Update on Spinal Cord Injury Clinical Trials

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DISCLOSURE

• Depuy Spine Teaching Honorarium
• Globus Spine Teaching Honorarium

Spinal Cord Injury
Cervical Spine Trauma Guidelines

- **2002 AANS/CNS**
  - Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries

- **2009 EAST**
  - Guidelines for Identification of Cervical Spine Injuries Following Trauma

- **2013 AANS/CNS**
  - Updated Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries

PAST SCI TRIALS

NASCIS II

- **487 patients randomized**
  - 291 patients excluded because treated with MP at >8 hours
  - MP → 5 point increase in ASIA motor score (max 50)
    - ONLY when treated < 8hr
    - MP → detrimental when given > 8 hrs

References:

Controversies in Pharmacologic Therapy

• Most pharmacotherapy research has been through investigation of the potential benefit of methylprednisolone (MP) administration

• National Acute Spinal Cord Injury Study (NASCIS) II and III (published between 1990 and 1998)
  – NASCIS I trial reported negative results in 306 patients comparing "high dose" to "low dose" MP


NASCIS II

• NASCIS II MP complications
  – 1.5x increase in gastrointestinal bleeds
  – 2x increase wound infections
  – 3x increase in pulmonary emboli

• Downgraded to Class III medical evidence
  – Omission of data from publication
  – No functional outcome measures
  – Inconsistent results

Methylprednisolone Complications

• Significant side effects reported in three Class I studies
  – Wound infection
  – Hyperglycemia requiring insulin administration
  – GI hemorrhage

• A study by Gerndt et al
  – Examined 140 SCI patients treated with MP
  – 4x increase in acute pneumonia
  – Increased # of ventilator days

CNS Position Statement on MP

- Administration of MP for the treatment of acute SCI is not recommended

- No Class I or Class II medical evidence supporting the clinical benefit of MP in treatment of acute SCI

- Class I, II, and III evidence exists that high-dose steroids are associated with harmful side effects including death

Canadian EM Position Statement on MP

Methylprednisolone is not recommended
ASCENT Trial

- SUN13837
  - Fibroblast growth factor (FGF) analog
  - Neuroprotection from glutamate excitotoxicity and promote axonal outgrowth
  - Similar to bFGF but does not promote cellular proliferation

ASCENT Trial

- SUN13837
  - PI: Sanjay Dhall
  - Grady Memorial Hospital: 2011-2013
  - Cervical AIS A,B,C SCI
  - Trial completed, results pending

NEW SCI TRIALS
Safety and Efficacy of Pulsed Electromagnetic Fields (Cervical-Stim) as an Adjunct to Enhance Union in Conservatively Treated Type II Fractures of the Odontoid Process

Slides courtesy of Orthofix, Inc. Lewisville, TX

The Problem: Dens Fractures

- Class II evidence
  - Risk of non-union of a Type II odontoid fracture in patients >50 years \( \rightarrow 21x \) greater than for younger patient
  - Must consider surgery in patients older than 50 yrs

Guidelines: Dens Fractures

Management of Isolated Fractures of the Axis in Adults

Operate in >50 yo with type II odontoid fracture
PEMF Odontoid Fractures

Purpose
To examine the safety and efficacy of pulsed electromagnetic fields as an adjunct to enhance union in conservatively treated Type II fractures of the odontoid process.

Hypothesis
The hypothesis of this study is that PEMF treatment will improve odontoid fracture healing, compared with standard conservative care, in subjects 50 years of age and over diagnosed with Type II odontoid fractures, and this effect will be evident by 6 months post-injury.

PEMF for Odontoid Fractures

Primary Objective
• To prospectively determine, at 6 months post-injury, the safety and efficacy of treating Type II odontoid fractures in subjects 50 years of age and over with a pulsed electromagnetic field (PEMF) regimen using the Orthofix Cervical Stim 2505OD device.
• Overall success will be determined using a composite endpoint with a radiographic component, a safety component, and a pain component.

Secondary Objectives
To demonstrate that PEMF therapy
1) increases the rate of fracture healing 3 months and 12 months after initiation of treatment.
2) decreases the time to complete union and
3) improves clinical outcomes measured by the NDI and SF-36 score at 3, 6 and 12 months after initiation of treatment.

Study Timelines
• IDE approval by FDA: September 27, 2014
• Approvable letter from Western IRB: October 28, 2014
• Expected enrollment period: 24 Months
• Number of sites: Up to 50
• Expected number of enrolled subjects: 360
Study Design

• This study is a prospective, double-blind, randomized, placebo-controlled multi-center clinical investigation.

• There will be two cohorts: those subjects who receive an active device and those subjects who receive a placebo control (inactive) device.

• Subjects will be randomized in a 2 to 1 ratio (active: placebo control) to either an active or placebo control (inactive) Cervical-Stim device.

• Efficacy will be measured at 6 months by comparing both cohorts and the proportion of subjects in each cohort who achieved success, where success is a composite endpoint of:
  1) odontoid fracture healing,
  2) lack of device-related SAEs and surgical interventions, and
  3) an improvement of at least 20 mm in VAS neck pain.

Study Design

• The physical configuration of the Cervical-Stim Model 2505OD has been modified for use on odontoid fractures; specifically, a lift collar has been created to raise the coil approximately 3 inches to ensure that the fracture site receives adequate signal strength.

• Subjects will be assessed for the presence of a Type II odontoid fracture by X-ray, MRI and CT scan.

• Eligible subjects will be treated for 4 hours daily for 6 months.

• All subjects will wear a rigid cervical collar minimally for the first 3 months.

  Miami, J. Philadelphia, Aspen (Investigator's discretion)

• Subject must wear the device for at least 65 minutes the first time in order to calibrate the Cervical-Stim device.
Inclusion Criteria

- Subjects must be 50 years (≥50) of age or older at the time of consent
- Subject must have radiographic evidence (X-ray, MRI and CT scan) of a Type II odontoid fracture
- Subject must have MRI evidence that the fracture occurred within 21 (change to 30) days of study enrollment
- Subject must have VAS neck pain score of greater than 4 (>4)
- Subject must have radiographic evidence that the fracture is displaced ≤5 mm in any direction and/or have a fracture gap of ≤3 mm due to angulation
- Subject must use a rigid cervical collar (Miami J, Philadelphia or Aspen) for a minimum of three months post-injury

Inclusion Criteria...cont.

- Subject must have a DEXA scan within 6 months prior to enrollment or, it can be done within one week of baseline visit
- Subject must be willing and able to follow all study procedures and return for all study visits
- Subject must be willing to sign an Informed Consent Document

Exclusion Criteria

- Subject has undergone systemic administration, within 30 days prior to the fracture, of any type of corticosteroid, antineoplastic, immunostimulation or immunosuppressive agents
- Subject is on chronic anticoagulation therapy, or has a bleeding disorder
- Subject is pregnant, nursing or plans to become pregnant during the study
- Subject has a chronic Type II odontoid fracture that occurred more than 21 days prior to enrollment
- Subject has a Type II odontoid fracture displaced >5 mm in any direction and/or a fracture gap >3 mm due to angulation
Exclusion Criteria…cont.

- Subject has a mental or physical condition that would prevent him from complying with the study protocol, including the physician obtaining an accurate neurologic exam.
- Subject was recommended for surgery to treat the fracture but subject refused surgery.
- Subject is a prisoner.
- Subject has participated in another clinical trial within the last 90 days.

INVESTIGATIONAL DEVICES

The Investigational Device

Cervical Slim Model 2500OD

Lift collar alone

Device viewed from the side with lift collar

Device viewed from the back with lift collar
Dens Fractures in Aging Population

- Dens fractures $\rightarrow$ poor healing in older patients
  - Risk of non-union of a Type II odontoid fracture in patients $>$50 years $\rightarrow 21x$ greater than for younger patient
  - Must consider surgery in patients older than 50 yrs
- Recent unpublished data from NTDB on C2 fractures in $>$80 yr old patient
  - 10% mortality in both surgery and non-surgery groups
  - Very high likelihood of needing nursing home after C2 fracture $\rightarrow$ 50% in non-surgical and 60% in surgical
  - No good treatment options!

PEMF Odontoid Fracture Trial

- UCSF and SF General Hospital both sites
- Going live this fall
NEW SCI TRIALS: CAMPER

The Question: Intrathecal Pressure in SCI?
- Acute traumatic SCI is devastating often permanent disability
- Very limited success at preventing secondary SCI after initial trauma

Guidelines - Hemodynamic Management

MAP 85-90 mm Hg for 7 days after SCI
Why Hypertension?

- Vale and Hadley, 1997, J Neurosurg
  - 77 pts with ASCI (C1-T12)
  - All got Swann-Ganz and A-line
  - IVF, colloids, vasopressors \( \rightarrow \) MAP > 85 mmHg
  - ASIA A (complete):
    - 60% improved at least 1 ASIA grade
    - 30% walked
    - 20% regained bladder function
  - Incomplete cervical SCI:
    - 92% walked again
    - 88% regained bladder function
  - NO complications reported

How does Intrathecal Pressure Impact Cord Perfusion?

- Counter-intuitive \( \rightarrow \) ITP increases after decompression
  - Removal of blockage
- Need prospective data on ITP and cord perfusion and outcomes

CSF Biomarkers of SCI?

- Cytokine impact possibly beneficial and detrimental after SCI
- Mostly based upon animal studies
- Need for human CSF after SCI to establish biomarkers
CAMPER Trial

- Canadian Multicentre CSF Pressure Monitoring and Biomarker Study
- San Francisco General Hospital (UCSF) to be first USA Site
- Going live August 2015

CAMPER Trial: Inclusion Criteria

- Male or Female ≥18
- Complete (AIS A) or incomplete (AIS B,C) acute spinal cord injury involving boy spinal levels between C0 and L1. Blunt (non-penetrating) spinal cord injury treated either surgically or non-surgically.
- Patient is admitted less than 48 hours from time of injury (must insert lumbar intrathecal catheter within 48 hours of injury).
- English speaking
- Willing and able to provide informed consent.

CAMPER Trial: Exclusion Criteria

- Spinal cord injury with sensory deficit only (i.e. no motor deficit).
- Penetrating spinal cord injury (including gunshot wounds).
- Isolated radiculopathy.
- Isolated cauda equina injury or injury below the spinal level L1.
- Associated head injury or other major cognitive deficit (i.e., condition where comprehension may be affected and affect the informed consent process or outcome assessment).
- Associated injury (soft tissue or bony) to the lumbar spine where the intrathecal catheter would be placed.
- Associated traumatic conditions that would interfere with the informed consent process or outcome assessment (e.g., chest, pelvis, abdomen, or femur injury requiring operative intervention).
- Pre-existing neurodegenerative disorder, such as Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, multiple sclerosis, amyotrophic lateral sclerosis.
- Pre-existing inflammatory or autoimmune disorder such as rheumatoid arthritis, systemic lupus, psoriasis.
- Any pre-existing non-disease that might interfere with patient safety, compliance, or evaluation of the condition under study (e.g., clinically significant cardiac disease, HIV, HTLV-1).
- Any other medical condition that in the investigator’s opinion would render the protocol procedures dangerous or impair the ability of the patient to receive protocol therapy.
- Female patients who are pregnant.
CAMPER Trial: Protocol

- Insertion of the intrathecal catheter by team
- Lumbar intrathecal catheter will remain in place for the next 5 days and ITP and MAP will be recorded hourly.
- A 4 ml sample of CSF will be taken through the catheter at time zero and then at ~8 hour intervals
- Concurrently, a 6-8 ml sample of blood will also be taken at time zero and at 8-hour intervals
- The MAP will be targeted to be between 80-85 mHg;
  - failure to sustain the MAP at this level will prompt the initiation of vasopressor support with DOPamine or NORpinephrine or both.

CAMPER Trial

- Canadian Multicentre CSF Pressure Monitoring and Biomarker Study
- San Francisco General Hospital (UCSF) to be first USA Site
- Going live August 2015
- For acute traumatic blunt SCI C0-L1 AIS A, B, C

FUTURE SCI DIRECTIONS?
Future Directions: Prospective Data

- TRACK-SCI
  - Transforming Research and Clinical Knowledge in Spinal Cord Injury
- Prospective study of SCIs from UCSF, SFGH, and UCSF-Fresno
- Launched in 2015

THANK YOU