Complex Regional Pain Syndrome: Interventional Pain Care

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Objectives

• To become aware of current perspectives of well-known Interventional therapies for CRPS
• To become familiar with new and emerging interventional therapies for CRPS
Outline

• Definition of CRPS
• Treatment plan
• Current therapies
• Emerging therapies
• Summary
• Conclusion
Definition of CRPS

CRPS is a syndrome characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of pain after trauma or other lesion.

The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor edema, and/or trophic findings.

The syndrome shows variable progression over time.

CRPS type I develops after any type of trauma, especially fracture, soft tissue lesion (see below).

CRPS type II occurs after major nerve damage.

Definition of CRPS

“Unfortunately CRPS I has become a catch all phase and there are serious questions on whether it exists at all…”

Definition

“at least 80 different names are found in the English literature alone, more than 100 terms can be encountered in other languages.”

### Summary of treatments for complex regional pain syndrome (CRPS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Category</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi disc</td>
<td>Standard</td>
<td>None</td>
</tr>
<tr>
<td>PT / OT</td>
<td>Standard</td>
<td>+</td>
</tr>
<tr>
<td>Steroids</td>
<td>Standard</td>
<td>+</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Standard</td>
<td>+ / -</td>
</tr>
<tr>
<td>Analg Antidep</td>
<td>Standard</td>
<td>None</td>
</tr>
<tr>
<td>Trans lido</td>
<td>Standard</td>
<td>None</td>
</tr>
<tr>
<td>Opioids</td>
<td>Standard</td>
<td>None</td>
</tr>
<tr>
<td>SNS blocks</td>
<td>Standard</td>
<td>-</td>
</tr>
<tr>
<td>SCS</td>
<td>Standard</td>
<td>+</td>
</tr>
<tr>
<td>Beh Tx</td>
<td>Standard</td>
<td>None</td>
</tr>
<tr>
<td>Mirror/Motor</td>
<td>Uncommon</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Category</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin</td>
<td>Uncommon</td>
<td>+</td>
</tr>
<tr>
<td>Vita C pre</td>
<td>Uncommon</td>
<td>+</td>
</tr>
<tr>
<td>DMSO</td>
<td>Uncommon</td>
<td>+ (warm)</td>
</tr>
<tr>
<td>N-Ac</td>
<td>Uncommon</td>
<td>+ (cold)</td>
</tr>
<tr>
<td>Biphosphonates</td>
<td>Uncommon</td>
<td>+</td>
</tr>
<tr>
<td>IV ketamine</td>
<td>Uncommon</td>
<td>+</td>
</tr>
<tr>
<td>IV IG</td>
<td>Uncommon</td>
<td>+</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Uncommon</td>
<td>+</td>
</tr>
<tr>
<td>IT baclofen</td>
<td>Uncommon</td>
<td>+</td>
</tr>
<tr>
<td>LD naltrexone</td>
<td>Uncommon</td>
<td>+</td>
</tr>
</tbody>
</table>

*Bruehl S: Complex Regional Pain Syndrome. BMJ 2015; 350;h2730*
CRPS Treatment Challenges

“The lack of adequate treatments for CRPS is the result of an incomplete understanding of its pathophysiology that involves inflammatory, vascular, sympathetic nervous system, cortical, and spinal mechanisms.”

Therapeutic Modalities

- Medications
- Interventions
  - Procedural
- Regenerative Medicine
- Physical therapies
- Behavioral therapies
Therapeutic Modalities

- Physical Therapy
  - Fluidotherapy
  - Graded tactile sensitizing
  - Flexibility
  - Range of motion
Medications
Oral

• Antidepressants
• Anticonvulsants
• Mixed modality medications
  – Tramadol
  – Tapentadol
• Opioids
Medications

Infusions

- Lidocaine
- Ketamine
- Mannitol
- Biphosphonates
- Calcitonin
- Magnesium
Emerging Therapeutic Modalities

- Intravenous Immunoglobulin therapy
- Plasma Exchange Therapy
- Low-dose naltrexone
- Control of gut permeability
Procedural Interventions

- Injections
  - IV regional blocks
  - Stellate ganglion blocks
  - Lumbar sympathetic ganglion blocks
- Scrambler Therapy
- Spinal Cord Stimulation
- DRG stimulation
- Intrathecal Drug Administration
IV regional blockade

- Invented by August Bier in 1908
- Tourniquet was placed on exsanguinated extremity
  - Guanethidine
  - Labetalol
  - Lidocaine + steroids
- No longer done widely for RSD, due to lack of insurance coverage

IV Regional Block
Bier Block

Source: New York School of Regional Anesthesia
Sympathetic Blockade

- Upper limb
  - Stellate ganglion blockade
- Lower limb
  - Lumbar sympathetic ganglion blockade

Success rate = 30%
- Still worth trying
- Probably more helpful in early stages

Stellate Ganglion Block
Lumbar Sympathetic Ganglion Block
Plasma Exchange Therapy for RSD/CRPS

• This study shows that PE is effective in a subset of patients with severe long-standing CRPS

• The reduction in pain following the initial series of PE treatments can be maintained on a weekly PE schedule, IVIG, or with other immune modulating drugs.

Plasma Exchange Therapy for RSD/CRPS

- All PEs were performed with 1.5 plasma exchange volumes.
- An isotonic solution containing
  - 5% albumin with a
  - sodium content of $145 \pm 15$ mEq/L was used as the replacement fluid.

IV Immunoglobulin Therapy for CRPS

• “...we found that low-dose IVIG reduced pain intensity by 30% or more in approximately 50% of patients.”

• Dosage
  – 0.25 g/kg in NS for each of 2 days

“Our results suggest that immune mechanisms play an important role in sustaining long-standing CRPS...Patients may be predisposed to CRPS after trauma because of the presence of serum autoantibodies, and IVIG may neutralize these antibodies”

Therapeutic Modalities

• New Stimulation Strategies
  - Scrambler technology
    • attempts to relieve pain by providing “no pain” information via cutaneous nerves to block the effect of pain information.
    • ST synthesizes 16 different types of nerve action potentials similar to endogenous ones, assembles them into sequences, and uses algorithms to determine a patient-specific cutaneous electrostimulation to reduce pain.

Scrambler Technology
Therapeutic Modalities

• Scrambler Therapy
  – “benign pain” protocol
    • 10-12 daily treatments
      – 30-60 min each
    • Booster treatments can be added if needed
Therapeutic Modalities

• Scrambler Therapy
  – Different than TENS
  • TENS provides an on-off biphasic current without variation
    – PW 200 microseconds
    – Frequency 80 Hz
  • Scrambler therapy provides continuously changing variable nonlinear waveforms.
    – PW 6.8-10.9 microseconds
    – Frequency 43-52 Hz

Therapeutic Modalities

- Scrambler Therapy
  - Indications
    - Chronic benign pain
      - Neuropathic pain
    - Cancer pain
  - Variables
    - Patients on anticonvulsants may not benefit as much

Spinal Cord Stimulation
Spinal Cord Stimulation

- RSD/CRPS is one of the main indications for Spinal Cord Stimulation
- Previously considered a procedure of late resort
  - Now considered much earlier
- Two phase process
  - Trial phase
    - 7-10 days
      - >50% improvement = success
  - Implant phase
Spinal Cord Stimulation Trial
Therapeutic Modalities

- Spinal Cord Stimulation
  - Low frequency (conventional)
    - 50% of patients preferred
  - Higher frequency (conventional)
    - 50% of patients preferred

Therapeutic Modalities

• Spinal Cord Stimulation
  – Conventional
    • Patient feels paresthesias
      – Buzzing / tingling sensation
        » Some patients don’t like the sensation
    • Patient’s cooperation needed for accurate placement
    • Lead migration can cause lack of satisfactory stimulation
Therapeutic Modalities

• Spinal Cord Stimulation (conventional)
  – Best results
    • Perception of pain relief
    • Reduction in pain scores
    • Patient satisfaction
  – Good results
    • Functional improvement
    • Psychological improvements

Therapeutic Modalities

- **Spinal Cord Stimulation (conventional)**
  - Less predictable
  - Analgesic sparing effects
    - Patients may want to stay on their current medications
  - Resolution of signs / symptoms
    - Pain often returns when the unit is turned off

Therapeutic Modalities

- **Spinal Cord Stimulation**
  - High frequency
    - Patient does not feel the stimulation
    - Patient only feels pain relief
    - Strictly anatomic placement
      - Patient feedback not needed
        » Good for patients with aphasia
        » good for patients with cognitive deficits
Spinal Cord Stimulation
High Frequency
Dorsal Root Ganglion Stimulation
Dorsal Root Ganglion Stimulation
Dorsal Root Ganglion Stimulation (DRG)

New FDA Approved stimulation for chronic regional pain syndromes with a custom fit, targeted approach

- Lower Abdominal and Visceral Pain
- Phantom and Stump Pain (Post Amputation)
- Chronic, Refractory and Post-Surgical Pain (i.e. hip, knee, foot, etc.)
- CRPS I / RSD (localized foot, knee, ankle)
- Groin and Testicular Pain
- Peripheral Causalgia, CRPS II (Specific nerve injury)

Focal stimulation of the DRG offers patients a superior pain relief than traditional Spinal Cord Stimulation for Complex Regional Pain Syndrome (CRPS) and other focal chronic pain syndromes.
Dorsal Root Ganglion Stimulation
In this comparative study of 12 patients, the majority of patients chose DRG stimulation for their preferred treatment.
All 8 subjects implanted with a DRG neurostimulator for CRPS reported some pain relief.

Good results (greater than or equal to 50% pain relief in the foot) were reported after 12 months of treatment for 6 of the 8 subjects.

This responder rate is similar to or better than reported outcomes with SCS for CRPS and confirms DRG stimulation as a viable and effective intervention for this difficult pain condition.

Recently analyzed data from the ACCURATE trial showed that DRG stimulation produced statistically significant improvements in both back and leg pain compared with traditional stimulation.

In addition, patients with chronic lower limb pain due to CRPS or peripheral causalgia showed that patients with DRG stimulation experienced greater pain relief than with traditional stimulation.

Spinal Cord Stimulation

- Is it safe?
  - It is safe in the hands of experienced providers
    - “...The patient’s pre-existing medical condition and the experience and skill of the implanting physician may contribute to or influence the likelihood of some complications.”

- Complications
  - Lead migration
  - Spinal cord injury
  - Infection

### Spinal Cord Stimulation Complication Rates

Table 4.
Neurological Complication Rates for Percutaneous and Surgical Dorsal Column Stimulation Leads.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percutaneous leads</th>
<th>Paddle leads</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious neurological complications</td>
<td>0–2.35%</td>
<td>0.54–1.71%</td>
</tr>
<tr>
<td>Paralysis/spinal cord injury</td>
<td>0.03*–2.35%</td>
<td>0.022–0.067%</td>
</tr>
<tr>
<td>Infection</td>
<td>3–6%</td>
<td>3–6%</td>
</tr>
<tr>
<td>Spinal/epidural hematoma</td>
<td>0.75%</td>
<td>0.19–0.63%</td>
</tr>
<tr>
<td>Cerebrospinal fluid leak</td>
<td>0.3%</td>
<td>0.05–0.001%</td>
</tr>
</tbody>
</table>

*Based upon on large series (1) of combined percutaneous/paddle leads with one case of paralysis (lead type not specified).
Spinal Cord Stimulation

• When should it be considered?
  – When all reasonable treatments have been ineffective
    • Medications
    • Physical therapy
    • Behavioral therapy
  – When functionality has continued to deteriorate
Implantable Drug Infusion System
Implantable Drug Infusion System

Figure 6: The Medtronic SynchroMed Programmable Implantable Infusion Pump. Courtesy of Medtronic Neurological Division.
Implantable Drug Infusion System

- Medications available
  - Local anesthetics
  - Opioids
  - Other Analgesic Agents
    - Ziconitide
    - Baclofen
    - Clonidine

Indications for Drug Infusion System

• Patient experiences inadequate pain relief and/or intolerable side effects from systemic opioid therapy
• Patient has objective evidence of pathology
• Patient obtains psychological clearance
• Patient has no untreated substance abuse
• Patient has sufficient body size to accept the bulk and weight of the pump
• Clear therapy goals and realistic expectations have been established
• No contraindications to surgery or the therapy exist
• Patient has a favorable response to the screening test

Source: Medtronics 2017
Intrathecal Ziconotide

• “Ziconotide is a nonopioid analgesic currently ...for the management of severe chronic pain in patients ...who are intolerant of, or whose pain is, refractory to other treatments.”

• “Each patient in this series who had marked improvements after ziconotide therapy had previously experienced inadequate symptom relief with numerous other therapies.”

Conus Magus
Intrathecal Ziconitide

- Non-opioid
- No withdrawal symptoms
  - Return of pain may occur if stopped
- Narrow therapeutic window
  - Small difference between dose for relief and dose causing side effects
Intrathecal Ziconitide

- Most Common Side Effects:
  - Nausea
  - Memory alterations
  - Mood disorders
  - Urinary retention
  - Confusion
  - Low blood pressure

Intrathecal Baclofen Infusion

- Reduction of global pain scores
  - Reduced, deep, sharp pain
  - Dull pain was relieved less
- Reduced dystonia / tremors

SCS + Intrathecal Therapy

- Combined therapy
  - Reduced pain
  - Improved movement disorders
    - Dystonia / tremors
  - Reduced pain fluctuations

Contraindications to Drug Infusion Systems

- Infection;
- implant depth greater than 2.5 cm below skin;
- insufficient body size;
- spinal anomalies;
- drugs with preservatives,
- drug contraindications,
- drug formulations with pH ≤3,
- use of catheter access port (CAP) kit for refills or of refill kit for catheter access,
- blood sampling through CAP in vascular applications,
- use of Personal Therapy Manager
  - to administer opioid to opioid-naïve patients
  - or to administer ziconotide.

Source: Medtronics 2017
Intrathecal Drug Administration

Complications

• Infections
• Catheter problems
  – Occlusion
  – Kinking
  – Migration
  – Breakage
• Medication adverse effects
• Programming errors
• Seroma
• Pump trauma
<table>
<thead>
<tr>
<th>Statement</th>
<th>Evidence level</th>
<th>Recommendation grade</th>
<th>Consensus strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathecal therapy should be utilized for active cancer-related pain.</td>
<td>I for opioids; I for ziconotide</td>
<td>A</td>
<td>Strong</td>
</tr>
<tr>
<td>Intrathecal therapy should be utilized for noncancer-related pain.</td>
<td>III-2 for opioids; II-3 for opioids in combination with bupivacaine; I for ziconotide</td>
<td>B</td>
<td>Strong</td>
</tr>
</tbody>
</table>

EMERGING THERAPIES

Regenerative Medicine

“Stem Cell” therapy
Regenerative Medicine Therapy

- What is it?
- Is it safe?
- What options are available?
- What options work best for CRPS?
Regenerative Medicine Therapy

• What is it?
  – Regenerative Medicine Therapy is designed to help the body repair itself by
    • Activating repair cells in our bodies
    • Supplying our own repair cells to the site of injury
    • Supplying repair cells from other sources
Regenerative Medicine Therapy
“Stem Cell Therapy”

• Before 2006, stem cell therapy was highly controversial
  – It was associated with living tissue taken from developing babies
    • Ethical and moral concerns
Shinya Yamanaka
Stem Cell Pioneer

Takahashi K, Yamanaka S: Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. Cell 126(4) 663-676, 2006
Shinya Yamanaka
Stem Cell Pioneer

• Co-winner of 2012 Nobel Prize
  – Physiology / Medicine
• “These cells, which we designated iPS (induced pluripotent stem) cells, exhibit the morphology and growth properties of ES cells…These data demonstrate that pluripotent stem cells can be directly generated from fibroblast cultures by the addition of only a few defined factors.”

Takahashi K, Yamanaka S: Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. Cell 126(4) 663-676, 2006
Sources of Regenerative Options

- **Autologous Sources**
  - Pediatric post-partum options
    - Tissue Banks
  - Adult options
    - Bone marrow harvest
    - Adipose tissue harvest
    - Dental pulp tissue harvest
Sources of Regenerative Options

• Allographic Sources
  – Postpartum options
    • Tissue Banks
  – Adult options
    • Induced Pluripotential Cells
      – Bone marrow harvest
      – Adipose tissue harvest
      – Dental Pulp harvest
Strategies for Regenerative Therapy

- **Risk**
  - Correlate therapy risk level with disease severity

- **Regulation**
  - Correlate therapy choice with regulatory environment
Risk-Based Regenerative Therapy

• **Low-Level Disease**
  - Wellness
  - Graceful Aging
  - Orthopedic Pathology

• **Low-Risk Therapy**
  - Autologous Therapies
    • Alpha 2 Macroglobulin
    • Platelet-rich plasma
  - Allogenic Therapies
    • Amniotic fluid
      - Local application
        » Orthopedic pathology


Platelet-Rich Plasma

- An autologous WBC-poor, platelet-rich tissue with numerous platelet-derived growth factors and bioactive compounds
  - Currently used for orthopedic indications
    - Tendinopathies
    - Plantar fasciitis
    - Joint osteoarthritis
      - Superior to Supartz, etc.

Amniotic Fluid

- An allographic product of conception which initially contains neonatal stem cells, which are typically filtered out
  - Amniocentesis: 2nd trimester
  - Amnioreduction: 3rd trimester
  - Elective Caesarean section

- Cell origins
  - Skin
  - GI
  - GU
  - Respiratory

Amniotic Fluid

• Contains numerous growth factors and bioactive compounds
• Cellular elements, if present, are not known to be tumorigenic
• Current uses
  – Orthopedic indications
  – Pulmonary indications
    • Cellular elements
Gestational Stem Cells

• In clinical and preclinical studies, gestational stem cells have shown efficacy in the treatment of
  – Crohn’s disease,
  – lung disease,
  – diabetes,
  – repair of bone defects,
  – heart disease,
  – kidney disease,
  – neural degeneration, and
  – blood disorders.

• Stem cells derived from the placenta, placental membranes, and amniotic fluid are a valuable resource for the field of regenerative medicine.

Gestational Stem Cell Sources

Murphy SV, Atala A: Amniotic Fluid and Placental Membranes: Unexpected Sources of Highly Multipotent Cells.
Semin Reprod Med 2013;31:62–68
Cord Blood

Mesenchymal Stem Cells

Hematopoietic Stem Cells

CORD TISSUE

CORD BLOOD
Cord Blood

- Çil N: Effects of umbilical cord blood stem cells on healing factors for diabetic foot injuries
  - Biotechnic & Histochemistry 2017, Early Online: 1–14
- El-Badawy A: Clinical Efficacy of Stem Cell Therapy for Diabetes Mellitus: A Meta-Analysis
- Reddi AS: The Use of Human Umbilical Cord Blood for Wound Healing, Burns, and Brain Injury in Combat Zones
  - MILITARY MEDICINE, 176,4:361,2011
Wharton‘s Jelly Stem Cells

• Hu J, et al: Long term effect and safety of Wharton's jelly-derived mesenchymal stem cells on type 2 diabetes

• Liu X: preliminary evaluation of efficacy and safety of Wharton’s jelly mesenchymal stem cell transplantation in patients with type 2 diabetes mellitus
  – Stem Cell Research & Therapy 2014, 5:57
Providers of Regenerative Therapy

• Credentialing
  – Evidence of education and training
    • Residencies
      – None currently
    • Fellowships
      – A4M:
        » American Association for Anti-Aging Medicine

• Training
  – Skills instruction
    • Weekend workshops
Regenerative Therapy
for Neuropathic Pain

- Numerous experimental studies demonstrating
  - Regenerative effects
  - Trophic effects
    - Growth factors
      - Healing qualities

“...the ability of stem cells to modify cellular processes provides for a protective and restorative microenvironment that can potentially fully reverse the causes behind the onset of neuropathic pain.”

Regenerative Therapy for neuropathic pain

• The literature to date is very limited for evaluating the therapeutic role of MSCs in treating neuropathic pain in humans.

Regenerative Therapy
for Neuropathic Pain

• Challenges:
  – Sourcing of stem cells,
    • quality
  – considerations on autologous versus allogeneic transplants,
    • Your cells v someone else’s
  – pre-commitment to neuronal lineages,
    • Cell types
  – characterization of neurotrophic factor release, and
    • Which factors are helpful?
  – dosing requirements
    • How many cells are necessary?

Regenerative Therapy for CRPS

- Adipose Stem/Stromal Cells in RSD, CRPS, Fibromyalgia (ADcSVF-CRPS)
  - ClinicalTrials.gov Identifier:
    - NCT02987855

- Nature of Study
  - Study is an interventional study to document the safety and efficacy of use of adipose-derived cellular stromal vascular fraction (AD-cSVF) in chronic pain and dysfunction disease groups

- Point of contact
  - Robert W. Alexander, MD, FICS,
    - 406.777.5312
    - Healeon Medical Inc

Source: ClinicalTrials.gov Website
Regenerative Medicine Therapy for CRPS

Estimated Enrollment: 100

Study Start Date: December 2016

Estimated Study Completion Date: June 2019

Estimated Primary Completion Date: December 2018 (Final data collection date for primary outcome measure)

Locations

United States, Montana
Regenevita LLC Recruiting
Stevensville, Montana, United States, 59870
Contact: Susan Riley, CMA 406-777-5312 irbtrials1@gmail.com
Contact: Nancy L Smith, MA, ORT 406777.5312 irbtrials2@gmail.com

Source: ClinicalTrials.gov Website
Interventional Therapy for CRPS

- **What works?**
  - At the present
    - IV Ketamine
    - Sympathetic Blocks
    - Neuraxial Stimulation
    - Scrambler Therapy
    - Intrathecal Pumps
  - Future
    - Regenerative Medicine
Conclusions

• Our lack of understanding has made CRPS a difficult disease to treat

• However, several interventions have proven to provide
  – Improved pain relief
  – Improvement in function

• Regenerative Medicine Therapy is very promising
  – But we are very early in our knowledge
Questions?