroma pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northwestern University/ Rehabilitation (NU/RIC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder Disarticulation</td>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Transhumeral</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>University of Washington / Harborview Medical Center (UW/HMC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder Disarticulation</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Transhumeral</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Transradial</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Above-knee</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Below-knee</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>San Antonio Military Medical Center (SAMMC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder Disarticulation</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transhumeral</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total (%)</td>
<td>48</td>
<td>34 (71%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>
Patient-reported outcomes

Pain Intensity SF3a
Pain Behavior SF7a
Pain Interference SF8a
Benchmarking Postamputation Pain

- Participants recruited from prosthetists, pain clinics, amputee clinics, support groups, trade shows, conferences,
- www.amputee-coalition.org
- Over 1200 surveys completed
- 727 surveys with complete data for major limb amputees

- **Residual limb (stump) pain** is moderate or severe in 52% of people living with limb loss
- **Phantom limb pain** moderate or severe in 51%
- **Only 16% of amputees are pain-free**

Benchmarks consistent with literature with more granular data

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TMR Treats Neuroma and Phantom Pain in Major Limb Amputees: A Randomized Clinical Trial

Reduction in **phantom limb pain** scores at one year was significantly greater in the TMR group compared to standard treatment.

Change scores for **residual limb pain** were favorable for TMR.
RCT Results: Burried in Muscle Failures with Crossover to TMR

RESIDUAL LIMB PAIN

RCT Results: Burried in Muscle Failures with Crossover to TMR

PHANTOM LIMB PAIN
Phantom limb pain originates with the amputated nerve but involves multiple levels of the PNS and CNS

- Opioids, neuromodulators, antidepressants (TCAs)
- Regional blocks
- Spinal cord stimulators
- Transcutaneous electrical stimulation (TENS)
- Mirror therapy
- Virtual reality
- ...
Pre-emptive Treatment of Postamputation Pain with TMR

N=51

TMR within 14 days

<table>
<thead>
<tr>
<th>Age (Mean, SD)</th>
<th>48.2 (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>30 (58.8%)</td>
</tr>
<tr>
<td>Reason for amputation</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>20 (39.2%)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>16 (31.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (15.7%)</td>
</tr>
<tr>
<td>Time since amputation</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>18 (35.3%)</td>
</tr>
<tr>
<td>1-9 years</td>
<td>33 (64.7%)</td>
</tr>
<tr>
<td>Level of amputation</td>
<td></td>
</tr>
<tr>
<td>Above elbow</td>
<td>4 (7.8%)</td>
</tr>
<tr>
<td>Above/ through knee</td>
<td>18 (35.3%)</td>
</tr>
<tr>
<td>Below elbow</td>
<td>4 (7.8%)</td>
</tr>
<tr>
<td>Below knee</td>
<td>18 (35.3%)</td>
</tr>
<tr>
<td>Shoulder disarticulation</td>
<td>7 (13.7%)</td>
</tr>
</tbody>
</table>

TMR at the Time of Major Limb Amputation for Pre-emptive Treatment of Postamputation Pain
Immediate TMR significantly reduces NRS pain scores

* Inverse probability of treatment (IPTW) weighting to balance demographics and amputation details

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TMR Median (IQR*)</th>
<th>General Median (IQR*)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phantom Limb Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst pain</td>
<td>1 (0-5)</td>
<td>5 (1-7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Best pain</td>
<td>0 (0-0)</td>
<td>0 (0-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current Pain</td>
<td>0 (0-1)</td>
<td>1 (0-4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Residual Limb Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst pain</td>
<td>1 (0-3)</td>
<td>4 (1-7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Best pain</td>
<td>0 (0-0)</td>
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<tr>
<td>Current Pain</td>
<td>0 (0-1)</td>
<td>1 (0-4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

2-points on the NRS is Clinically Meaningful

Immediate TMR significantly reduces PROMIS pain scores

* Inverse probability of treatment (IPTW) weighting to balance demographics and amputation details

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TMR Median (IQR*)</th>
<th>General Median (IQR*)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phantom Limb Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity</td>
<td>36.3 (31-40)</td>
<td>48.4 (41-54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Behavior</td>
<td>50.1 (37-52)</td>
<td>56.6 (51-61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interference</td>
<td>40.7 (41-41)</td>
<td>55.8 (41-63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Residual Limb Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity</td>
<td>30.7 (31-36)</td>
<td>46.8 (41-52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Behavior</td>
<td>36.7 (37-50)</td>
<td>57.3 (52-61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interference</td>
<td>40.7 (41-41)</td>
<td>57.3 (41-64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Opioid prescription refills after major limb amputation with immediate TMR

<table>
<thead>
<tr>
<th></th>
<th>PRE-OP</th>
<th>12-MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>46%</td>
<td>21%</td>
</tr>
<tr>
<td>Cancer</td>
<td>63%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Ohio Automated Rx Registry System (OARRS) was consistent with self-reported opioid use (percent agreement 91%, Cohen’s kappa 0.713).
Immediate TMR increases the odds of less severe pain

* *Inverse probability of treatment (IPTW) weighting to balance demographics and amputation details

Phantom limb pain
**OR 3.03** (95% CI 1.46, 6.31); p=0.003

Residual limb pain
**OR 3.92** (95% CI 1.89, 8.15); p<0.001
Speaker has not provided a handout for this presentation.