

Methylprednisolone for acute spinal cord injury: not a standard of care

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It is time to clear the confusion about the utility of steroids in cases of acute spinal cord injury. A committee of Canadian neurosurgical and orthopedic spine specialists, emergency physicians and physiatrists (listed at the end of the article) has reviewed the evidence and concluded that high-dose methylprednisolone infusion is not an evidence-based standard of care for patients with such an injury.¹

The consequences of a spinal cord injury are often devastating, and any possibility of mitigating neurologic loss is attractive. To this end, management of acute spinal cord injuries has included the use of steroids for the past 30 years, based in large part on physiological hypotheses with limited clinical support.^{2,3} Mechanical injury to the spinal cord initiates a cascade of secondary events that include ischemia, inflammation and calcium-mediated cell injury. Animal experiments have shown that methylprednisolone exhibits potential neuroprotective effects through its inhibition of lipid peroxidation and calcium influx and through its anti-inflammatory effects.^{4,5} Three well-designed, large, randomized clinical trials (the National Acute Spinal Cord Injury Studies [NASCIS I, II and III]) examined the effect of steroid administration in patients with acute spinal cord injury.⁶⁻¹¹

NASCIS I examined the change in motor function in specific muscles and changes in light touch and pinprick sensation from baseline.^{6,7} The study detected no benefit from methylprednisolone, but the dose was considered to be below the therapeutic threshold determined from animal experiments. Therefore, NASCIS II used a much higher dose, and patients were randomly assigned to receive a 24-hour infusion of methylprednisolone, naloxone or placebo within 12 hours after acute spinal cord injury.^{8,9} Again, there was no benefit overall in the methylprednisolone group; however, post hoc analyses detected a small gain in the total motor and sensory score in a subgroup of patients who had received the drug within 8 hours after their injury. As a result, this 24-hour, high-dose methylprednisolone infusion, if started within 8 hours after injury, quickly became an implied standard of care despite considerable criticism of the validity of such a post hoc analysis.

Subsequent clinical trials have provided conflicting evidence about steroid treatment in acute spinal cord injury. A Japanese study attempted to replicate the results seen in the 8-hour subgroup from NASCIS II and reported improved function at 6 months in a larger number of muscles and

sensory dermatomes among subjects who received high-dose methylprednisolone infusion than among those who received only low doses of the drug or no drug.¹² However, the study lacked detail about randomization and outcome measures, and it included only 74% of the enrolled subjects in the outcome analysis. Conversely, an underpowered prospective randomized trial that used a methylprednisolone regimen similar to that used in NASCIS II found no improvement in motor and sensory scores at 1 year.^{13,14} NASCIS III compared a 48-hour infusion of methylprednisolone with a 24-hour infusion started within 8 hours after injury and found no benefit from extending the infusion beyond 24 hours. Again, only post hoc analysis showed a benefit from extending the infusion to 48 hours when treatment was started between 3 and 8 hours after injury. No other study has verified the primary outcome of 48 hours versus 24 hours or the post hoc conclusion of benefit from starting treatment between 3 and 8 hours after injury.

A meta-analysis of all of the trials concluded, on the basis of the controversial subgroup post hoc analyses in NASCIS II and III and the data from the Japanese study, that a 24-hour high-dose methylprednisolone infusion within 8 hours after injury is efficacious.¹⁵ Despite this meta-analysis, the efficacy of such a regimen remains uncertain and will require further study. The controversy about the post hoc analyses of NASCIS data continues,¹⁶⁻²³ and unfortunately the studies that could have clarified the efficacy of such a regimen have lacked the rigour to do so.

Steroid therapy is not without risk. Most patients with acute spinal cord injury are treated in intensive care units, have polytrauma, have impaired lung capacity and are vulnerable to sepsis. In all 3 NASCIS studies and other, smaller studies, the incidence of sepsis and pneumonia was higher in the high-dose methylprednisolone groups than in the placebo or other treatment groups;^{6-11,24-26} the differences were not significant except in NASCIS III. Hyperglycemia and gastrointestinal complications were also reported following high-dose methylprednisolone treatment.^{13,24} Therefore, it has been proposed that, without compelling evidence for its efficacy, methylprednisolone should be used with caution and may even be harmful, particularly if infusion goes beyond 24 hours.¹⁷

The cost of a 24-hour methylprednisolone infusion is not prohibitive, and a gain of antigravity strength in one or more muscles below a spinal segment can provide an impor-

tant functional gain, especially for patients with cervical spinal cord injuries. Therefore, even the small improvement observed in the NASCIS subgroups could be viewed as a benefit in cases of complete or incomplete cervical cord injury. Despite the risk of complications and as long as the outcomes in the NASCIS subgroups remain a possibility, physicians may still opt to administer a high-dose methylprednisolone infusion within 8 hours after injury. However, they should no longer feel compelled to do so. Physicians who conduct the initial triage and resuscitation of patients with acute spinal cord injury should consult their specialist colleagues who will be continuing the care of these patients regarding their preference for methylprednisolone infusion.

The Canadian Neurosurgical Society, the Canadian Spine Society and the Canadian Association of Emergency Physicians have adopted the committee's recommendation that a high-dose, 24-hour infusion of methylprednisolone started within 8 hours after an acute closed spinal cord injury is not a standard treatment nor a guideline for treatment but, rather, a treatment *option*, for which there is very weak level II and III evidence.²⁷

This article has been peer reviewed.

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Competing interests: None declared.

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