

Steroids in acute spinal cord injury

Canadian Association of Emergency Physicians

Position Statement: Methylprednisolone for acute spinal cord injury is not a standard of care; it is only a treatment option.

Summary

Confusion persists about the utility of high-dose methylprednisolone infusion for acute spinal cord injury. This treatment was widely adopted following the report of the Second National Acute Spinal Cord Injury Study (NASCIS II) in 1990 and became an implied standard of care.¹ Despite the fact that subsequent clinical studies and critical reviews have challenged the validity of the recommendations that followed the NASCIS studies, failure to administer steroids in acute spinal cord injury has been cited in litigation against physicians.²⁻¹⁰ A survey of attendees at the First Annual Canadian Spine Society Meeting in Mont Tremblant, Que., on Mar. 23, 2001, revealed that 75% of respondents were using methylprednisolone either “because everyone else does” or out of fear of litigation for failing to do so.

A systematic review of this treatment (see Table 1¹¹⁻¹⁸) was conducted at the request of the Canadian Spine Society and the Canadian Neurosurgical Society in order to provide current, evidence-based recommendations about its utility for practising physicians.¹⁹ A committee of neurosurgeons, orthopedic surgeons, emergency physicians and physiatrists, some with a Masters in Clinical Epidemiology reviewed the evidence and concluded the following.

1. There is insufficient evidence to support the use of high-dose methylprednisolone within 8 h following an acute closed spinal cord injury as a treatment *standard* or as a *guideline* for treatment.
2. Methylprednisolone prescribed as a bolus intravenous infusion of 30 mg/kg of body weight over 15 min within 8 h of acute closed spinal cord injury, followed 45 min later by an infusion of 5.4 mg/kg of body weight per hour for 23 h is a treatment *option* for which there is weak clinical evidence (Level II, III).
3. There is insufficient evidence to support extending methylprednisolone infusion beyond 23 h if chosen as a treatment option.¹⁹ These recommendations were then presented to the annual meetings of the two sponsoring societies and adopted.

Review of evidence

Because of the controversy surrounding the use of methylprednisolone in acute spine cord injury, a systematic review of this treatment (see Table 1) was conducted at the request of the Canadian Spine Society and the Canadian Neurosurgical Society in order to provide current, evidence-based recommendations about its utility for practising physicians. A committee of neurosurgeons, orthopedic surgeons, emergency physicians and physiatrists (Appendix 1) critically reviewed the available literature and assigned levels of evidence based upon established criteria.

The committee identified serious methodological deficiencies in the NASCIS II and NASCIS III studies as well as Otani and colleagues' study.¹² The committee also concluded that the apparent a priori intent of the original NASCIS protocol to conduct the post hoc analyses that led to the recommendations for methylprednisolone within 8 h of acute spinal cord injury could not be substantiated.¹⁹ Otani and colleagues' study, which reported improved neurological outcome as a consequence of high-dose methylprednisolone administered within 8 h of acute spinal cord injury, is the only clinical study that attempted to replicate the under-8-hour subgroup of patients in the NASCIS II study. Unfortunately, Ortani and colleagues' subjects were not properly randomized, and the investigators were not blinded to the treatments.¹² Furthermore, the recommendations from the subsequent Cochrane review of this treatment (which was written by the principal author of the NASCIS studies) were based on the questionable post hoc analyses described above and on Otani and colleagues' study, which was not properly randomized and blinded.¹¹

Patients with acute spinal cord injuries are a desperate group for whom any neurological recovery can have a major impact on their subsequent functional independence. A

return of antigravity strength to even a single muscle at or immediately below a zone of injury is particularly significant to a tetraplegic patient, while a return of a flicker of movement to several muscles below a zone of injury is of little functional value unless antigravity strength can be attained.²⁰ There may be some utility for methylprednisolone in tetraplegics and in incomplete conus injuries, but only if the results from the post hoc analyses of the NASCIS II study and Otani and colleagues' study can be substantiated in future randomized, blinded trials.

A treatment such as high-dose methylprednisolone infusion should only be considered if its potential benefit outweighs the risk of associated complications. In well de-

signed studies, high-dose methylprednisolone therapy has not caused a statistically significant increase in major complications. However, the trend to a higher incidence of sepsis and hyperglycemia cannot be ignored in the absence of Level I evidence of benefit for this treatment.^{21–24}

Physicians should not feel intimidated into prescribing high-dose methylprednisolone for acute spinal cord injuries. The utility of high-dose methylprednisolone infusion within 8 h following acute spinal cord injury has not been adequately tested.

References

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Table 1. Summary of Level I evidence of methylprednisolone effect at neurologic examination

Study	No. of subjects		Study design	Neurologic findings	Result
	MPSS*	Control			
Bracken ¹¹	159	135	Cochrane meta-analysis of NASCIS II, ¹ Otani et al ¹² and Petitjean ¹³	WMD 4.07 (95% CI, 0.58–7.55) final motor function score improvement at 6 mo and 1 yr	Positive
Bracken et al (NASCIS I) ^{14,15}	152†	154‡	Prospective, randomized, double-blind	No difference in neurologic outcome at 6 wk and 1 yr post-injury	Negative§
Bracken et al (NASCIS II) ^{1,16}	157	168	Prospective, randomized, double-blind placebo-controlled	No significant effect from MPSS within 12 h of injury on total neurologic scores at 6 wk, 6 mo post-injury	Negative§
	(62)	(67)	Subgroup analysis of subjects who received MPSS within 8 h of injury	Significant improvement: motor scores of 16.0 vs. 11.2 ($p = 0.03$), pinprick of 11.4 vs. 6.6 ($p = 0.02$) and touch of 8.9 vs. 4.3 ($p = 0.03$) at 6 mo in intent-to-treat analysis	(Positive)¶
	[62]	[65]	Subgroup analysis of subjects who received MPSS within 8 hr of injury	Significant improvement: motor scores of 176.2 vs. 12.0 ($p = 0.03$), pinprick of 10.8 vs. 8.4 ($p = 0.25$) and touch of 9.4 vs. 6.0 ($p = 0.12$) at 1 yr in intent-to-treat analysis	[Positive]¶
Bracken et al (NASCIS III) ^{17,18}	145**	145*	Prospective, randomized, double-blind	Non-significant motor score gain of 18.0 vs. 15.2 for 48-hr MPPS** vs. 24-hr MPPS* group at 1 yr for compliers; small non-significant improvement in FIM scores for self-care and sphincter control for 48-hr** MPPS group at 1 yr	Negative§
	(80)**	(71)*	Subgroup analysis of subjects who received MPSS 3–8 h post-injury	Significant motor score gain of motor scores of 19.4 vs. 13.3 for 48-hr** MPPS group ($p = 0.03$) in compliers	(Positive)¶
Petitjean et al ¹³	27	25	Prospective, randomized, blinded assessments	No effect from MPSS given within 8 h of injury in ASIA motor, pinprick and touch scores at 1 yr post-injury	Negative§

MPPS = methylprednisolone sodium succinate; WMD = weighted mean difference (in motor score); CI = confidence interval; FIM = functional independence measure; ASIA = American Spinal Injury Association score

*Methylprednisolone 30 mg/kg, then 5.4 mg/kg hourly × 24 h

†Methylprednisolone 1000-mg bolus, then 1000 mg/d for 10 d

‡Methylprednisolone 100-mg bolus, then 100 mg/d for 10 d

§Not statistically significant

¶In the absence of concrete evidence from the initial protocol that this was an a priori intent to treat and analyze, this is considered a post hoc analysis to which no level of evidence or significance can be assigned.^{2,5}

**Methylprednisolone 30-mg/kg bolus, then 48-h infusion of 5.4 mg/kg hourly

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Appendix 1. Committee membership

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Consultation on the relevance of outcome measures was provided to the committee by Drs. C. Short, physiatrist, Halifax, NS, and N. Bharatwal, physiatrist, Toronto, Ont.