The Use of Steroid Therapy in Acute Spinal Cord Injury

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Disclosures

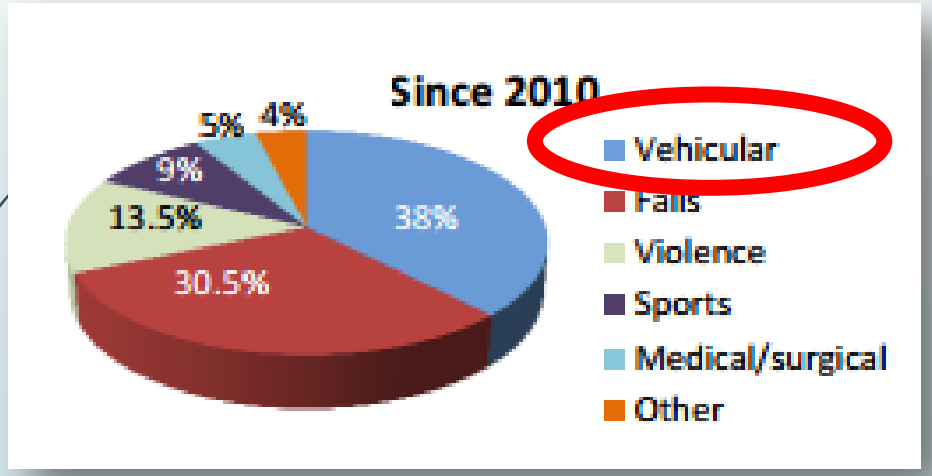
- None

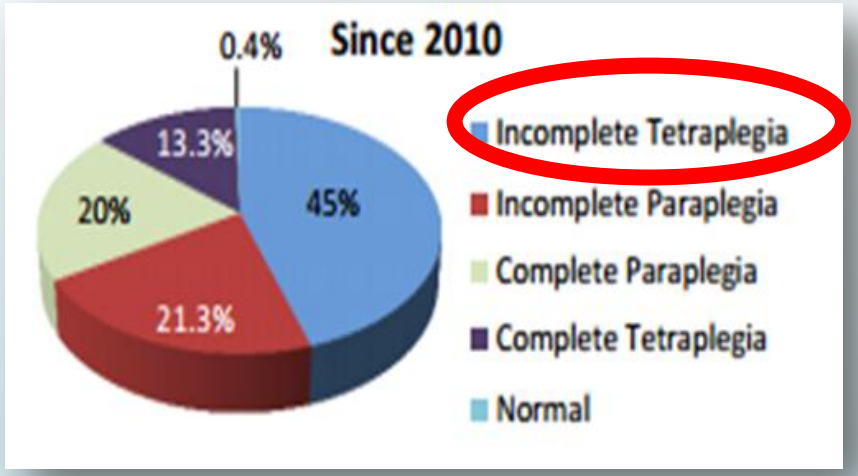
Background

- The administration of **methylprednisolone (MP)** for patients with acute **spinal cord injury (SCI)** has been **highly controversial**.

Epidemiology

- ~ **54** cases per million population in the U.S. (approximately 17,000 new SCI cases each year)
- Average age ~ **42** and **81% male** victims

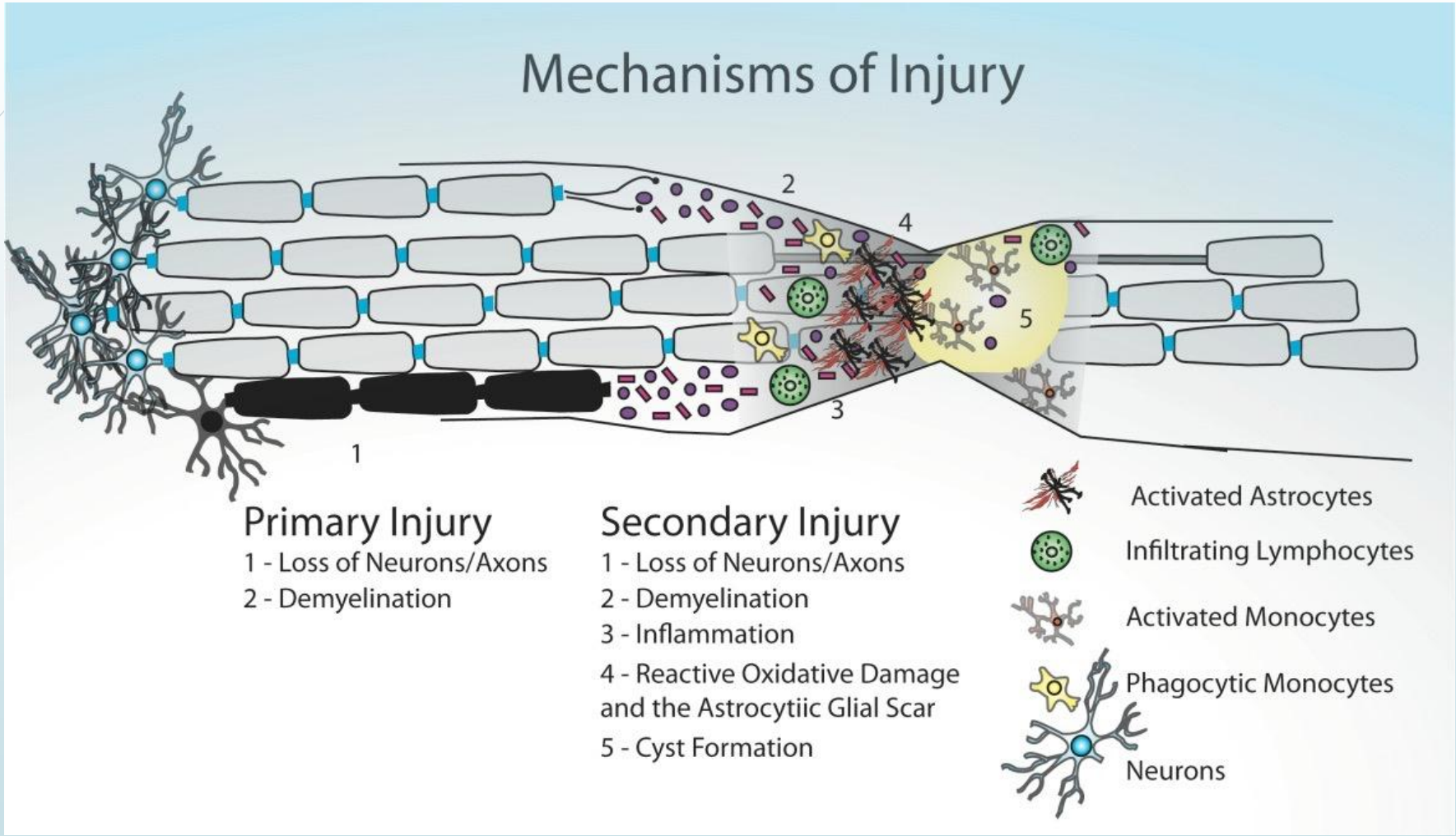




- The number of people in the U.S. who are alive in 2016 who have SCI has been estimated to be approximately **282,000 persons**
- Causes of death: **pneumonia** and **septicemia**

National SCI Statistical Center 16' Data

Pathophysiology



Ruff and Fehlings (2010)

Classification

- Complete SCI
- Incomplete SCI

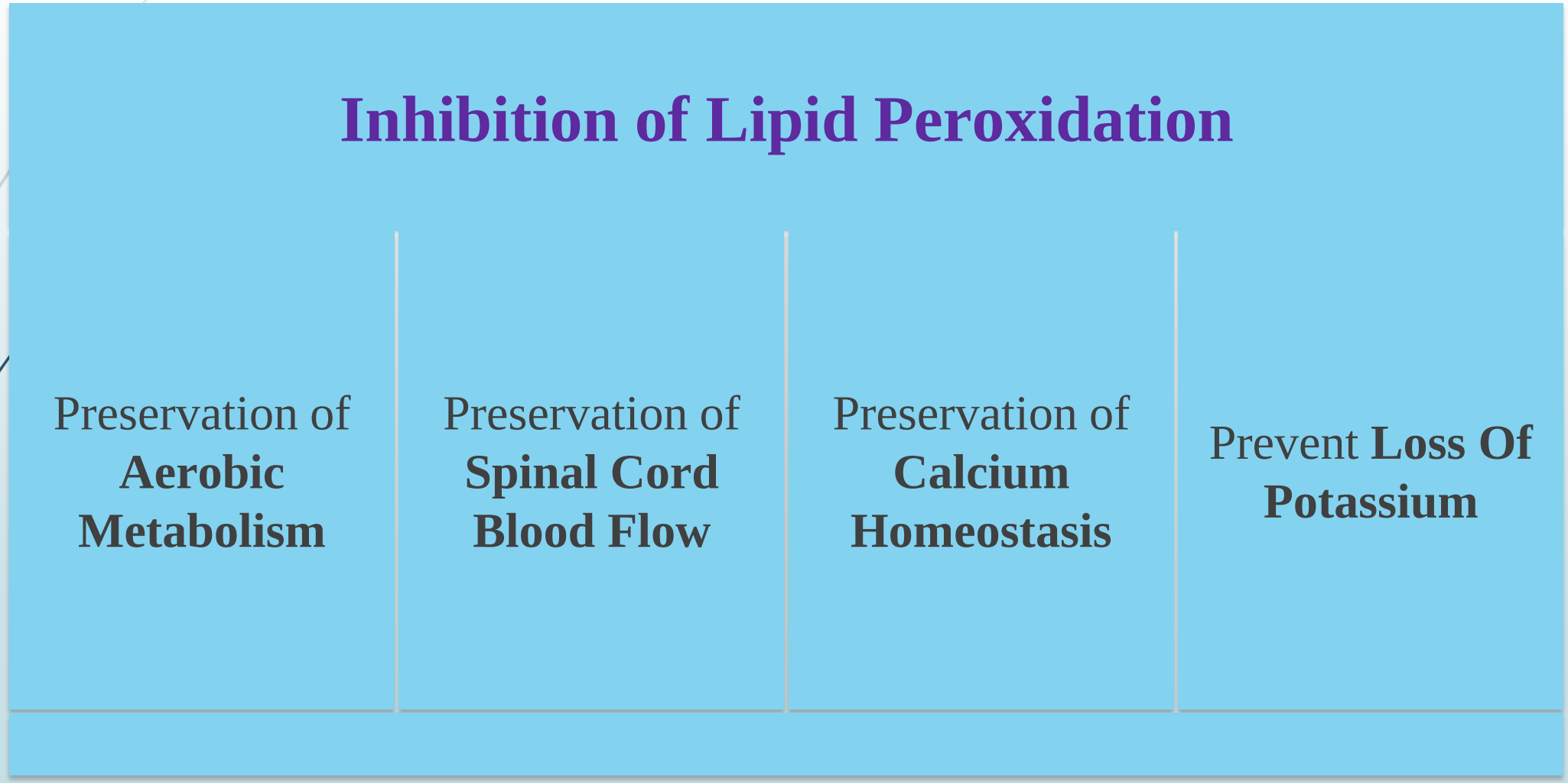
The Goals of Treatment

- To prevent secondary injury
- Alleviate cord compression
- Establish spinal stability

Special Consideration of

CORTICOSTEROIDS

Suggested Mechanism of Action for Neuroprotection with MP (Animal Models)



Tintinalli 8th edition

Methylprednisolone (MP) Possible Complications

- **Infection**
- **Hyperglycemia**
- **GI Bleeding**
- Myopathy
- Pneumonia
- Respiratory Failure
- Peptic Ulcer Disease

CNS/AANS 2013' guidelines

2002 recommendations

- "**Treatment with Methylprednisolone for either 24 or 48 hours is recommended as an option** in the treatment of patients with acute spinal cord injuries. It should be undertaken only with the knowledge that **the evidence suggesting harmful side effects is more consistent than any suggestion of clinical benefit.**" -American Association of Neurological Surgeons and Congress of Neurological Surgeons

LITERATURE REVIEW

- The National Acute Spinal Cord Injury Study (**NASCIS**) group published three prospective, double-blind and multi-center studies to evaluate the efficacy of MP in **blunt spinal cord injury.**

NASCIS I

- Compared **high-dose vs lower-dose MP** regimen (n = 330).

No placebo group.

- High-dose = 11g MP in 10 days, **10x** higher than lower dose MP.

- **No evidence of recover**y of motor function, pin prick or light touch between the groups at 6 weeks, 6 months and 1 year

Bracken MB et al. JAMA 1984; 251:45-52.

After NASCIS I

- Better understanding of MP mechanism of action in SCI (inhibition of lipid peroxidation) raised question of ideal dose for study as it would require higher doses .

Bracken MB et al. JAMA 1984; 251:45-52.

NASCIS II

- Compared **MP**, **Naloxone**, and **Placebo** (N:427)
- MP protocol: 30mg/kg IV then 5.4mg/kg/hr x 23 hrs (higher than NASCIS I)
- At one year, no significant difference in neurologic function among treatment groups (primary endpoint)
- Within the subset of patients treated within 8 hours, marginal improvements in motor function

Bracken MB et al. N Eng J Med 1990; 322:1405-1411

After NASCIS II

- NASCIS II researchers (and public) assumed steroids /MP worked within 8 hours
- **Goal** was to study **ideal duration of MP treatment& reproduce** subgroup analysis **findings from NASCIS II**

Bracken MB et al. N Eng J Med 1990; 322:1405-1411

NASCIS III

- Goal: Is there benefit from MP within 8 hours that was seen in NASCIS II?
- Compared three treatment groups (*N*=499)
- No placebo b/c MP had become “standard of care”
  - MP ……high-dose for 48h
  - MP…….high-dose for 24h
  - Tirilazad Mesylate…….for 48h
- Majority of patients enrolled were excluded from post-hoc analysis

Bracken MB et al. AMA 1997; 277:1597-1604

NASCIS III

- Within 3h: there was **no difference in outcomes** among treatment groups at one year
- Between 3-8h: 48 hours of MP was associated with a **greater motor but not functional recovery**
- Patients who received the longer duration infusion of MP had more severe sepsis and severe pneumonia compared with the shorter duration of infusion
- Mortality was similar in all treatment groups

- In all three trials, patients who received high-dose methylprednisolone and longer duration protocols were more likely to develop complications such as **severe sepsis, severe pneumonia, wound infection , GI bleeding…**

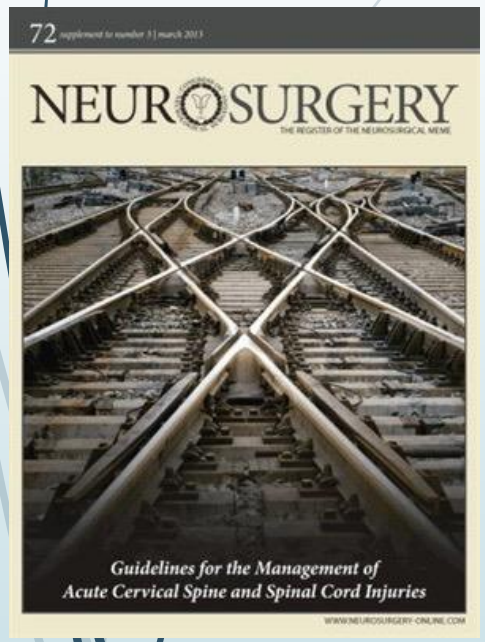
- Conclusions of **NASCIS II and III** that high-dose methylprednisolone **was beneficial** when administered within 8 hours of injury (even though primary endpoints all negative)
  - Based on subgroup analysis which is only hypothesis-generating. Requires new study to confirm findings (no randomized trials have reproduced these findings).
  - Neurologic effects determined only through **post-hoc analysis (not pre-planned) of subgroups.**
  - Can't draw such sweeping conclusion from subgroup analysis of any study

- **Healthy patients with normal neuromuscular exams were enrolled**
  - And more likely to be in MP groups
- **MP more likely to cause complications**
- Cochrane review written by Bracken, author of all 3 NASCIS studies (**vested interest? intellectual bias?**)

- Results of the NASCIS clinical trials have been criticized
- Reassessment, meta-analysis, and studies have questioned of the effectiveness of high dose steroid therapy
- There is no sufficient clinical evidence to support the use of steroids in acute spinal cord injury

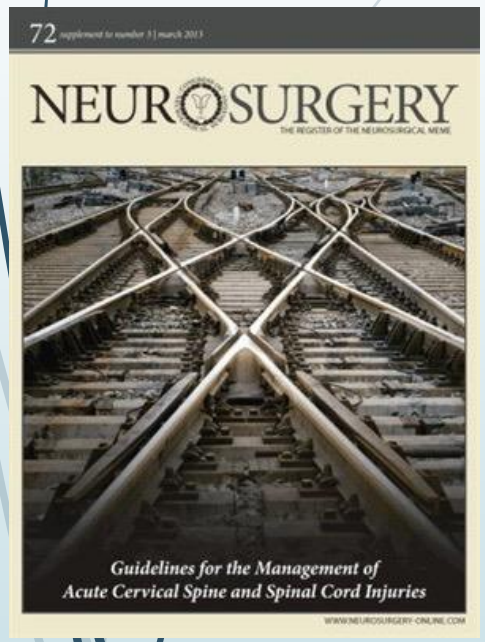
- In 2008, ATLS guidelines (8th edition) stated there was **insufficient evidence** to recommend routine use of steroids in spinal cord injury.

American Association of Neurological Surgeons and Congress of Neurological Surgeons



- *"Administration of methylprednisolone (MP) for the treatment of acute spinal cord injury (SCI) is* ***not recommended****. Clinicians considering MP therapy should bear in mind that the drug is* ***not Food and Drug Administration (FDA) approved*** *for this application…"*

American Association of Neurological Surgeons and Congress of Neurological Surgeons (2012 recommendation)



- *"There is no Class I or Class II medical evidence supporting the clinical benefit of MP in the treatment of acute SCI. Scattered reports of Class III evidence claim inconsistent effects likely related to* ***random chance or selection bias****. However, Class I, II, and III evidence exists that high-dose steroids are associated with harmful side effects including death."*

March 2013 - Volume 72

For **Pediatric** Spinal Cord Injury?

- The National Association of Spinal Cord Injury Study trials excluded children

No trials have shown a benefit of steroids in children

- **Steroids are not considered standard practice for pediatric spinal cord injuries**

JEM, In Press On Line 5/21/10

Apprehensions

- Some Physicians may
  - genuinely believe in the benefits of MP
  - believe doing something is better than doing nothing
  - fear litigation

Steroids for penetrating trauma?

Neurosurgery. 1996 Dec;39(6):1141-8; discussion 1148-9.

Use of methylprednisolone as an adjunct in the management of patients with penetrating spinal cord injury: outcome analysis.

Levy ML[1], Gans W, Wijesinghe HS, SooHoo WE, Adkins RH, Stillerman CB.

Author information

Abstract

OBJECTIVE: Since the results of the Second National Acute Spinal Cord Injury Study were published in 1990, methylprednisolone has become a mainstay in the treatment of nonpenetrating spinal cord injury. Although potential significant relationships between the prompt administration of high-dose methylprednisolone after blunt spinal cord injury and outcome have recently been addressed, the relationship between the prompt administration of high-dose methylprednisolone after penetrating spinal cord injury and outcome remain unanswered.

METHODS: To explore this relationship, we performed a retrospective nonrandomized study on a series of 252 patients with penetrating missile injuries to the spine who presented to our institution from March 1980 to July 1993. One hundred eighty-one patients (71%) were treated conventionally without adjunctive steroid therapy before 1990. Sixteen patients followed up during the 13-year study period received steroid protocols that were not consistent with the Second National Acute Spinal Cord Injury Study protocol and were excluded from the study. Since 1990, 55 patients (21%) were treated with intravenous methylprednisolone according to the Second National Acute Spinal Cord Injury Study protocol. All patients were subsequently transferred for rehabilitative care, and prospective evaluations of their neurological status were performed at admission and discharge.

RESULTS: The study included 236 men and 16 women (mean age, 25.6 yr). The mean duration of stay for initial hospitalization was 94.6 days, and the mean duration of stay in rehabilitation was 78.6 days. Frankel scores were used to assess outcome ($P < 0.05$) and were assessed at admission and at the time of definitive discharge from the Spinal Cord Injury Care System. The hypothesis that methylprednisolone therapy significantly improves functional outcomes in patients with gunshot wound injuries to the spine was rejected. Only the total number of days in rehabilitation and the degree of neurological injury at admission contributed significantly to explaining outcome at discharge.

CONCLUSION: The administration of methylprednisolone did not significantly improve functional outcomes in patients with gunshot wound injuries to the spine or increase the number of complications experienced by patients during their hospitalizations.

Steroids in traumatic brain injury

Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months

*CRASH trial collaborators**

MRC CRASH is a randomised controlled trial (ISRCTN74459797) of the effect of corticosteroids on death and disability after head injury. We randomly allocated 10 008 adults with head injury and a Glasgow Coma Scale score of 14 or less, within 8 h of injury, to a 48-h infusion of corticosteroid (methylprednisolone) or placebo. Data at 6 months were obtained for 9673 (96·7%) patients. The risk of death was higher in the corticosteroid group than in the placebo group (1248 [25·7%] *vs* 1075 [22·3%] deaths; relative risk 1·15, 95% CI 1·07–1·24; p=0·0001), as was the risk of death or severe disability (1828 [38·1%] *vs* 1728 [36·3%] dead or severely disabled; 1·05, 0·99–1·10; p=0·079). There was no evidence that the effect of corticosteroids differed by injury severity or time since injury. These results lend support to our earlier conclusion that corticosteroids should not be used routinely in the treatment of head injury.

The MRC CRASH trial (corticosteroid randomisation after significant head injury) is a large international allocation remained concealed from patients, carers, and interviewers.

Lancet 2005; 365: 1957–59

Published online May 26, 2005 DOI:10.1016/S0140-6736(05)66552-X

*See end of paper

Correspondence to: CRASH Trials Co-ordinating Centre, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, UK
crash@lshtm.ac.uk

- ***Contraindicated***
- ***Increased mortality*** *(21% vs 18% at 2 weeks, 26% vs 22% at 6-month follow up)*

How about **Clinical Practice** for SCI?

Survey of Cervical Spine Research Society Members on the Use of High-Dose Steroids for Acute Spinal Cord Injuries

Schroeder, Gregory D. MD*; Kwon, Brian K. MD, PhD, FRCSC†; Eck, Jason C. DO‡; Savage, Jason W. MD*; Hsu, Wellington K. MD*; Patel, Alpesh A. MD, FACS*

Spine: 20 May 2014 - Volume 39 - Issue 12 - p 971–977
doi: 10.1097/BRS.0000000000000297
Health Services Research

- "There has been a statistically significant decrease in the number of spine surgeons using high-dose MP for the treatment of acute spinal cord injuries between 2006 and 2013 (89% vs. 56%)
- **30% of all respondents** were still using high-dose steroids **even though they did not believe in the efficacy of the treatment**."

Current Practice of Methylprednisolone Administration for Acute Spinal Cord Injury in Germany: A National Survey

Druschel, Claudia MD*,†; Schaser, Klaus-Dieter MD†; Schwab, Jan M. MD, PhD*,‡

Spine: 15 May 2013 - Volume 38 - Issue 11 - p E669–E677
doi: 10.1097/BRS.0b013e31828e4dce
Health Services Research

- **55%** of departments that treat SCI prescribe MP
  - Among them, 73% are "frequent" users administering MP to more than 50% of their patients.
  - **10% prescribe according to NASCIS I**, 43% NASCIS II, 33% NASCIS III, and 13% 'generic protocols'.

Science is to be vetted **by researchers**, not the public

- March 30, 1990: NASCIS II results disseminated to mass media
- **Full publication** of study didn't happen until **6 weeks later**
- Mass media dissemination ⟶ public perception of efficacy&safety
- NIH pressured by public to release to hospitals steroid protocol (without research being vetted)
- Became "standard of care" despite lack of scientific vetting
  - In part b/c lawsuit were filed against those who didn't use MP

Conclusion

- Steroids for acute blunt spinal cord injury (SCI) are **NOT recommended**
- Steroids are **contraindicated** for **traumatic brain injury** (polytrauma)
- No indication for steroids in pediatric SCI
- No indication for steroids in penetrating SCI
- Research should be vetted **by scientists**, not the public

We’re praying for Syrian Brothers and Sisters

Thank you for your patience…