Cochrane in CORR

Cochrane in CORR®: Steroids for Acute Spinal Cord Injury (Review)

Nathan Evaniew MD, Marcel Dvorak MD, FRCSC

Importance of the Topic

Approximately 500,000 people experience traumatic spinal cord injuries worldwide each year, and the development of potential therapies to reduce their morbidity and socioeconomic impact remains an urgent research priority [5]. Lifetime

direct and indirect costs related to spinal cord injuries are estimated to exceed USD 3 million per person [12], and annual total related healthcare costs in the United States alone are estimated to exceed more than USD 10 billion [4].

Studies have suggested that methylprednisolone may minimize the secondary inflammatory damage that

occurs after acute spinal cord injuries and in so doing, facilitate some measure of neurologic recovery, but the effectiveness of this treatment has been vigorously debated [5, 13] and its use has been linked to harms such as sepsis, infections, gastrointestinal hemorrhage, and even death [9]. In this Cochrane review, the pooled evidence from three randomized controlled trials failed to demonstrate a benefit attributable to methylprednisolone versus placebo for neurological recovery at 6 months or 1 year, but a subgroup analysis suggested that it might be associated with better recovery in patients who received treatment within 8 hours of their injuries. Evidence from one trial each failed to demonstrate an overall difference between high-dose and low-dose methylprednisolone, and between 24 hours and 48 hours of methylprednisolone.

A Note from the Editor-In-Chief: We are pleased to publish the next installment of Cochrane in CORR®, our partnership between CORR®, The Cochrane Collaboration®, and McMaster University's Evidence-Based Orthopaedics Group. In it, researchers from McMaster University and other institutions will provide expert perspective on an abstract originally published in The Cochrane Library that we think is especially important.

(Bracken MB. Steroids for acute spinal cord injury. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD001046. DOI: [10.1002/14651858.CD001046.pub2](https://doi.org/10.1002/14651858.CD001046.pub2).)
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Reproduced with permission. The institution of one of the authors (MD) has received, during the study period, funding from Rick Hansen Institute.

The opinions expressed are those of the writers, and do not reflect the opinion or policy of CORR® or The Association of Bone and Joint Surgeons®.

Cochrane Reviews are regularly updated as new evidence emerges and in response to

feedback, and The Cochrane Library (<http://www.thecochranelibrary.com>) should be consulted for the most recent version of the review.

This Cochrane in CORR® column refers to the abstract available at: DOI: [10.1002/14651858.CD001046.pub2](https://doi.org/10.1002/14651858.CD001046.pub2).

N. Evaniew MD
Division of Orthopaedics, Department of Surgery, McMaster University, Hamilton, ON, Canada

M. Dvorak MD, FRCSC
International Collaboration on Repair Discoveries (ICORD), Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

N. Evaniew MD (✉)
Center for Evidence-Based Orthopaedics, 293 Wellington Street North, Suite 110, Hamilton, ON L8L 8E7, Canada
e-mail: nathan.evaniew@medportal.ca

Upon Closer Inspection

For the subgroup of patients who received treatment within eight hours, the evidence from three randomized controlled trials can be described as conflicting and inconsistent. Only one trial reported a neurologic benefit to

Cochrane in CORR

treatment with methylprednisolone at 6 months and 1 year [2, 3], while another failed to do so at 6 months [14] and another failed to do so at 12 months [15]. The conclusions of this review were based on a pooled estimate that combined 6-month data with 1-year data and favored methylprednisolone, but the pooled effect using data at 1-year followup alone was not different from placebo.

Missing data threaten the validity of all meta-analyses, and readers should look for sensitivity analyses that test assumptions about the nature of the missing data because even plausible assumptions can change the magnitude or direction of the pooled effects [1]. For example, missing data might result from dropouts, losses to followup, nonadherence, or data entry errors, and each of these problems could potentially be related to patient outcomes in an important way. None of the three trials performed such an analysis, raising the question of whether in fact missing data could have had an important impact on the conclusions of the individual trials or even of the meta-analysis when those trials' data were pooled. The largest trial that evaluated methylprednisolone versus placebo ($n = 333$) had missing data for at least 11% of participants at six months and at least

14% at 1 year [2, 3]. To put this in perspective, Akl et al. identified a median of 6% losses to followup among 235 randomized controlled trials from top journals; up to one-third of these trials would have lost statistical significance if plausible assumptions about the nature of the missing data had been implemented [1].

Take-Home Messages

Meta-analyses are powerful tools to support evidence-based care, but they require high methodological credibility in order to avoid misleading conclusions [6]. This Cochrane review did not assess confidence in the pooled estimates, and it did not consider whether small but statistically significant treatment effects were clinically meaningful. It also did not use multiple reviewers to perform the selection of studies, assessments of risk of bias, or the extraction of data, which raises the possibility that it was neither exhaustive nor reproducible. As such, this review does not permit strong inferences about the effectiveness of methylprednisolone in patients with acute spinal cord injuries. Until an updated review with more rigorous methodology is available, clinicians,

researchers, and other evidence users should exercise caution when interpreting the results and applying them to patient care.

Metaregression, a technique of meta-analysis that combines individual participant-level data from existing prospective observational or randomized trials, could assist in further clarifying the role of methylprednisolone for enhancing neurological recovery in these severely injured patients by acknowledging the influence of strong confounding variables [7, 17]. Additional randomized controlled trials would also be helpful, but the high costs and clinical burden inherent to prospective analyses of steroid use in spinal cord injury may limit their feasibility.

Although many clinicians still report a belief in the effectiveness of methylprednisolone or a fear of litigation if they do not administer it, utilization has decreased in many countries over the last decade [10, 16]. The 2013 guidelines of the American Association of Neurological Surgeons and Congress of Neurological Surgeons recommended against the routine administration of methylprednisolone for acute traumatic spinal cord injuries [18], and several other groups have previously contributed to similar statements [8, 11].

Cochrane in CORR

Appendix

Steroids for acute spinal cord injury (Review)

Bracken MB

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 1

<http://www.thecochranelibrary.com>

WILEY

Steroids for acute spinal cord injury (Review)
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Cochrane in CORR

[Intervention Review]

Steroids for acute spinal cord injury

Michael B Bracken¹

¹Department of Epidemiology & Public Health, Yale University Medical School, New Haven, CT, USA

Contact address: Michael B Bracken, Department of Epidemiology & Public Health, Yale University Medical School, Box 20834, 60 College Street, New Haven, CT, 06520-8034, USA. michael.bracken@yale.edu.

Editorial group: Cochrane Injuries Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 10, 2012.

Review content assessed as up-to-date: 2 August 2011.

Citation: Bracken MB. Steroids for acute spinal cord injury. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.: CD001046. DOI: 10.1002/14651858.CD001046.pub2.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Acute spinal cord injury is a devastating condition typically affecting young people, mostly males. Steroid treatment in the early hours after the injury is aimed at reducing the extent of permanent paralysis during the rest of the patient's life.

Objectives

To review randomized trials of steroids for human acute spinal cord injury.

Search methods

We searched the Cochrane Injuries Group's Specialised Register (searched 02 Aug 2011), The Cochrane Central Register of Controlled Trials 2011, issue 3 (The Cochrane Library), MEDLINE (Ovid) 1948 to July Week 3 2011, EMBASE (Ovid) 1974 to 2011 week 17, ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to Aug 2011, ISI Web of Science: Conference Proceedings Citation Index- Science (CPCI-S) 1990 to Aug 2011 and PubMed [www.ncbi.nlm.nih.gov/sites/entrez/] (searched 04 Aug 2011) for records added to PubMed in the last 90 days). Files of the National Acute Spinal Cord Injury Study (NASCIS) were reviewed (NASCIS was founded in 1977 and has tracked trials in this area since that date). We also searched the reference lists of relevant studies and previously published reviews.

Selection criteria

All randomized controlled trials of steroid treatment for acute spinal cord injury in any language.

Data collection and analysis

One review author extracted data from trial reports. Japanese and French studies were found through NASCIS and additional data (e.g. SDs) were obtained from the original study authors.

Main results

Eight trials are included in this review, seven used methylprednisolone. Methylprednisolone sodium succinate has been shown to improve neurologic outcome up to one year post-injury if administered within eight hours of injury and in a dose regimen of: bolus 30mg/kg over 15 minutes, with maintenance infusion of 5.4 mg/kg per hour infused for 23 hours. The initial North American trial results were replicated in a Japanese trial but not in the one from France. Data was obtained from the latter studies to permit appropriate meta-analysis of all three trials. This indicated significant recovery in motor function after methylprednisolone therapy, when administration commenced within eight hours of injury. A more recent trial indicates that, if methylprednisolone therapy is given for an additional 24

Steroids for acute spinal cord injury (Review)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Cochrane in CORR

hours (a total of 48 hours), additional improvement in motor neurologic function and functional status are observed. This is particularly observed if treatment cannot be started until between three to eight hours after injury. The same methylprednisolone therapy has been found effective in whiplash injuries. A modified regimen was found to improve recovery after surgery for lumbar disc disease. The risk of bias was low in the largest methylprednisolone trials. Overall, there was no evidence of significantly increased complications or mortality from the 23 or 48 hour therapy.

Authors' conclusions

High-dose methylprednisolone steroid therapy is the only pharmacologic therapy shown to have efficacy in a phase three randomized trial when administered within eight hours of injury. One trial indicates additional benefit by extending the maintenance dose from 24 to 48 hours, if start of treatment must be delayed to between three and eight hours after injury. There is an urgent need for more randomized trials of pharmacologic therapy for acute spinal cord injury.

PLAIN LANGUAGE SUMMARY

Steroids for acute spinal cord injury

Every year, about 40 million people worldwide suffer a spinal cord injury. Most of them are young men. The results are often devastating. Various drugs have been given to patients in attempts to reduce the extent of permanent paralysis. Steroids have probably been used more for this purpose than any other type of drug. The review looked for studies that examined the effectiveness of this treatment in improving movement and reducing the death rate. Nearly all the research, seven trials, has involved just one steroid, methylprednisolone. The results show that treatment with this steroid does improve movement but it must start soon after the injury has happened, within no more than eight hours. It should be continued for 24 to 48 hours. Different dose rates of the drug have been given and the so-called high-dose rate is the most effective. The treatment does not, however, give back the patient a normal amount of movement and more research is necessary with steroids, possibly combining them with other drugs.

Cochrane in CORR

References

1. Akl EA, Briel M, You JJ, Sun X, Johnston BC, Busse JW, Mulla S, Lamontagne F, Bassler D, Vera C, Alshurafa M, Katsios CM, Zhou Q, Cukierman-Yaffe T, Gangji A, Mills EJ, Walter SD, Cook DJ, Schunemann HJ, Altman DG, Guyatt GH. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): Systematic review. *BMJ*. 2012;344:e2809.
2. Bracken MB, Shepard MJ, Collins WF, Holford TR, Baskin DS, Eisenberg HM, Flamm E, Leo-Summers L, Maroon JC, Marshall LF. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second National Acute Spinal Cord Injury Study. *J Neurosurg*. 1992;76:23–31.
3. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, Eisenberg HM, Flamm E, Leo-Summers L, Maroon J. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med*. 1990;322:1405–1411.
4. DeVivo MJ. Causes and costs of spinal cord injury in the United States. *Spinal Cord*. 1997;35:809–813.
5. Evaniew N, Noonan V, Fallah N, Kwon BK, Rivers CS, Ahn H, Bailey C, Christie S, Fournery DR, Hurlbert RJ, Linassi G, Fehlings M, Dvorak MF. Methylprednisolone for the treatment of patients with acute spinal cord injuries: A propensity score-matched cohort study from a Canadian multicenter spinal cord injury registry. [Published online ahead of print July 17, 2015]. *J Neurotrauma*. DOI: [10.1089/neu.2015.3963](https://doi.org/10.1089/neu.2015.3963).
6. Evaniew N, van der Watt L, Bhandari M, Ghert M, Aleem I, Drew B, Guyatt G. Strategies to improve the credibility of meta-analyses in spine surgery: A systematic survey. *Spine J*. 2015;15:2066–2076.
7. Fu R, Selph S, McDonagh M, Peterson K, Tiwari A, Chou R, Helfand M. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: A systematic review and meta-analysis. *Ann Intern Med*. 2013;158:890–902.
8. Hugenholtz H, Cass DE, Dvorak MF, Fewer DH, Fox RJ, Izukawa DM, Lexchin J, Tuli S, Bharatwal N, Short C. High-dose methylprednisolone for acute closed spinal cord injury—only a treatment option. *Can J Neurol Sci*. 2002;29:227–235.
9. Hurlbert RJ. Methylprednisolone for the treatment of acute spinal cord injury: Point. *Neurosurgery*. 2014;61 Suppl 1:32–35.
10. Hurlbert RJ, Hamilton MG. Methylprednisolone for acute spinal cord injury: 5-year practice reversal. *Can J Neurol Sci*. 2008;35:41–45.
11. Hurlbert RJ, Moulton R. Why do you prescribe methylprednisolone for acute spinal cord injury? A Canadian perspective and a position statement. *Can J Neurol Sci*. 2002;29:236–239.
12. Krueger H, Noonan VK, Trenaman LM, Joshi P, Rivers CS. The economic burden of traumatic spinal cord injury in Canada. *Chronic Inj Can*. 2013;33:113–122.
13. Lenzer J. Why we can't trust clinical guidelines. *BMJ*. 2013;346:f3830.
14. Otani K, Abe H, Kadoya S. Beneficial effect of methylprednisolone sodium succinate in the treatment of acute spinal cord injury [in Japanese]. *Sekitsui Sekizui*. 1994;7:633–647.
15. Petitjean ME, Pointillart V, Dixmierias F, Wiart L, Sztark F, Lassie P, Thicoipe M, Dabadie P. Medical treatment of spinal cord injury in the acute stage [in French]. *Ann Fr Anesth Reanim*. 1998;17:114–122.
16. Schroeder GD, Kwon BK, Eck JC, Savage JW, Hsu WK, Patel AA. Survey of cervical spine research society members on the use of high-dose steroids for acute spinal cord injuries. *Spine Phila Pa* 1976. 2014;39:971–977.
17. Simmonds MC, Brown JV, Heirs MK, Higgins JP, Mannion RJ, Rodgers MA, Stewart LA. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: A meta-analysis of individual-participant data. *Ann Intern Med*. 2013;158:877–889.
18. Walters BC, Hadley MN, Hurlbert RJ, Aarabi B, Dhall SS, Gelb DE, Harrigan MR, Rozelle CJ, Ryken TC, Theodore N. Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update. *Neurosurgery*. 2013;60:S82–S91.