Methylprednisolone for Spinal Cord Injury

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NNTS
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Gregory Hawryluk MD, PhD, FRCSC
HS Clinical Instructor and Neurotrauma Fellow, UCSF
Assistant Professor of Neurosurgery, University of Utah

Great Debates in History

My Background/Disclosures

- I did a PhD under Michael Fehlings
- Completed high-level biostatistics courses
- John Hurlbert was my Chief Examiner
- I have written numerous chapters/review articles on therapeutics for SCI
- I write Brain Trauma Foundation TBI guidelines
- I sit on the AANS/CNS Joint Guidelines Committee
- Declined to review the SCI guidelines
**2002 Guidelines:**

- **Curtetiethan:**
  - **Guideline:** Standards.
  - **Guideline:** Options.

- **2013 Guidelines:**
  - **Guideline:** Standards.
  - **Guideline:** Options.

- **I am not so much in favor of MPSS as I am opposed to having an unreasonable viewpoint imposed upon me**

- **I am “Pro-Choice”**

- **My Position**
  - I’m not asking you to agree with me
  - I’m hoping you will look at the data yourself instead of listening to what Sanjay, Michael Fehlings, John Hurlbert or I say

- **I think there are 2 different issues:**
  1. Do steroids work and does the efficacy/risk profile justify use
  2. What guideline is appropriate given the rules inherent to converting evidence into clinical guidelines
Regarding the first issue:

1. Do steroids work and does the efficacy/risk profile justify use

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**NASCIS I:**

**Efficacy of Methylprednisolone in Acute Spinal Cord Injury**

Michael S. Brocker, MD; William F. Collins, MD; David J. Freeman, MD; Mary Jo Shepard, MPH; Franklin W. Wagner, MD; Robert M. Silver, MPH; Karen G. Helberson, MPH; Joseph Rascoff, MD; William E. Hunt, MD; Runa L. Peretti, MD; Robert G. Grams, MD; Beth A. Green, MD; Howard M. Ecker, MD; Nathan Phillips, MD; Joseph H. Dinner, MD; John V. Meagher, MD; Egbert Fischer, MD; Guy L. Ciffler, MD; Eugene S. Pann, MD; Stephen E. Rowe, MD

**Table 3 - Flows and Relative Risk of Complications by Randomized Protocol**

<table>
<thead>
<tr>
<th>Complication</th>
<th>High Dose</th>
<th>Low Dose</th>
<th>Relative Risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral edema</td>
<td>2.4</td>
<td>2.1</td>
<td>0.82</td>
<td>0.265</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.0</td>
<td>0.95</td>
<td>0.91</td>
<td>0.651</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17.0</td>
<td>18.0</td>
<td>0.97</td>
<td>0.674</td>
</tr>
<tr>
<td>Dissemination</td>
<td>18.0</td>
<td>15.0</td>
<td>0.84</td>
<td>0.120</td>
</tr>
<tr>
<td>Gastrintestinal tract injury</td>
<td>9.5</td>
<td>9.5</td>
<td>1.01</td>
<td>0.899</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9.5</td>
<td>9.5</td>
<td>1.01</td>
<td>0.899</td>
</tr>
</tbody>
</table>

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**NASCIS II:**

**The New England Journal of Medicine**

Volume 232 MAY 17, 1990 Number 20

A RANDOMIZED, CONTROLLED TRIAL OF METHYLPRERIDNSOLONE OR NALOXONE IN THE TREATMENT OF ACUTE SPINAL-CORD INJURY

Results of the Second National Acute Spinal Cord Injury Study

**NASCIS II:**

- Randomized:
  - 161 patients to 30mg/kg bolus then 5.4mg/kg MPSS for 23h
  - 154 to naloxone
  - 171 to placebo

- At 8mo in a planned secondary analysis, improved motor function (p=0.03), light touch (p=0.03) and pinprick (p=0.02) in 66 patients within 8h of injury
- Improved motor function continued to be seen at 1y in those treated within 8h of injury (p=0.019 if initially complete, p=0.024 if some residual function)
- Benefit in complete patients a noteworthy finding
- No effect of naloxone

**NASCIS II:**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Treatment Group</th>
<th>Methypridisolone</th>
<th>Naloxone Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>156</td>
<td>154</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>urinary tract infection</td>
<td>45.3</td>
<td>49.4</td>
<td>46.1</td>
<td>0.77</td>
</tr>
<tr>
<td>pneumonia</td>
<td>28.2</td>
<td>29.1</td>
<td>24.4</td>
<td>0.55</td>
</tr>
<tr>
<td>decubitus (breakdown)</td>
<td>18.6</td>
<td>18.2</td>
<td>19.2</td>
<td>0.39</td>
</tr>
<tr>
<td>paralytic ileus</td>
<td>8.3</td>
<td>7.8</td>
<td>10.8</td>
<td>0.04</td>
</tr>
<tr>
<td>meningitis</td>
<td>5.8</td>
<td>6.5</td>
<td>5.6</td>
<td>0.95</td>
</tr>
<tr>
<td>gastrointestinal perforation</td>
<td>7.8</td>
<td>6.6</td>
<td>6.5</td>
<td>0.23</td>
</tr>
<tr>
<td>gastrointestinal hemorrhage</td>
<td>4.3</td>
<td>3.0</td>
<td>3.5</td>
<td>0.84</td>
</tr>
<tr>
<td>pulmonary embolus</td>
<td>3.9</td>
<td>5.2</td>
<td>1.2</td>
<td>0.13</td>
</tr>
<tr>
<td>congestive heart failure</td>
<td>1.3</td>
<td>1.3</td>
<td>1.2</td>
<td>0.99</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>paralytic ileus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

**NASCIS III:**

- All 499 received the 30mg/kg bolus of MPSS
- Randomized:
  - 166 to 24h of MPSS
  - 166 to 48h of MPSS
  - 167 to 48h of tirilizad mesylate
- No comparison to placebo ➔ does not provide information on whether MPSS or TM works!
- 48h dose associated with improved motor recovery at 6w (p=0.09) and 6mo (p=0.07); in analyzing within 8h at 6w p=0.04 and 6mo p=0.01
- Critical to understand what this study actually tested

**NASCIS III:**

Even if the small increases in wound infection and gastrointestinal bleeding found in methylprednisolone-treated patients were truly related to treatment (in this study, they cannot be distinguished from chance), they are manageable conditions and the risk associated with them would be well worth the potential therapeutic benefits of methylprednisolone administration.
NASCIS III:

- "infinitely more" PEs and GI bleeds

Confirmatory RCTs post NASCIS II
(All patients treated <8 hours after SCI)

- Otani et al, 1994; Sekitsy Sekizui* – 353 patients: NASCIS II MPSS vs usual care without MPSS
- Trend towards improved motor score recovery in MPSS patients at 6 mos
- Pointillart et al, 2000, Spinal Cord** – 106 patients: NASCIS II MPSS vs Nimodipine vs Combination vs No treatment
- No differences in neurological outcome at 1 year
- Matsumoto, 2001, Spine*** – 46 patients: NASCIS II MPSS vs placebo
- Trend toward increased incidence of complications in MPSS (56.5%) vs placebo (34.8%) patients (p=0.14)

* No placebo group, no blinding, high loss to F/U
** No placebo, underpowered
*** imbalanced with ++less severe SCI in placebo group

STASCIS:

- A benefit of MPSS administration was found and had to be controlled for statistical benefit
- Complications were less likely in those receiving MPSS (p=0.02)

Cochrane Review:

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Cochrane Review:

- 31 Forest Plots

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Cochrane Review:

Lies, Damn Lies and Statistics...

- There are no true rules, easily mis-used
- Guise of authority and expertise
  - Hard for anyone not trained in statistics to argue
  - Hard for someone trained in statistics to argue if not familiar with the data
- Statistical significance (p=0.05) is arbitrary
  - Ignorant of sample size (type II error), trends, other studies
  - Easy to support almost any view point with a sufficiently stringent or lax test
- Disparity between ratios and incidence

Statistics are a Black Art...
Funding for clinical trials is limited and investigators are more likely to attract funding with overly-optimistic power calculations. We need to remember that neurotrauma patients are extremely heterogeneous and trials are universally under-powered. IMPACT showed us that only patients who have the potential of a change in outcome contribute to statistical power. The result is that any completed neurotrauma trial is vulnerable to a critic who demands more stringent testing.

Results are not black and white (p< or >0.05). Effects exist on a gradient. Variability and sample size are critical. Consistent effects/trends between studies are probably more important than the results of a single study.

Most have substantial flaws – even when exceptionally well done. Sense of superiority/makes you feel smart. Common in those early in their reviewing careers. ‘Reasonable criticism’ takes experience and wisdom.

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This has become a philosophical debate.
This Has Become a Philosophical Debate

- The p-values and subgroup analyses amongst multiple studies are dizzying
- Spinal cord injury is different!
  - Patients (and clinicians) are desperate for something (anything) that improves neurological function
  - Patients travel across the world at great cost and risk to pursue unproven therapies (i.e., cell transplants)

Increased risk and less benefit is acceptable for severe conditions like cancer
- Chemotherapy and radiation are extremely toxic
- Accutaine for pimples

Steroids are in the Nadir of a Well-Described Curve for Innovation

Points We Can Probably Agree On:

- People need to read the papers and come up with their own opinion
- In the absence of iron clad data people should be free to generate their own opinion
- If steroids were a panacea or clearly ineffective we wouldn’t be having this debate
  - We are not debating naloxone or tirilizad mesylate
- It is time for new figures to have this debate
  - Investigators are biased by their historical viewpoints
  - Guidelines chapters written by Hurlbert or Cochrane reviews by Bracken won’t help settle the debate
Points We Can Probably Agree On:

- Professors at Yale probably know how to do statistics and interpret them
- John Hurlbert had better be willing to subject his minocycline trial to his own criticisms
- We need to take this debate to SCI patients and ask their opinion
- With new promising agents on the way, this debate will probably die a natural death

Problems with the Pro-Steroid Debate:

- There was financial pressure in the face of budget cuts to produce a positive result
- Faxing emergency rooms instructions to administer steroids for SCI prior to peer review of the data didn’t help the cause
- Michael Bracken isn’t helping the cause by making further contributions to the argument
- Michael Fehlings’ new guideline likely won’t settle the debate either

Problems with the Anti-Steroid Debate:

- Unrealistic expectations and statements:
  - “There is no evidence for steroids”
  - “Tirilizzad mesylate doesn’t work”
  - “A Bonferroni correction wasn’t done”
  - ‘Mis’-use of scales and ratios
- The 2013 guidelines provide dramatically different recommendations despite little change in the pool of evidence
- John Hurlbert should not have been allowed to write the chapter
- Data presentation suggests bias: re-publishing low-quality original source data in the guidelines

Why were figures from LoE III studies reproduced in guideline?

Problems with the Anti-Steroid Debate:

- The accusation of post-hoc testing is ignorant of the stated hypothesis that steroids would be more efficacious early after injury and grants written before the trial
- Since when are secondary analyses in RCTs equivalent to expert opinion?
- They don’t want to debate anymore
- Failure to consider the breadth of the data: ignorant of the mortality benefit

Lee et al. Surg Neuro, 2007
Retrospective review (LoE=3)
Problems with the Anti-Steroid Debate:

- The notion that 1y follow-up data is ‘buried’ in the literature
- Apparently Dr. Hubert does not read Journal of Neurosurgery
- Extrapolating TBI results to SCI is inappropriate
- The MPSS recommendation has been very controversial, does not enjoy wide acceptance and is being subject to independent re-analysis funded in part by the AANS/CNS Joint Section on Neurotrauma and Critical Care

Summary of Data Supporting MPSS for SCI:

- Though the effect size has been weak, numerous studies have found a benefit inherent to MPSS
- Too frequent to be explained by type I error
- An evil statistician would have a hard time manufacturing such a benefit
- The benefit of MPSS has been dose-dependent
- Effect early after injury makes biological sense and is consistent with other SCI research

I think there are 2 different issues:

2. What guideline is appropriate given the rules inherent to converting evidence into clinical guidelines
Conclusions:

- Steroids should be administered selectively for those with SCI
- Published evidence suggests to me that steroids are modestly efficacious
- Small differences are important for SCI patients
- The suggested mortality improvement trumps morbidity concerns
- Given that the evidence for efficacy of steroids and their complications I don’t understand how you can believe in one but not the other

Conclusions:

- Let’s ask SCI patients what to do
- New agents are needed - fortunately they are on their way
- The cost of a non-definitive trial is far greater than one that is definitive
- We need to better manage conflict of interest in publications that synthesize the literature