Novel Treatments in Stroke Rehabilitation

**Electrical Stimulation**

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Disclosures

• Grant support from the NIH
• Will discuss devices evaluated under IDE
• SPR Therapeutics
  – Consultant and Chief Medical Advisor
  – Grant support
  – Own equity in the company
Objectives

• Evaluate the efficacy of electrical stimulation (ES) in reducing hemiplegic shoulder pain (HSP)
• Evaluate the efficacy of ES in restoring post-stroke motor function
• Discuss emerging techniques
Concepts and Outline

Concepts

• **Therapeutic effect:** A benefit that remains when the device is not being used after a period of use
  - Pain reduction: i.e. shoulder pain
  - Motor relearning: Re-acquisition of motor skills after CNS injury

• **Neuroprosthetic effect:** The ability to perform functional tasks while the device is being used

Outline

• **Upper Limb**
  - Shoulder pain
  - Motor relearning
  - [Neuroprosthesis]

• **Lower Limb**
  - Neuroprosthesis
  - Motor relearning
Hemiplegic Shoulder Pain
Stroke

Spasticity

Weakness

Muscle Atrophy

Mechanical Instability

Subluxation
Joint malalignment
Reduced ROM
Scapular malrotation

Immobility

Micro and macro trauma

Inflammation/degeneration

Complex Regional Pain Syndrome

Surface

ES

Periosteal traction

Capsulitis

Capsule

Inflammation/degeneration

Bursitis

Tendons

Muscles

Sheffler and Chae, Muscle Nerve, 2007
Hemiplegic Shoulder Pain

**Surface ES**

**Best Practice**

- There is strong evidence that “Functional electrical stimulation improves muscle function, pain, subluxation, and range of motion of the hemiplegic shoulder.” (Teasell et al., Top Stroke Rehabil 2003)
- Corroborated by:
  - Ottawa Panel Evidence-based Clinical Practice Guidelines for Post-stroke rehabilitation. (2006)

**Not the Standard of Care**

- Unable to tolerate 6-hrs of stimulation per day for 6-wks
- Need for skilled personnel for:
  - Reliable electrode placement
  - Adjustment of stimulation parameters to facilitate tolerance and minimize fatigue
Hemiplegic Shoulder Pain

**Percutaneous Intramuscular ES**

- **Chronic**
- **Subluxation and pain**
- **6-hrs/d, 6-wks**
- **Blinded assessments:** 3, 6 and 12-mo
- **Vs sling and usual care**

NICHD-R44HD34996 (PI: Fang)
K12 HD010973 (PI: Yu)
NeuroControl Corp.
Hemiplegic Shoulder Pain

**Percutaneous Intramuscular ES**

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Yu et al, Arch PMR 2004; Chae et al, Am J Phys Rehabil 2005
Implant
Explant
Stimulation

4-lead, 6-wks

Pilot Comparative Effectiveness RCT

Single-lead IM ES

Physiological Therapy

Single-lead, 3-wks

Outcome:
- Pain
- Pain interference
- QoL

NIH/NICHD R01HD059777 (ARRA), PI: Chae
Hemiplegic Shoulder Pain

**Percutaneous Intramuscular ES**

Why the relatively low success rate?

Yu et al, Arch PMR 2004; Chae et al, Am J Phys Rehabil 2005
Hemiplegic Shoulder Pain

**Percutaneous Intramuscular ES**

If > 18-mo post-stroke, may need a permanent implant…

Chae et al., NNR 2007
Hemiplegic Shoulder Pain

**Fully Implanted Intramuscular ES System**
Hemiplegic Shoulder Pain

**Fully Implanted Intramuscular ES System**

- Short-term PNS Therapy
  - Placebo effect = 3 (Start Short-term PNS Therapy)
  - Treatment effect = 3 (System removed)

- Long-term PNS Therapy
  - Implantation
  - Restarted

- Pain Intensity (BPI 3)

Weeks:
- Short-term PNS Therapy: 0, 3, 6
- Long-term PNS Therapy: 0, 1, 2, 3

Acute Illness
- Resolved

Unrelated Acute Illness Occurred

Long-term PNS Therapy Turned Off

Long-term PNS Therapy Restarted
Central Sensitization (-) IM ES

- No effect on subluxation, ROM, motor impairment or spasticity
- Similar benefit for those without subluxation

Stroke
- Spasticity
  - Weakness
  - Mechanical Instability
    - Subluxation
    - Joint malalignment
    - Reduced ROM
    - Scapular malrotation

Immobility
- Capsulitis
  - Capsule
  - Inflammation/degeneration

Pain
- Periosteal traction
  - Tendinitis
  - Tendinosis
  - Muscle tears
  - Bursitis

Micro and macro trauma
- Complex Regional Pain Syndrome
Upper Limb Motor Relearning
Motor Relearning

- **Activity dependent neuroplasticity** (Nudo et al, Muscle Nerve, 2001)
  - High repetition
  - Novel (skill acquisition)
  - Cognitively engaging
  - Functionally meaningful

- **Timing** (Teasell et al., Top Stroke Rehabil, 2005)
  - Hyperacute (within hrs) may be harmful
  - Acute is better than chronic

- **Can ES mediated repetitive movement therapy also facilitate motor relearning?**

Biernaskie et al., J Neurosci 2005
Upper Limb Motor Relearning

Quantitative Review

• Bowman et al., 1979
• Powell et al., 1999
• Chae et al., 1998
• Francisco et al., 1998
• Sonde et al., 1998
• Cauraugh et al., 2000

• “The present review suggests a positive effect of ES [electrostimulation] on motor control.”
• “[However] At this stage, no conclusion can be drawn with respect to functional ability.”
• EMG-triggered ES may be more effective than cyclic ES

Upper Limb Motor Relearning

Meta-Analysis

- 8 RCT
- 157 patients
- Wrist and or finger extensors

- No evidence of statistically significant treatment effect
- “...all studies except two investigated the effects of EMG-NMES in the chronic phase after stroke, whereas the literature suggests that an early start, within the time window in which functional outcome of the upper limb is not fully defined, is more appropriate.”

Meilink et al., Clin Rehabil 2008; 22: 291-305
Upper Limb Motor Relearning

*Other Reviews and Studies*

- **Pomeroy et al., Cochrane Review, 2006:** “At present, there are insufficient robust data to inform clinical use of electrostimulation for neuromuscular re-training.”

- **Hayward et al., Disabil Rehabil 2010** (Cochrane Review): “limited evidence that electrical stimulation...provide a large beneficial effect on function.”

- **Subsequent studies:**
  - All continue to report statistically significant reduction in arm impairment.
  - However, no real effect on arm related activities limitations
  - Small sample sizes
Multisite Randomized Clinical Trial

- Subacute Stroke survivors (<6-mo post-stroke)
- 3 sites, N = 122
- Surface Cyclic vs EMG-triggered vs Placebo (sensory) of finger extensors
- 1-hr/day x 8-wks at home
- Blinded assessments at 1, 3 and 6-mo after end of treatment
- Primary Outcome: Fugl-Meyer
- Secondary Outcome: Arm Motor Ability Test
- Results:

Surface Cyclic and EMG-triggered ES were no better than placebo in improving hand function

NIH/NICHD: R01R01HD49777 (PI: Chae)
Contralaterally Controlled Functional Electrical Stimulation Therapy

- Novel
- Repetitive
- Cognitive engaging
- Functionally relevant

Volitional opening of the unaffected hand...

...produces a proportional intensity of stimulation to the paretic hand extensors.

NCRR: K12HD049091; PI: Knutson

Knutson et al, 2007; Knutson et al., 2009
Upper Limb Motor Relearning

Contralaterally Controlled FES

Contralaterally Controlled FES Therapy Lab Sessions
Upper Limb Motor Relearning

Contralaterally Controlled FES

Before Treatment

Grasp-Release Test at Baseline

Subject 5
10/11/06

After Treatment

Grasp-Release Test at End of 12-Week Treatment

Subject 5
1/11/07
New Study-CCFES in chronic hemiplegia:
NIH/NICHD: R01 HD 059814; PI: Knutson
Upper Limb Motor Relearning

**Other Approaches**

- **Multichannel systems and exercise**: Plavsic et al., 2011
- **Hybrid ES and orthotics**: Shindo et al., 2011; Hardy et al., 2010; Boyn et al., 2010
- **Hybrid ES and robots**: Hu et al., 2012; Meadmore et al., 2011; Hughes et al., 2011
- **Bilateral arm training with ES**: Fang-Chen et al., 2011; Chan et al., 2009
- **Accelerometer based ES**: Mann et al., 2011
- **Implanted ES**: Chae et al., 2009, Turk et al., 2008
Lower Limb Neuroprosthesis
Lower Limb Neuroprosthesis

*Surface Peroneal Nerve Stimulation*

- **Active electrode:** common peroneal nerve at the level of head of the fibula
- **Return electrode:** common peroneal nerve or over TA
- **Deep branch:** TA for ankle DF and inversion
- **Superficial branch:** Peroneus longus and brevis for eversion
- **Triggered:** heel switch or a tilt sensor
Lower Limb Neuroprosthesis

Surface Peroneal Nerve Stimulation

PNS Off

PNS On
Lower Limb Neuroprosthesis

*Surface Peroneal Nerve Stimulation*
Lower Limb Neuroprosthesis

**Peroneal Nerve Stimulation**

- Waters et al., 1975 (implant)
- Bogataj et al., 1995 (surface)
- Granant et al., 1996 (surface)
- Burridge et al., 1997 (surface)
- Burridge et al., 1997 (surface)
- Kenney et al., 2002 (implant)

- Peroneal nerve stimulation
- Before/after, with/without and experimental
- Outcome: Walking speed
- **38% increase in walking speed with the stimulator**

Kottink et al., Artificial Organs 2004; 28: 577-586
Lower Limb Neuroprosthesis

**Peroneal Nerve Stimulation**

**Eligibility**
- Tolerate stimulation
- No sensitivity to adhesive
- Produces balanced ankle dorsiflexion to at least neutral with knee extended (no contractures or severe equinovarus tone)
- Adequate knee control
- Able to ambulate with supervision with appropriate device

**Limitations**
- Poor medial lateral stability of the ankle/foot during stance
- In general, does not correct for genu recurvatum or quad weakness
- High cost
- Surface: FDA, but not CMS approved
- Implant: Not available in US
- *Is it better than an AFO? ($700)*
Lower Limb Neuroprosthesis

**Peroneal Nerve Stimulation and AFO**

- 14 chronic stroke survivors with foot-drop
- No device, PNS vs AFO
- mEFAP

- **PNS = AFO for walking speed** (Van Swigchem et al., 2010)
- **PNS may be superior to AFO in negotiating obstacles** (Van Swigchem et al., 2011)
- **PNS may provide improved balance control over AFO** (Ring et al., 2009)
- Two industry funded RCTs of PNS vs AFO.

Sheffler et al., NNR 2006; 20: 355-360
Lower Limb Neuroprosthesis

**Emerging Approaches**

Actigait, Neurodan (Implant)
Burridge et al., 2007

StimUStep, Finetech (Implant)
Kottink et al., 2007

Surface Stimulation that provide both ankle dorsiflexion and plantarflexion:
• Kesar et al., 2009
• Embry et al., 2010

- PNS improves mobility modestly, comparable to an AFO.
- A more robust improvement will likely require control of the knee and hip.
Lower Limb Motor Relearning

• On the other hand, although PNS and AFO appear to be comparable, if motor relearning could be demonstrated with PNS (but not with the AFO), this might justify the use of PNS over an AFO and lead to the establishment of a new standard of care.

• “On several occasions we observed, after training with the electrophysiologic brace [peroneal nerve stimulator]...patients acquire the ability of dorsiflexing the foot by themselves.” Lieberson et al., 1961
Lower Limb Motor Relearning

Quantitative Review

- Alon and Ring, 2003 (Multichannel FES)
- Bogataj et al., 1995 (Multi-channel FES)
- Burridge et al., 1997 (Single-channel FES)
- Burridge and McLellan, 2000 (Single-channel FES)
- Chen et al., 2005 (Single-channel TENS)
- Granat et al., 1996 (Single-channel FES)
- Peurala et al., 2002 (Single-channel TENS)
- Sonde et al., 2000 (Single-channel TENS)

- Objective: To determine the effects of previous treatments of FES and TENS on improving gait speed in subjects post-stroke
- Effect size range: FES: -0.11 to 1.43
  TENS: 0.19 to 0.42
- Only 3 RCT
- Small n

Peroneal Nerve Stimulation vs Usual Care

• >6-mo post-stroke
• N = 105
• PNS vs Usual Care (AFO or no device)
• PT x 5 weeks
• Device use x 12 weeks
• FU to 6-mo after completion of Device Use
• Outcomes:
  - Fugl-Meyer
  - mEFAP
  - QoL

Results:

Severely impaired: PNS may be superior to Usual Care
Mildly impaired: Usual Care may be superior to PNS
Lower Limb Motor Relearning

Other Approaches

- Multi-channel IM ES + weight supported treadmill and over-ground training. Daly et al., 2011
- FES Cycling. Ambrosini et al., 2011
- FES + orthosis + visual feedback. Krishnamoorthy et al., 2008

Contralaterally Controlled ES
NIH/NICHD R21 HD061593; PI: Knutson
Summary

Shoulder Pain
• Surface ES is probably effective as treatment
• Implanted ES is probably more effective and clinically more viable

Upper Limb Motor Relearning
• Cyclic and EMG-triggered ES is probably not effective
• Need functionally relevant paradigm approach

Lower Limb Neuroprosthesis
• PNS is probably superior to no device
• PNS may not be superior to AFO
• Implanted and multichannel systems need to be investigated

Lower Limb Motor Relearning
• PNS MAY mediate modest effect in select group
• Likely will need multichannel approach
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