EBEM Commentators
Matthew T. Spencer, MD
Jeffrey J. Bazarian, MD, MPH

From the Department of Emergency Medicine, University of Rochester Medical Center, Rochester, NY.

0196-0644/2003/$30.00 + 0
doi:10.1067/mem.2003.84

Are Corticosteroids Effective in Traumatic Spinal Cord Injury?

[*Ann Emerg Med.* 2003;41:410-413.]

SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Bracken MB. Steroids for acute spinal cord injury (Cochrane Review). In: *The Cochrane Library.* Issue 3. Oxford, United Kingdom: Update Software; 2002.

The *Annals'* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To determine whether systemic corticosteroids are safe and effective therapy in acute traumatic spinal cord injury.

DATA SOURCES

The author used the Cochrane Injuries Group search strategy to identify trials, as well as an electronic search of MEDLINE from 1966 to 2001, and a manual search of more than 40 journals and conference abstracts. In addition, the files from the National Acute Spinal Cord Injury Study were explored.

STUDY SELECTION

Trials were selected if patients were randomly assigned to receive systemic corticosteroids in the treatment of acute spinal cord injury. Trials including whiplash injury and lumbar disc disease were also included in this review. Most trials excluded patients with only nerve root injury or cauda equina syndrome, but varied individually with regard to exclusion for age, penetrating injury, and severe comorbidity.

DATA EXTRACTION

One reviewer assessed trial quality and extracted data based on intervention and outcome blinding, number of research subjects, and adequacy of randomization. Mortality and neurologic improvement scores for motor function, pinprick, and

touch sensation were reported for most trials; however, fewer trials reported infectious complications and gastrointestinal hemorrhage. The primary outcome was improvement in neurologic function scores. To better compare these scores across trials, the author obtained additional information through personal communication with the authors of 2 trials. Scores were reported as weighted mean differences (WMD) with 95% confidence intervals (CIs). Because differences in the many arms of each trial limited the ability to compare mortality, only the 180-day mortality of 2 trials was examined.

MAIN RESULTS

Eight trials were chosen for review representing a total of 1,698 patients. The 8 trials were divided into 5 groups based on steroid dose and duration of treatment. One group did not contain patients with acute traumatic spinal cord injury. Of the remaining 4 groups, only 1 included more than 1 trial for meta-analysis. Although all 5 groups were analyzed, the conclusions were based primarily on this multi-trial group, which is the focus of this review.

In the group consisting of 4 trials and 797 patients, patients were randomized to receive either high-dose methylprednisolone or placebo for 24 hours after the injury. One trial was only used to discuss complications. The other 3 evaluated neurologic outcomes at varying follow-up intervals. This limited the reviewer from combining results for all 3 outcomes (motor function, pinprick, touch) across all 3 follow-up intervals (6 weeks, 6 months, and 1 year).

In patients treated with high-dose methylprednisolone, there was no significant improvement in overall motor function scores at 6 weeks (WMD=1.23; 95% CI 1.08 to 3.54), 6 months (WMD=0.85; 95% CI 1.79 to 3.49), and 1 year (WMD=–1.17; 95% CI 4.80 to 2.47). Patients who received high-dose methylprednisolone who were treated within 8 hours of injury were analyzed as a subgroup. This analysis revealed a significant improvement in motor function scores at 6 weeks (WMD=3.47; 95% CI 0.02 to 6.92) and 6 months (WMD=4.44; 95% CI 0.96 to 7.93), but not 1 year (WMD=4.17; 95% CI –0.28 to 8.61). When patients from trials with 1-year end point data were combined with patients from trials with 6-month end point data (final outcome category), there was a statistically significant improvement in motor function scores (WMD=4.06; 95% CI 0.58 to 7.55).

Pinprick and touch sensation scores among patients treated with high-dose methylprednisolone were significantly improved at 6 months (pinprick WMD=4.82, 95% CI 0.91 to 8.73; touch WMD=2.88, 95% CI 0.10 to 5.66) but not at 6 weeks or 1 year. Post hoc analysis revealed the same pattern of significance for those treated within 8 hours.

The weighted risk of death at 180 days was slightly lower in the placebo group compared with the high-dose methylprednisolone group, but did not reach statistical significance (relative risk [RR]=0.54; 95% CI 0.24 to 1.25). In the 1 trial reporting wound infection rate (333 patients), no differences were observed between the groups (RR=2.11; 95% CI 0.81 to 5.49). In the 2 trials reporting gastrointestinal hemorrhage (397 patients), no differences were observed between the groups (RR=2.18; 95% CI 0.80 to 5.93).

CONCLUSIONS

High-dose methylprednisolone therapy improves neurologic outcome in patients with acute spinal cord injury when given within 8 hours of injury and should be given to all such patients. The duration of infusion depends on time of patient presentation. Although high-dose methylprednisolone does improve neurologic recovery, it does not improve mortality and is unlikely to lead to complete return of normal neurologic function. Continued research into different methylprednisolone protocols and combinations of agents is still necessary.

Cochrane Systematic Review Author Contact

Michael B. Bracken, MD
Division of Chronic Disease Epidemiology
Department of Epidemiology and Public Health
Yale School of Medicine
New Haven, CT
E-mail brackenmb@maspo3.mas.yale.edu

COMMENTARY: CLINICAL IMPLICATION

The incidence of acute spinal cord injury in the United States is estimated at 40 per million people, with a mortality of approximately 11%.[1] It affects primarily younger patients and results in severe disability requiring prolonged hospitalization, rehabilitation, and extended care, with the overall cost for both the patient and community being enormous. Treatments that could reduce neurologic injury and improve neurologic recovery are desperately needed. The results of this systematic review suggest that high-dose methylprednisolone may be effective in spinal cord injury, provided it is administered within 8 hours of injury.

Although encouraging, this Cochrane review raises a few methodologic issues that need to be examined before we can accept their recommendations. First, the clinical

relevance of the outcome measures in the 4 core trials in this review is a concern. The primary outcome is neurologic improvement at 6 weeks, 6 months, and 1 year. Neurologic improvement is measured by calculating the difference between 2 neurologic examination scores taken on admission and at each follow-up time interval. Motor function was evaluated over 14 muscle segments on a 6-point scale between 0 and 5, yielding a total score between 0 and 70. Sensory function was evaluated over 29 dermatomal segments on a 3-point scale between 1 and 3, with a total score between 29 and 87. Although rigorous, such a large range of values introduces a possible source of error because there is not any evaluation of interrater reliability. Looking only at motor function, if 2 examiners differed in scoring by 1 point over each muscle segment, it could lead to a 14-point fluctuation in the final motor score. More importantly, the clinical relevance of small changes in scores is unclear. Overall, high-dose methylprednisolone was associated with a 4-point improvement in motor function score. Although statistically significant, 4 points distributed over 14 muscle segments might not translate into a clinically significant improvement.

Another possible confounder of corticosteroid effect is that the conclusions are based primarily on a post hoc analysis of a small subgroup of patients from 1 trial treated within 8 hours of injury. The arms of each trial in question are reduced from approximately 160 patients per arm overall, to approximately 65 patients per arm in the subgroup alone. In addition to a reduction in sample size, the advantages and strengths of randomization are lost when performing such analyses, yet another reason to be cautious when evaluating post hoc subgroup results. This type of analysis inherently carries a higher risk of finding a difference where one actually does not exist and should be used primarily to stimulate future research questions and not to change clinical practice.

Finally, systemic corticosteroids are not benign treatments. In this review, although not statistically significant, gastrointestinal hemorrhage and wound infections were observed more frequently in patients treated with corticosteroids for 24 hours, and severe sepsis (RR=4.00; 95% CI 0.45 to 35.38) and severe pneumonia (RR=2.25; 95% CI 0.71 to 7.15) were seen more frequently in those treated for 48 hours. The range of values within the 95% CIs suggest that these complications may outweigh the benefits of the treatment effect (4-point difference in motor scores).

TAKE HOME MESSAGE

Acute spinal cord injury is a devastating cause of disability and an enormous burden to the health care system. Effective therapy is needed in the management of this disease. This Cochrane review provides only weak support for the use of high-dose methylprednisolone therapy in acute spinal cord injury, while indicating there may be an increased risk of severe adverse outcomes. The issue of high-dose methylprednisolone therapy is much more controversial than the review suggests, with some considering it no more than experimental therapy,[2] yet despite the controversy, high-dose methylprednisolone is used in many centers to treat patients with acute spinal cord injury. Until more research is produced to either support or refute this practice, emergency physicians involved with trauma care will need to debate the pros and cons for their site and reach a local consensus with others involved in the care of these patients.

EBEM Commentators' Contact

Matthew T. Spencer, MD
Jeffrey J. Bazarian, MD, MPH
Department of Emergency Medicine
University of Rochester School of Medicine and Dentistry
Rochester, NY
E-mail Matthew_spencer@urmc.rochester.edu
E-mail Jeff_bazarian@urmc.rochester.edu

EVIDENCE-BASED MEDICINE TEACHING POINTS

Subgroup analysis is a common and important aspect of medical research, helping to identify categories of patients that will benefit the most from specific therapeutic intervention; however, if performed or used incorrectly, it can lead to erroneous conclusions. All subgroup types suffer from 2 common sources of error depending on how they are analyzed. The first is low power, or a lower chance of finding a difference where one actually exists. This is usually the result of small sample sizes in each of the subgroup cells. The second is an increased risk of a false positive result. This type of error increases as the number of subgroups being analyzed increases.

The most credible type of subgroup analysis are those that are defined *a priori,* are based on previous research, are biologically feasible, exhibit large effect sizes, and are observed in within-study as well as between-study analyses.[3] The least credible subgroup examination is a post hoc analysis. Because the data have already been collected and analyzed, any number of arbitrary subgroups can be created to support the author's hypothesis, and significant results should be suspect. Post hoc subgroups carry the highest rate of false-positive results, and when

the overall study results are not significant, they should be analyzed using more rigorous α levels (*P* values) than the primary outcome itself. When significant results are found, it is best to use them only as a source of hypotheses to be tested by future research.[4]

REFERENCES

1. Bracken MB, Freeman DH, Hellenbrand K. Incidence of acute traumatic hospitalized spinal cord injury in the United States, 1970-1977. *Am J Epidemiol.* 1981;113:615-622.

2. Hurlbert RJ. The role of steroids in acute spinal cord injury: an evidenced-based analysis. *Spine.* 2001;26(24S):S39-S46.

3. Oxman AD, Guyatt GH. Guidelines for reading literature reviews. *Can Med Assoc J.* 1988;138:697-703.

4. Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials.* 3rd ed. New York, NY: Springer-Verlag; 1998:304-406.