ACUTE SPINAL CORD INJURY
MEDICAL TREATMENT

ผศ.นพ.ต่อพงษ์ บุญมาประเสริฐ
หน่วยโรคกระดูกสันหลัง ภาควิชาออร์โทปิดิกส์
คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่
Acute Spinal Cord Injury (SCI)

- **Incidence:**
  11.5-53.4 per 1 million people

- **Prevalence:** 700 SCI cases per 1 million people or about 260,000 patients alive (JAAOS 2010) in USA

- **Age:** 16-40 years

- **Gender:** M/F = 4:1

- MVA, fall, gun-shot wound, sports injury

- Incomplete quadriplegia > complete paraplegia > complete quadriplegia > incomplete paraplegia
Acute Spinal Cord Injury

- Devastating injury
- High mortality & morbidity
- Prolonged hospitalization
- Enormous physical, social, psychological impacts

Causes of Injury
- Motor vehicle accident***
- Fall from heights
- Sports injury
- Perioperative trauma

Blunt & Penetrating trauma
Isolated Acute SCI or Associated with Fractures & Dislocations
Evaluation of the Spinal-Injured Patients

- **Prehospital care**
  - Immobilization, Transportation
- **Primary emergency care**
  - Primary survey & resuscitation, secondary survey, diagnostic test & medical management
- **Anatomical realignment**
- **Surgical decompression & stabilization**
- **Rehabilitation**
  - Physical & Occupational therapy
Initial Evaluation of the Spine

**ER:** history taking, physical examination, vital sign, neurologic examination, GCS, Bulbocavernosus reflex (spinal shock), plain film trauma series lateral C-spine, CXR

**Management:** spinal immobilization, oxygenation, fluid replacement, retain Foley’s cath., analgesics, NPO, start Methylprednisolone (controversial)
Physical Examination

- HEENT: lacerated wound at forehead, no palpable stepping
- Neck: tenderness at middle C level
- Chest: negative Chest Compression Test, clear and equal breath sound both lungs
- Abdomen: soft, no tenderness
- Pelvic: negative compression test
- Extremities: no gross deformity, hardly move
# Neurologic Examination

<table>
<thead>
<tr>
<th>Motor</th>
<th>Rt.</th>
<th>Lt.</th>
<th>Reflex</th>
<th>Rt</th>
<th>Lt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deltoids</td>
<td>I</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td>II</td>
<td>II</td>
<td>Biceps</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Triceps</td>
<td>II</td>
<td>II</td>
<td>Brachioradialis</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>ECRL/ECRB</td>
<td>0</td>
<td>0</td>
<td>Triceps</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>ECU</td>
<td>0</td>
<td>0</td>
<td>Quadriceps</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>FCR</td>
<td>0</td>
<td>0</td>
<td>Achilles</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>FCU</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iliopsoas</td>
<td>II</td>
<td>II</td>
<td>BBK ↓, ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadriceps</td>
<td>III</td>
<td>III</td>
<td>Clonus -ve , -ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>III</td>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EHL</td>
<td>II</td>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHL</td>
<td>II</td>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Neurologic Examination

Decreased sensation of pin prick C6 ↓ both,
Loss of light touch sensation C6 ↓ both
Loss of proprioception sense of both upper & lower extremities

PR: presence of perianal sensation & voluntary anal contraction
Bulbocarvenosus reflex: present

ผู้ป่วยรายนี้ผ่านพ้นภาวะ spinal shock แล้วหรือยัง ?
ผู้ป่วยรายนี้มี sacral sparing หรือไม่ ? และเป็น cord syndrome ?
Plain X-rays
MRI Acute Spinal Cord Injury
Neurologic examination-ASIA score
Allen-Ferguson classification of Lower Cervical Spine Injury
Subaxial Injury Classification (SLIC) Scale

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No abnormality</td>
<td>0</td>
</tr>
<tr>
<td>Compression + burst</td>
<td>1+1 = 2</td>
</tr>
<tr>
<td>Distraction (e.g., facet perch, hyperextension)</td>
<td>3</td>
</tr>
<tr>
<td>Rotation or translation (e.g., facet dislocation, unstable teardrop or advanced staged flexion compression injury)</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discoligamentous complex</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Indeterminate (e.g., isolated interspinous widening, MRI signal change only)</td>
<td>1</td>
</tr>
<tr>
<td>Disrupted (e.g., widening of anterior disk space, facet perch or dislocation)</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological status</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Root injury</td>
<td>1</td>
</tr>
<tr>
<td>Complete cord injury</td>
<td>2</td>
</tr>
<tr>
<td>Incomplete cord injury</td>
<td>3</td>
</tr>
<tr>
<td>Continuous cord compression (neuro modifier in the setting of a neurologic deficit)</td>
<td>+1</td>
</tr>
</tbody>
</table>
Subaxial Injury Classification (SLIC) Scale

- The Spine Trauma Study Group (STSG)
  48 expert spine surgeons
  (neurosurgical and orthopaedic)

- Score 5 or more treated *surgically*
- Score 3 or less treated *nonsurgically*
- Score 4 is *equivocal*
Compressive Flexion with Acute Spinal Cord Injury
### Algorithmic approaches for compression burst injuries

<table>
<thead>
<tr>
<th>Vertebral Burst Fracture</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>= 2</td>
</tr>
<tr>
<td>DLC (likely intact)</td>
<td>= 0</td>
</tr>
<tr>
<td>Neurology (Cord Injury + Compression)</td>
<td>= 2, 3, or 4</td>
</tr>
<tr>
<td>SLIC Total</td>
<td>= 4-6</td>
</tr>
</tbody>
</table>

**Anterior Cervical Vertebrectomy Cage or Strut Graft (Allo or Auto)**
**Anterior Cervical Plate**
Compressive Extension Injury with Incomplete Cord Injury
Compressive Extension Injury with Incomplete Cord Injury
Algorithmic approaches for hyperextension injuries

Hyper-extension Injury +/- Avulsion Fractures
Morphology = 3
DLC (likely disrupted) = 2
Neurology (Cord Injury + Compression) = 0 - 4
SLIC Total = 5 + Neuro

Anterior Discectomy Fusion and Plate
In a very stiff spine (DISH) may choose to add posterior fixation
Mechanism of Acute Spinal Cord Injury

- **Primary spinal cord injury**
  - Physical deformation & destruction at the initial event
  - Magnitude & severity of injury
  - **Blunt injury**: contusion, compression, stretching
  - **Penetrating injury**

- **Secondary spinal cord injury**
  - Multifactorial secondary injury process
  - Biochemical process: reactive oxygen-induced lipid peroxidation (LP)
Cervical Spine Fracture/Dislocation with Spinal Cord Compression
Secondary Spinal Cord Injury

- Continued destruction of spinal cord
- Biomechanical and electrolyte shifts
- Cellular and molecular changes
- Vascular abnormalities
- Ischemia, loss of autoregulation, hemorrhage
- Apoptosis $\rightarrow$ “Cell Death”

Secondary damage zone
Areas of edema, hemorrhage & myelin destruction
Pathophysiology of Secondary SCI
Pathophysiology of Secondary SCI

- Free-radical theory
- Calcium theory
- Opiate receptor theory
- Inflammatory theory

Cell death

Necrosis
Apoptosis
Secondary Spinal Cord Injury
Management of Acute Spinal Cord Injury (SCI)

- Multidisciplinary approach
- Life-threatening conditions
- Careful physical examination, transfer, immobilization
- Record neurological change
- Medical treatment
- Early surgical treatment

*controversy*
Neuroprotective Agents

• High-dose of glucocorticoid steroid “Methylprednisolone (MP)”
• Non-glucocorticoid 21-aminosteroid “Tirilazad”
• Opiate receptor antagonist “Naloxone”
• Monosialoganglioside GM-1
• Thyrotropin-releasing hormone (TRH)
• Erythropoietin (EPO)
Primary Injury

- Petechial Hemorrhage
- Iron Release
- Voltage Dependent Channel Opening Na⁺, K⁺, Ca²⁺
- Glutamate Release
- NMDA and AMPA Receptor Activation
- Dynorphin Release
- Opiate Receptor Activation

Depolarization

- Intracellular Ca²⁺ Overload

Cytochrome Oxidase (COX) Activity

- Energy Failure
- Energy Failure →↑Lactate
- Reactive Oxygen Formation (ONOO⁻)
- Prostaglandins (PGF₂α, TXA₂)
- Leukotrienes (LTs)
- Lipid Peroxidation

Calpain Activation

- Cytoskeletal Degradation
- Axonal Damage
- Myelin Damage

Neurological Deficit

- Axonal Damage
- Myelin Damage

Microvascular Damage

- PMN and Macrophage Influx
- Ischemia

Mitochondrial Dysfunction

- NOS Activation
- AA Cascade Activation (COX1, COX2, 5-LO)
- Mitochondrial Dysfunction

GM-1

Tirilazad

Naloxone

MP
## Completed Prospective RCTs of Pharmacologic Approaches to the Management of Acute SCI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arms</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone***</td>
<td>MP (100 mg for 10 d), MP (1,000 mg for 10 d) MP, naloxone, placebo</td>
<td>No difference</td>
</tr>
<tr>
<td>NASCIS I</td>
<td></td>
<td>Significant improved neurologic recovery with early (&lt;8 h of SCI) MP treatment (p=0.03)</td>
</tr>
<tr>
<td>NASCIS II</td>
<td>MP (24 hr), MP (48 hr), MP 30 mg/kg bolus + TM 2.5 mg/kg bolus q 6 hr over 48 h</td>
<td>Improved neurologic recovery with MP treatment</td>
</tr>
<tr>
<td>NASCIS III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM1 ganglioside</td>
<td>GM1 vs placebo, MP + low-dose GM1, MP + high-dose GM1, MP + placebo</td>
<td>Improved neurologic recovery with GM1 Negative primary outcomes, trend for enhanced secondary outcomes</td>
</tr>
<tr>
<td>Maryland GM1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sygen GM1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRH</td>
<td>TRH vs placebo</td>
<td>Improved neurologic recovery with TRH</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>MP, nimodipine, nimodipine + MP, placebo</td>
<td>No difference. Study likely was too underpowered to detect a difference.</td>
</tr>
<tr>
<td>(Nimodipine)</td>
<td>MP, nimodipine, nimodipine + MP, placebo</td>
<td>No difference. Increased infection in MP group. Trend for increased motor recovery in cervical incomplete SCI patient starta</td>
</tr>
<tr>
<td>Petitjean et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pointillart et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gacyclidine (GK-11)</td>
<td>Gacyclidine (0.005, 0.01, or 0.02 mg/kg; two doses) vs placebo</td>
<td></td>
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</tbody>
</table>
Summary of NASCIS I
Treatment Arms and Results

• 330 patients randomized and treated within 48 hours of spinal cord injury
  1. Methylprednisolone 100 mg bolus, then 25 mg every 6 hours for 10 days
  2. Methylprednisolone 1000 mg bolus, then 250 mg every 6 hours for 10 days

• Findings:
  ▪ No significant difference was found in neurologic recovery between the two groups at 6- and 12-month follow up.

(NASCIS = National Acute Spinal Cord Injury Study)
High-dose Methylprednisolone Therapy for Acute SCI

- **High-dose MP**
  - (30 mg/kg)
  - inhibit post-traumatic LP
  - inhibit post-traumatic ischemia
  - support aerobic energy metabolism
  - improve recovery of extracellular calcium

**Hypothesized central role of inhibition of LP in the neuroprotective effects of high-dose MP in acute SCI**
Pharmacological Characteristics of High-Dose MP Therapy for Acute SCI

- Inhibition of post-traumatic lipid peroxidation appears to be the principal neuroprotective mechanism and this is unrelated to glucocorticoid receptor-mediated actions.
- Microvascular and neuroprotective effects are both involved.
- Large intravenous doses are required (30 mg/kg).
- Antioxidant protective effects of MP follow a biphasic (U-shaped) dose-response curve; doubling the dose from 30 to 60 mg/kg results in a loss of the protective efficacy.
- Early treatment is required since lipid peroxidation develops rapidly and is irreversible.
- Time course of antioxidant protection parallels the spinal cord tissue pharmacokinetics; there is consequently a need for constant i.v. infusion to maintain effective tissue concentrations.
- Optimal treatment duration is uncertain, but needs to continue as long as conditions within the injured spinal cord favor lipid peroxidative reactions (i.e., at least 24 to 48 h).
- Glucocorticoid receptor-mediated anti-inflammatory effects play only a minor role in comparison to lipid antioxidant effects.
Summary of NASCIS II
Treatment Arms and Results

- 487 patients randomized and treated within 12 hours of spinal cord injury
  1. Methylprednisolone- 30 mg/kg bolus then 5.4 mg/kg/hr for 23 hours
  2. Naloxone- 5.4 mg/kg bolus then 4.5 mg/kg/hr for 23 hours
  3. Placebo

- **Findings:**
  - No significant difference was found in neurologic recovery among the three groups at 6 or 12 months after injury
  - *Patients receiving methylprednisolone within 8 hours of injury, significant motor and sensory improvement was observed at 6 months* (*Bracken et al. 1990*) *and at 12 months after injury* (*Bracken et al. 1992*). Naloxone was not shown to be effective.
  - Patients with incomplete lesions, Naloxone was subsequently shown to promote significant neurologic recovery (*Bracken et al. 1993*).
NASCIS study

- **NASCIS II:**
  - Methylprednisolone 30 mg/kg bolus followed by 5.4 mg/kg/hr for 23 hr
  - Naloxone 5.4 mg/kg bolus followed by 4.0 mg/kg/hr for 23 hr
  - Placebo

  - Must start within 12 hours of injury
  - Assessed at 6 weeks and 6 months
NASCIS study

- **NASCIS II:**
  - Conclusion: Intravenous Methylprednisolone administration by 8 hours of injury significantly increased motor function.

  - *Sounds great!* This study established steroids as a medico-legal requirement in the case of the SCI patient.
NASCIS study

- NASCIS II:
  - Methodological flaws:
    - Patients enrolled within 12 hours of injury, but benefit reported for those who received steroids within 8 hours (retrospective combining of data to find significance)
    - Assessed bilateral motor and sensory function, but only used right-sided motor to draw conclusions
    - No change in sensory function seen
    - Lack of minimum motor impairment for inclusion
**NASCIS study**

- **NASCIS II:**
  - Methodological flaws:
    - 487 patients enrolled but only 127 were included in the final analysis (62 steroid, 65 placebo), thus the other 70% were excluded
    - Beneficial effect of MP was only shown in patients with incomplete SCI who presented & treated with in 8 hours
    - No consistency between centers for BP management, monitoring, DVT prophylaxis, respiratory care, nutritional support, surgical techniques, rehabilitation
    - No report on FUNCTIONAL improvement
Summary of NASCIS III

Treatment Arms and Results

499 patients randomized and treated within 8 hours of spinal cord injury

1. Methylprednisolone- 30 mg/kg bolus then 5.4 mg/kg/hr for 23 hours
2. Methylprednisolone- 30 mg/kg bolus then 5.4 mg/kg/hr for 47 hours
3. Tirilazad mesylate- 2.5 mg/kg every 6 hours for 48 hours

Findings:

- No significant difference was found in neurologic recovery among the three groups at 6 or 12 months after injury.
- If treatment was initiated 3-8 hours after injury, patients receiving methylprednisolone for 48 hours had significant recovery over those who received methylprednisolone for 24 hours; p=0.01 at 6 months after injury (Bracken et al. 1997); p=0.53 at 12 months after injury (Bracken et al. 1998). Neurologic recovery with Tirilazad was equivalent to that observed with 24-hour methylprednisolone.
NASCIS I, II, III

• **NASCIS III:**
  – Conclusions:
    • If steroid started within 3 hours of injury, give 23 hours
    • If steroid started between 3-8 hours after injury, give 48 hrs
  – Showed improvement in motor score but **NOT** in functional independence measures
NASCIS study

- **NASCIS III:**
  - Criticisms are similar for NASCIS II
    - Only reported right-sided motor scores
    - More patients with normal motor score were randomized into the 24-hour MP group
    - Lack of standardized medical & surgical treatment
    - Lack of minimum motor impairment for inclusion
    - No functional improvement
    - Rate of complications: pneumonia, sepsis
High-dose Methylprednisolone (MP)

- Stabilize cellular membranes
- Reduce vasogenic edema
- Enhance spinal cord blood flow
- Alter the concentration of electrolytes at the injury site
- Inhibit endorphin release
- Scavenge damaging free radicals
- Limit the inflammatory response after injury
Suggested Indications for the Use of MP in Acute SCI

• **Acute non-penetrating SCI (<3 hr after injury)**
  - MP should be given as per NASCIS II protocol (i.e. 24 hours of treatment)

• **Acute non-penetrating SCI (after 3 hr, within 8 hr)**
  - MP should be given as per NASCIS III protocol (i.e. 48 hours of treatment)

• **Acute non-penetrating SCI (>8 hr after injury)**
  - MP should **not** be used

• **Acute penetrating SCI**
  - MP is **not recommended**
    - MP 30 mg/kg bolus then, 5.4 mg/kg/hrs
Penetrating Trauma

Methylprednisolone is contraindicated !!!
Summary of NASCIS I, II, III Protocols

• Methylprednisolone bolus 30 mg/kg, then infusion 5.4 mg/kg/hr
• Infusion for 24 hours if bolus given within 3 hours of injury
• Infusion for 48 hours if bolus given within 3 to 8 hours of injury
• No benefit of methylprednisolone started more than 8 hours after injury
• No benefit with naloxone
• No benefit with tirilazad
Evidence-Based Knowledges

• Grades of Recommendation
  – **A**: Good evidence (Level I studies with consistent findings) for or against recommending intervention
  – **B**: Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention
  – **C**: Poor quality evidence (Level IV or V studies) not allowing a recommendation for or against intervention
  – **I**: Insufficient evidence to make a recommendation
## Summary of Recommendation

<table>
<thead>
<tr>
<th>STATEMENT</th>
<th>LEVEL OF EVIDENCE / GRADE OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Corticosteroids are a treatment option in the management of acute spinal cord injury without proven benefit</td>
<td>A</td>
</tr>
<tr>
<td>2. Corticosteroids used in the setting of acute spinal cord injury increase complications</td>
<td>A</td>
</tr>
</tbody>
</table>
Opiate Blockers “Naloxone”

- Nonselective opioid receptor antagonist
- Improve spinal cord conduction
- Reduce allodynia and edema
- However, it failed to provide therapeutic effects when administered for the NASICIS II trial
- Remain unclear for management of acute SCI
Tirilazad

- Non-glucocorticoid 21-aminosteroid
- Duplicate the antioxidant neuroprotective efficacy of MP in SCI models
- Evidence of human efficacy was obtained in NASCIS III study
GM1 Ganglioside

- Sialic acid-containing glycoprophingolipids
- Potentially better option than MP
  - No effect on gray matter at the level of trauma
  - Longer therapeutic window
- Has not been approved for generally use in the acute SCI
- No clinical trials are currently underway
Future Neuroprotective Pharmacological Approaches
Future SCI Drug Development

• Novel antioxidant strategies that could replace high-dose MP.
• Anti-inflammatory strategies
• Role of Calpain in acute SCI and potential neuroprotective efficacy of Calpain inhibitors
• Role of apoptosis in acute SCI and anti-apoptotic therapeutic strategies
• Caspase-3 apoptotic cascade
Stem Cell Therapy

• **Rationale**
  – Replace damaged cells
  – Provide cell-based electrical relay between neurons above and below the injury
  – Ameliorate clinical deterioration and/or facilitate regeneration by providing neuroprotective or growth factors

• **Types of stem cell therapy**
  – Embryonic stem cell
  – Progenitor stem cell
    • Neural Stem Cells (NSCs)
    • Mesenchymal Stem Cells (MSCS)
Stem Cell - Spinal Cord Injuries

The Promise of Stem Cell Research

- Identify drug targets and test potential therapeutics
- Study cell differentiation
- Understanding prevention & treatment of birth defects
- Cultured Pluripotent Stem Cells
  - Tissues/Cells for Transplantation
  - Bone marrow for leukemia & chemotherapy
  - Nerve cells for Parkinson's & Alzheimer's disease
  - Heart muscle cells for heart disease
  - Pancreatic islet cells for diabetes

Add different growth factors

Nerve
Muscle
Blood
CMU SPINE INJURY UNIT
Methylprednisolone for Acute SCI
...is a treatment option ...
NOT a standard of care !!!

Early Decompression for Acute SCI
should be performed in
the selected patients
Save Your Date !!!

The 16th Operative Spine Course
17-20 มกราคม 2555
ณ ศูนย์ประชุมนานาชาติเอ็มเพรส
จังหวัด เชียงใหม่
THANK YOU
FOR YOUR ATTENTION