Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: **James I. Ausman,** MD, PhD University of California, Los Angeles, CA, USA

Review Article

Methylprednisolone in the management of spinal cord injuries: Lessons from randomized, controlled trials

Vincent Cheung, Reid Hoshide, Vishal Bansal[1], Ekkehard Kasper[2], Clark C. Chen

Division of Neurosurgery, University of California, [1]Department of Surgery, University of California, San Diego, CA, [2]Division of Neurosurgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

E-mail: Vincent Cheung - vjcheung@ucsd.edu; Reid Hoshide - rhoshide@ucsd.edu; Vishal Bansal - v3bansal@ucsd.edu; Ekkehard Kasper - ekasper@BIDMC.harvard.edu; *Clark C. Chen - clarkchen@ucsd.edu
*Corresponding author

Received: 17 June 15 Accepted: 02 July 15 Published: 24 August 15

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/2152-7806.163452
Quick Response Code:

Abstract

The efficacy of glucocorticoid for treatment of acute spinal cord injuries remains a controversial topic. Differing medical societies have issued conflicting recommendations in this regard. Here we review the available randomized, controlled trial (RCT) data on this subject and offer a synthesis of these data sets.

Key Words: Critical care, National Acute Spinal Cord Injury Study, Spine, trauma

BACKGROUND

Traumatic spinal cord injury (SCI) is defined as physical trauma to the spinal column yielding altered motor, sensory, or autonomic function.[14] These injuries occur predominantly in young adults and in severe cases can cause devastating neurologic deficits, including complete or incomplete para/tetraplegia.[22] Despite advances in care, patients suffering from severe SCI are more likely to die prematurely[21] and are more prone to suffer from medical morbidities. Patients are also less likely to actively contribute to the economy.[10,15] As such, there has been long-standing interest in developing pharmacological interventions that either preserve or restore neurological function after injury.

The pathogenesis of SCI can be divided into two stages. The first stage involves the initial physical trauma with resulting tissue damage. Following this stage, a cascade of destructive biological changes occurs, resulting in secondary injury.[6] Most therapeutic strategies for SCI aim to mitigate these "secondary" events, which include inflammation, lipid peroxidation, and excitotoxicity.[1,3-5,13,20] Because glucocorticoids suppress many of these secondary events, investigators have explored its utility as SCI therapy.[12] While there are compelling data in experimental models, randomized control trails (RCTs) have generally not demonstrated compelling efficacy.[2,12,23] This article summarizes five landmark RCTs that examined the use of glucocorticoids in the setting of acute traumatic SCI.

RANDOMIZED CONTROL TRIALS

National Acute SCI Study I (NASCIS I, 1984) was a multicenter, double-blinded RCT that randomized 330 patients with SCI into two treatment arms:

- 100 mg bolus methylprednisolone followed by 25 mg every 6 h for 10 days or
- 1000 mg bolus methylprednisolone followed by 250 mg every 6 h for 10 days.

How to cite this article: Cheung V, Hoshide R, Bansal V, Kasper E, Chen CC. Methylprednisolone in the management of spinal cord injuries: Lessons from randomized, controlled trials. Surg Neurol Int 2015;6:142.
http://surgicalneurologyint.com/Methylprednisolone-in-the-management-of-spinal-cord-injuries:-Lessons-from-randomized,-controlled-trials/

The study design did not involve a placebo group because the prevailing belief at the time was that glucocorticoid treatment was likely beneficial and could not be withheld based on ethical considerations. Exclusion criteria were: Age <13, pregnancy, risk factors for steroid morbidity (e.g., concurrent infection or gastrointestinal [GI] bleeding), isolated radiculopathy or cauda equina injury, presentation >48 h after injury, and steroid administration prior to presentation. Motor and sensory assessments were performed using a customized grading scale developed by the investigators. At 6 months, 179 patients (54%) were available for follow-up. Of these patients, 70.6% demonstrated an improvement in motor score, 6.1% were unchanged, and 23.3% showed worsened motor score. There was no difference in observed improvements between high and low dose groups. Due to the absence of a true placebo group, it remains unclear whether the observed improvement can be attributed to steroid use. There was a statistically significant increase in wound infections in the high-dose group (9.3% vs. 2.6%). There were also trends toward increased incidence of sepsis, pulmonary embolism, and death within 14 days in the high-dose group (8.6 vs. 5.2%; 4.6% vs. 2.6%; and 5.9 vs. 1.9%, respectively), though these associations did not reach statistical significance.[7]

NASCIS II, 1990 was a multicenter, double-blinded RCT that randomized 487 patients with acute traumatic SCI to three arms: (1) 30 mg/kg bolus followed by 5.4 mg/kg for 23 h; (2) naloxone 5.4 mg/kg bolus followed by 0.5 mg/kg/h for 23 h; and (3) placebo. Exclusion criteria were: Age <13, pregnancy, addiction to narcotics, high-risk for steroid morbidity (e.g., concurrent infection or GI bleeding), patients who suffered isolated radiculopathy or cauda equina injury, patient with life-threatening comorbidities or who suffered injury more than 12 h prior to presentation, and patients who received steroid administration prior to presentation. Motor and sensory assessments were performed using the standardized American SCI Assessment (ASIA) scale. At 1-year, 427 patients (95%) were available for follow-up. No differences in the motor or sensory scores were observed when comparing the three arms. However, in a *post-hoc* analysis stratifying patients by time to treatment, the patients who received steroids within 8 h (38%) showed a five-point improvement in motor score ($P = 0.03$) relative to those receiving steroid after 8 h (72%). Notably, the baseline characteristics of the two groups in this analysis were not balanced. For instance, placebo patients who received steroid within 8 h fared worse compared to placebo patients receiving steroid after 8 h. As such, the validity of the *post-hoc* analysis remained controversial to date.

Two additional RCTs specifically explored whether high-dose steroid administration within 8 h of SCI is associated with improved neurologic recovery. Both studies failed to recapitulate the findings yielded by the *post-hoc* analysis of NASCIS II. In 1994, Otani *et al*. reported a nonblinded RCT, randomizing 117 patients from 11 centers to: (1) Methylprednisolone (30 mg/kg) bolus then (5.4 mg/kg/h) for 23 h ($n = 82$) or (2) routine medical management ($n = 76$). Of note, control subjects were allowed to receive a nonmethylprednisolone corticosteroid at a dose equivalent of 100 mg/day methylprednisolone for a maximum of 7 days. Exclusion criteria were similar to those used in NASCIS II, except for the exclusion of patient age <15 or >65. In addition, 41 patients were excluded due to protocol violations. Neurological assessments were the same as those employed for NASCIS 2. At 6 months, 116 of the 117 patients were available for follow-up. There were no significant differences in the motor or sensory recovery between treatment arms.[16]

In 2000, a single center, double-blinded RCT by Pointillart *et al*. reported similar negative findings. In this study, 106 SCI patients treated within 8 h of injury were randomized to 4 treatment arms: (1) Methylprednisolone 30 mg/kg bolus then 5.4 mg/kg/h for 23 h, (2) nimodipine 0.5 mg/kg/h for 2 h then 0.03 mg/kg/h for 7 days, (3) combined methylprednisolone and nimodipine, or (4) placebo. Exclusion criteria were identical to those reported by Otani *et al*. that 100 out of 106 patients were available for follow-up at 1-year. While there were significant neurological improvements in each group at the 1-year follow-up, no significant differences in the motor or sensory function scores were noted between the two groups.[18]

NASCIS III, 1997 was a multicenter study that examined whether extending methylprednisolone infusion times (to 48 h) is associated with the therapeutic benefit. In this trial, 499 patients with acute traumatic SCI who presented within 8 h of injury were recruited and received a 30 mg/kg methylprednisolone bolus. Study subjects were then randomized to: (1) 5.4 mg/kg/h methylprednisolone for 24 h, (2) 5.4 mg/kg/h methylprednisolone for 48 h, and (3) tirilazad 2.5 mg/kg every 6 h for 48 h.

Exclusion criteria and neurologic assessment tools were similar to those used in NASCIS II. Functional disability was scored using the Functional Independence Measure to determine the quality of life. 452 of the 499 patients (92%) were available for follow-up at 1-year. There were no significant differences in any of the primary endpoints between the three arms. *Post-hoc* analysis suggested motor function improvement by five ASIA motor points in those patients who received 48-h methylprednisolone infusion beginning 3–8 h after injury. NASCIS III additionally reported that prolonged steroid use was associated with increased risk of severe pneumonia ($P = 0.02$).[8]

EXPERT OPINIONS

"There is convincing and undeniable data justifying the clinical use of glucocorticoid, particularly in those who suffered from incomplete SCI" by Ekkehard Kasper, M.D., Ph.D., Beth Israel Deaconess Medical Center, Boston, MA, USA.

The American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) released a consensus statement in 2013 that the use of glucocorticoids in acute traumatic SCI is no longer recommended. This view was balanced by position statement by the American Academy of Emergency Medicine stating that treatment with glucocorticoids remains an acceptable treatment option though not a standard. It is my opinion that there is convincing and undeniable data justifying the clinical use of glucocorticoid, particularly in those who suffered from incomplete SCI. I would reference two important studies to support this opinion. First, Pettersson and Toolanen randomized 40 patients who suffered Quebec Task Force Classification Grade II and III whiplash injury from motor vehicle collisions to high-dose methylprednisolone (30 mg/kg bolus followed by 5.4 mg/kg/h for 23 h) or no treatment. At the 6 months follow-up, the treated patients displayed fewer disabling symptoms ($P = 0.047$) and fewer sick days referable to injury ($P = 0.01$).[17] Second, in the surgical timing in acute SCI study, a prospective cohort study was designed to determine whether timing of surgery influenced functional recovery from acute traumatic cervical SCI, early decompression (<24 h), incomplete SCI, and steroid administration were associated with better neurologic outcomes.[9] In terms of the safety of high-dose methylprednisolone, Sauerland *et al*. performed a systematic review of approximately 2500 patients from 51 trials that involved the use of high-dose methylprednisolone. They found no evidence that methylprednisolone increased the risk of GI bleeding, wound complication, pulmonary complications, or death.[19]

"We should avoid the medieval tendencies to use whatever agents available to us, whether leeches or corticosteroids, to treat diseases for which we have little fundamental understanding" by Vishal Bansal, MD, University of California, San Diego.

Enthusiasm for glucocorticoid treatment following SCI has waned quickly following the NACIS II and III studies. This is not coincidental but rather heavily supported by several "postNACIS" clinical trials. Indeed, Level 1 evidence has bolstered current AANS/CNS and Advance Trauma Life Support guidelines precluding the use of steroids in the treatment of acute SCI. As detailed in the above concise summary, NACIS II had several statistical flaws. Moreover, only neurologic scores from the right half of the body were reported. The slight improvement in motor scores (five-point change) in the treatment arm has questionable biological significance. In a review of medical complications in patients enrolled in NACIS II, Gerndt *et al*., found a 4-fold increase in the incidence of acute pneumonia, ventilator days, and Intensive Care Unit (ICU) length of stay in steroid patients versus control.[11] Therefore, the hallmark study used to justify steroid use in SCI showed minimal neurologic improvements and likely worsen ICU outcomes. Given the available data, we should avoid the medieval tendencies to use whatever agents available to us, whether leeches or corticosteroids, to treat diseases for which we have little fundamental understanding.

RECOMMENDATIONS

It is not that the RCTs conclusively demonstrate that steroids do not work in SCI. It is that there is no RCT data suggesting that steroid is effective in SCI. The term "acute traumatic SCI" is useful as an intellectual construct. However, it is important to recognize that this term encapsulates a wide spectrum of disease states that differed in the mechanism and severity of injuries. This complexity is further confounded by the inherent variability in the baseline functional reserve of the patient population as well as in their physiologic response to injury. When these factors are not taken into consideration during RCT design, detection of efficacy is possible only if the potency of therapy overwhelms the influences of the various confounding factors. The above presented RCTs suggest that the efficacy of high-dose glucocorticoid therapy did not reach this threshold for the heterogeneous population of patients who present with "acute traumatic SCIs". In the over 1500 patients enrolled in the five RCTs, high-dose glucocorticoid treatment did not meaningfully improve the functional recovery of acute traumatic SCI patients when analyzed by the primary endpoint of the trial. While it may be the case that glucocorticoid may be efficacious in a subset of traumatic SCI patients, e.g. those with incomplete SCI, this thesis has not been formally subjected to the scrutiny of a properly designed RCT and warrants future investigations. Notably, all three NASCIS studies demonstrated increased risk of adverse events in the steroid-treated populations. Though high-dose steroid treatment may be safe in other patient populations,[19] caution should be exercised in the setting of acute traumatic SCI given the data from NASCIS.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Acarin L, González B, Castellano B. Neuronal, astroglial and microglial cytokine expression after an excitotoxic lesion in the immature rat brain. Eur J Neurosci 2000;12:3505-20.
2. Anderson DK, Means ED, Waters TR, Green ES. Microvascular perfusion and metabolism in injured spinal cord after methylprednisolone treatment. J Neurosurg 1982;56:106-13.
3. Bartholdi D, Schwab ME. Expression of pro-inflammatory cytokine and chemokine mRNA upon experimental spinal cord injury in mouse: An *in situ* hybridization study. Eur J Neurosci 1997;9:1422-38.
4. Bethea JR, Castro M, Keane RW, Lee TT, Dietrich WD, Yezierski RP. Traumatic spinal cord injury induces nuclear factor-kappaB activation. J Neurosci 1998;18:3251-60.
5. Bethea JR, Nagashima H, Acosta MC, Briceno C, Gomez F, Marcillo AE, *et al.* Systemically administered interleukin-10 reduces tumor necrosis factor-alpha production and significantly improves functional recovery following traumatic spinal cord injury in rats. J Neurotrauma 1999;16:851-63.
6. Borgens RB, Liu-Snyder P. Understanding secondary injury. Q Rev Biol 2012;87:89-127.
7. Bracken MB, Collins WF, Freeman DF, Shepard MJ, Wagner FW, Silten RM, *et al.* Efficacy of methylprednisolone in acute spinal cord injury. JAMA 1984;251:45-52.
8. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, *et al.* Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the third national acute spinal cord injury randomized controlled trial. National acute spinal cord injury study. JAMA 1997;277:1597-604.
9. Fehlings MG, Vaccaro A, Wilson JR, Singh A, Cadotte DW, Harrop JS, *et al.* Early versus delayed decompression for traumatic cervical spinal cord injury: Results of the surgical timing in acute spinal cord injury study (STASCIS). PLoS One 2012;7:e32037.
10. Furlan JC, Fehlings MG. Cardiovascular complications after acute spinal cord injury: Pathophysiology, diagnosis, and management. Neurosurg Focus 2008;25:E13.
11. Gerndt SJ, Rodriguez JL, Pawlik JW, Taheri PA, Wahl WL, Micheals AJ, *et al.* Consequences of high-dose steroid therapy for acute spinal cord injury. J Trauma 1997;42:279-84.
12. Hall ED. The neuroprotective pharmacology of methylprednisolone. J Neurosurg 1992;76:13-22.
13. Klusman I, Schwab ME. Effects of pro-inflammatory cytokines in experimental spinal cord injury. Brain Res 1997;762:173-84.
14. Kraus JF, Franti CE, Riggins RS, Richards D, Borhani NO. Incidence of traumatic spinal cord lesions. J Chronic Dis 1975;28:471-92.
15. Lidal IB, Huynh TK, Biering-Sørensen F. Return to work following spinal cord injury: A review. Disabil Rehabil 2007;29:1341-75.
16. Otani K, Abe H, Kadoya S, Nakagawa H, Ikata T, Tominaga S. Beneficial effect of methylprednisolone sodium succinate in the treatment of acute spinal cord injury. Sekitsui Sekizui 1994;7:633-47.
17. Pettersson K, Toolanen G. High-dose methylprednisolone prevents extensive sick leave after whiplash injury. A prospective, randomized, double-blind study. Spine (Phila Pa 1976) 1998;23:984-9.
18. Pointillart V, Petitjean ME, Wiart L, Vital JM, Lassié P, Thicoipé M, *et al.* Pharmacological therapy of spinal cord injury during the acute phase. Spinal Cord 2000;38:71-6.
19. Sauerland S, Nagelschmidt M, Mallmann P, Neugebauer EA. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: A systematic review. Drug Saf 2000;23:449-61.
20. Schnell L, Fearn S, Klassen H, Schwab ME, Perry VH. Acute inflammatory responses to mechanical lesions in the CNS: Differences between brain and spinal cord. Eur J Neurosci 1999;11:3648-58.
21. Strauss DJ, Devivo MJ, Paculdo DR, Shavelle RM. Trends in life expectancy after spinal cord injury. Arch Phys Med Rehabil 2006;87:1079-85.
22. System SCIM. Spinal Cord Injury (SCI) Facts and Figures at a Glance; 2014. Available from: https://www.nscisc.uab.edu/PublicDocuments/fact_figures_docs/Facts%202014.pdf [Last accessed on 2015 Jun 10].
23. Young W, Flamm ES. Effect of high-dose corticosteroid therapy on blood flow, evoked potentials, and extracellular calcium in experimental spinal injury. J Neurosurg 1982;57:667-73.