

A Clinical Practice Guideline for the Management of Patients With Acute Spinal Cord Injury: Recommendations on the Use of Methylprednisolone Sodium Succinate

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Abstract

Introduction: The objective of this guideline is to outline the appropriate use of methylprednisolone sodium succinate (MPSS) in patients with acute spinal cord injury (SCI).

Methods: A systematic review of the literature was conducted to address key questions related to the use of MPSS in acute SCI. A multidisciplinary Guideline Development Group used this information, in combination with their clinical expertise, to develop recommendations for the use of MPSS. Based on GRADE (Grading of Recommendation, Assessment, Development and Evaluation), a strong recommendation is worded as “we recommend,” whereas a weaker recommendation is indicated by “we suggest.”

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Results: The main conclusions from the systematic review included the following: (1) there were no differences in motor score change at any time point in patients treated with MPSS compared to those not receiving steroids; (2) when MPSS was administered within 8 hours of injury, pooled results at 6- and 12-months indicated modest improvements in mean motor scores in the MPSS group compared with the control group; and (3) there was no statistical difference between treatment groups in the risk of complications. Our recommendations were: (1) “We suggest not offering a 24-hour infusion of high-dose MPSS to adult patients who present after 8 hours with acute SCI”; (2) “We suggest a 24-hour infusion of high-dose MPSS be offered to adult patients within 8 hours of acute SCI as a treatment option”; and (3) “We suggest not offering a 48-hour infusion of high-dose MPSS to adult patients with acute SCI.”

Conclusions: These guidelines should be implemented into clinical practice to improve outcomes and reduce morbidity in SCI patients.

Keywords

spinal cord injury, MPSS, methylprednisolone sodium succinate, guideline, acute spinal cord injury

Summary of Recommendations

We suggest not offering a 24-hour infusion of high-dose MPSS to adult patients who present after 8 hours with acute spinal cord injury.

Quality of Evidence: Moderate

Strength of Recommendation: Weak

We suggest a 24-hour infusion of high-dose MPSS be offered to adult patients within 8 hours of acute spinal cord injury as a treatment option.

Quality of Evidence: Moderate

Strength of Recommendation: Weak

We suggest not offering a 48-hour infusion of high-dose MPSS to adult patients with acute spinal cord injury.

Quality of Evidence: No included studies

Strength of Recommendation: Weak

Introduction

Within the context of acute spinal cord injury (SCI), preclinical animal studies have demonstrated mixed results with regard to the neuroprotective actions of methylprednisolone sodium succinate (MPSS).¹⁻⁴ Several randomized controlled trials, including the National Acute Spinal Cord Injury Studies (NASCIS), have investigated the efficacy and safety of MPSS in patients with acute SCI and comprise the largest therapeutic studies completed in the history of SCI research.⁵⁻⁸ Although the interpretation of and reaction to the results of these studies have varied over time, their publication led to the widespread adoption of this therapy by clinicians throughout the world. As evidence of this, in a 2006 survey study polling the membership of the North American Spine Society, 86% of respondents indicated that they would choose to administer MPSS to SCI patients as per the recommendations of the NASCIS II and III studies; however, concerns surrounding medicolegal reprisal for not administering MPSS was listed as the major factor motivating decision making in a large fraction of these respondents.⁹

In spite of the extensive use of MPSS for SCI over the past several decades, the appropriateness of this treatment remains a contentious topic.^{10,11} Opponents of the routine use of MPSS for acute SCI have highlighted concerns regarding the conduct of the NASCIS trials and the reported results. These include the reliance on subgroup analysis (particularly based on timing of MPSS initiation), the small reported effect size for neurologic improvement, and the potential for harmful and serious adverse events.¹² In order to resolve the existing controversy, a number of attempts have been made to review the existing evidence, with an aim to provide clinicians with specific evidence-based recommendations related to this treatment.^{13,14}

Two clinical practice guidelines were developed by the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS).^{13,15} Despite a similar evidence base, there were significant differences in the recommendations proposed in 2002 versus those developed in 2013. Specifically, in 2002, the expert panel recommended the administration of MPSS for either 24 or 48 hours in patients with SCI, with the caveat that this treatment should be undertaken with the knowledge that the evidence suggesting harmful side effects is more consistent than any suggestion of clinical benefit.¹⁵ In contrast, the 2013 guidelines proposed a level I recommendation against the use of MPSS based on the following reasoning: (1) MPSS is not approved by the Food and Drug Administration for this application; (2) there is no Class I or Class II evidence supporting a clinical benefit of MPSS; and (3) there is Class I, II, and III evidence indicating that high-dose steroids are associated with harmful side effects including death.¹³ These conflicting recommendations, as well as ongoing debate within the clinical community, has left the attending physician in a precarious position when faced with the decision to administer this treatment in the acute care setting.

This guideline aimed to reexamine existing evidence to clarify the controversy surrounding the use of MPSS in patients with acute SCI. Furthermore, in order to bridge the gap between the 2002 and 2013 recommendations, this guideline distinguished between (1) a 24- versus a 48-hour infusion of

MPSS and (2) the administration of MPSS within versus after 8 hours of injury. The Guideline Development Group (GDG) agreed that it was necessary to separate our recommendations based on these groups given reported differences in the literature.

The ultimate goal of this guideline is to improve outcomes and reduce morbidity in patients with SCI by promoting standardization of care and encouraging clinicians to make more evidence-informed decisions. As is typical, this guideline is not intended to supersede professional judgement or clinical decision making that considers individual patient circumstances, interests, and needs. An introductory article in this focus issue provides further background on SCI and summarizes the rationale, scope, and specific aspects of care covered by this guideline. This article is titled “A Clinical Practice Guideline for the Management of Acute Spinal Cord Injury: Introduction, Rationale, and Scope.” These guidelines are intended for use by first responders, emergency room physicians, critical care specialists, neurologists, and spine surgeons. The public should also be aware of the potential risks and benefits of MPSS in order to facilitate shared decision making.

Methods

This guideline was developed under the auspices of AOSpine North America, AOSpine International, and the AANS/CNS. A multidisciplinary GDG was formed and consisted of clinicians from a broad range of specialties as well as patient representation. The GDG was solely responsible for guideline development and was editorially independent from all funding sources. Members were required to disclose financial and intellectual conflicts of interest (see Appendix, Chapter 2, available in the online version of the article). A guideline development protocol, based on the Conference on Guideline Standardization checklist,^{16,17} was created to outline the rationale and scope of the guideline and to direct its development. Systematic reviews were conducted based on accepted methodological standards to summarize the evidence informing our recommendations. Differences between this systematic review and those previously published include the following: (1) our review was conducted by external methodologists with no intellectual conflicts of interest and (2) studies were only included in this review if they were randomized controlled trials or observational studies that controlled for baseline motor status and/or completeness of injury. As a result, our meta-analysis summarizes the results from the highest quality studies published to date. For the sake of thoroughness, this review also evaluated previous systematic reviews using the AMSTAR score in order to better gauge how other groups, including the AANS/CNS, assessed the evidence on this topic.

Methods outlined by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group were used to assess the overall quality (strength) of evidence for critical outcomes.^{18,19} The GRADE Guideline Development Tool was used to document the process, rank the importance of outcomes, weigh the benefits and harms of

various options, and determine the strength of recommendations.²⁰⁻²³ Methodologists with no financial or intellectual conflicts of interest worked closely with clinical authors to conduct the systematic reviews and provided methodological expertise on the guideline development process. Guideline development methods are provided in another article included in this focus issue: “Guidelines for the Management of Degenerative Cervical Myelopathy and Acute Spinal Cord Injury: Development Process and Methodology.”

Clinical Recommendations

Part 1. The Use of 24-Hour High-Dose Methylprednisolone Sodium Succinate After 8 Hours of Spinal Cord Injury

Population Description: Patients with acute SCI

Key Question: Should a 24-hour infusion of high-dose MPSS be administered to adult patients with acute SCI after 8 hours after injury?

Recommendation 1: We suggest not offering a 24-hour infusion of high-dose MPSS to adult patients who present after 8 hours with acute SCI.

Quality of Evidence: Moderate

Strength of Recommendation: Weak

Evidence Summary

A systematic review of the literature and meta-analysis were conducted to address the following key questions: In adult patients with acute complete or incomplete traumatic SCI, (1) What is the efficacy and effectiveness of MPSS compared with no pharmacological treatment? (2) What is the safety profile of MPSS compared with no pharmacological treatment? (3) What is the evidence that MPSS has differential efficacy or safety in subpopulations? With respect to study design, all randomized controlled trials were included as well as observational studies that controlled for baseline severity of injury. This systematic review is published elsewhere in this focus issue.

Three randomized controlled trials (4 publications)^{5,6,24,25} and one prospective cohort study²⁶ evaluated the efficacy of MPSS compared with no pharmacological treatment. Based on the results from the trials, there was no effect of MPSS on motor function at 6 weeks (mean difference = 1.23, 95% confidence interval [CI] = -1.08 to 3.54, $P = .30$), 6 months (mean difference = 1.19, 95% CI = -2.34 to 4.72, $P = .51$), or 12 months (mean difference = -1.17, 95% CI = -4.80 to 2.47, $P = .53$). Furthermore, the observational study by Evanniew et al reported no difference between patients who did and did not receive MPSS in terms of total motor recovery at 3 months (mean difference = -0.40, 95% CI = -8.27 to 7.47).²⁶ Pinprick sensation was significantly improved at 6 months in one randomized controlled trial (mean difference = 3.37, 95% CI = 0.75 to 5.99, $P = .01$)⁶ but not in 2 other trials at 12 months (mean difference = 0.18, 95% CI = -2.66 to 3.02, $P = .90$).^{6,25} Similar results were observed for light touch. In summary, there is moderate evidence that MPSS

administered according to the dose and duration of the NASCIS protocol confers no benefit compared with no treatment or placebo in motor recovery, pinprick, or light touch when initiated at indiscriminate time periods following SCI.

In terms of safety, there was no statistically significant difference between groups in the pooled risk of death (risk difference = -1.51 , 95% CI = -4.13 to 1.12 , $P = .26$), wound infection (risk difference = 0.98 , 95% CI = -1.70 to 3.66 , $P = .47$), gastrointestinal hemorrhage (risk difference = 4.51 , 95% CI = -1.92 to 10.94 , $P = .17$), sepsis (risk difference = 0.74 , 95% CI = -2.88 to 4.35 , $P = .69$), pulmonary embolism (risk difference = 2.94 , 95% CI = -0.15 to 6.03), urinary tract infection (risk difference = 1.73 , 95% CI = -5.04 to 8.49 , $P = .62$) or pneumonia (risk difference = 4.69 , 95% CI = -3.19 to 12.57 , $P = .24$; moderate level evidence). One prospective nonrandomized study, however, evaluated the risk of one or more complications and found a lower risk in those receiving MPSS, after controlling for severity of injury and other baseline differences (risk difference = -12.59% , 95% CI = -22.10 to -3.09 , $P = .009$; very low level evidence).²⁷

Rational for Recommendation

The outcomes ranked as critical for decision making were change in motor and sensory scores and risk of major complications. The strength of evidence for findings related to these outcomes was moderate; across studies, there was no serious risk of bias, no serious inconsistency or indirectness, and undetected publication bias. The majority of the GDG agreed that the overall certainty of evidence was moderate (low = 2; moderate = 18).

The GDG unanimously agreed that there was probably no important uncertainty or variability about how much stakeholders value the main outcomes. Clinicians, patients, and payers would similarly value improved motor and sensory scores and reduced risk of major complications.

The anticipated desirable effects were improved motor scores, pinprick sensation, and light touch. There were no differences in motor scores at 6 weeks ($P = .30$), 3 months ($P = .92$), 6 months ($P = .51$), or 12 months ($P = .53$) in patients treated with MPSS compared with those not receiving steroids. Furthermore, there were no differences in pinprick or light touch at 6 weeks or 12 months between treatment groups. At 6 months, however, patients treated with MPSS had significantly better pinprick sensation and light touch than patients not treated with steroids. The GDG agreed that the desirable anticipated effects are (probably) not large (no = 11; probably no = 10; probably yes = 2) since the existing evidence (moderate strength) does not support a treatment of MPSS after 8 hours of injury.

The anticipated undesirable effects of MPSS include complications such as death, wound infection, gastrointestinal hemorrhage, sepsis, urinary tract infection, pneumonia, and decubiti. Based on the evidence, there is no statistically significant difference between treatment groups in the pooled risk of any of these complications. There was a weak trend for

increased risk of pulmonary embolism in the MPSS group; however, the clinical impact of this complication on long-term outcomes is largely unknown. The GDG unanimously agreed that the undesirable anticipated effects are probably small. Furthermore, the anticipated desirable effects are probably not large relative to the undesirable effects given that MPSS administered after 8 hours of injury does not result in statistically or clinically significant improvements (no = 4; probably no = 17).

In the absence of literature, the GDG used their clinical expertise to discuss the resources required to administer MPSS to patients with SCI. The GDG unanimously agreed that the resources required are probably small since MPSS is an off-patent drug with low associated costs. Unfortunately, there were no studies evaluating the cost-effectiveness of MPSS in patients with SCI; as a result, the cost-benefit ratio is uncertain.

The GDG unanimously believed that a recommendation for MPSS in patients with SCI would reduce health inequities since this drug is available at most health centers and is inexpensive. The option of administering MPSS after 8 hours of injury is probably not acceptable to key stakeholders as it does not result in long-term neurologic recovery. Finally, the GDG unanimously agreed that this option is probably feasible to implement. There are limited foreseeable barriers from a cost and process standpoint, although this may be variable across different institutions.

Considering all these factors, the GDG voted that the undesirable consequences probably outweigh the desirable consequences in most settings ($n = 16/18$); this led to the formation of a weak recommendation against the use of a 24-hour infusion of high-dose MPSS to adult patients who present after 8 hours of injury ($n = 16/21$). Although this treatment is feasible to implement, is unlikely to increase health inequity, and has not shown statistically or clinically significant evidence of harm, these factors are mitigated by the lack of demonstrated efficacy.

Part 2. The Use of 24-Hour High-Dose Methylprednisolone Sodium Succinate Within 8 Hours of Spinal Cord Injury

Population Description: Patients with acute SCI

Key Question: Should a 24-hour infusion of high-dose MPSS be administered to adult patients with acute SCI within 8 hours of injury?

Recommendation 2: We suggest a 24-hour infusion of high-dose MPSS be offered to adult patients within 8 hours of acute SCI as a treatment option.

Quality of Evidence: Moderate

Strength of Recommendation: Weak

Evidence Summary

The systematic review also aimed to evaluate whether MPSS has differential efficacy or safety issues in subpopulations. In the study by Bracken et al, there was a differential effect of

MPSS on motor recovery compared with controls depending on the timing of MPSS administration.⁵ Patients receiving MPSS within 8 hours had a mean 4.8- and 5.2-point improvement in motor scores at 6- and 12-month follow-up compared with a mean 3.9- and 5.8-point deterioration when administered after 8 hours. There was no evidence of a differential effect of the timing of MPSS administration on pinprick or light touch.

Two additional randomized controlled trials^{24,25} and one prospective observational study²⁶ compared MPSS versus control in patients receiving treatment within 8 hours. Based on the randomized controlled trials, pooled results at final follow-up (6 or 12 months) demonstrated a modest improvement of 3.88 (95% CI = 0.50 to 7.27, $P = .02$) in mean motor scores in the MPSS group compared with the control group. When adding the results of the prospective cohort study, this mean difference decreased to 3.21 (95% CI = 0.10 to 6.33, $P = .04$). In summary, there is moderate evidence suggesting a small benefit in motor recovery when MPSS is administered within 8 hours of injury compared with no treatment.

With respect to safety, risk of complications was not separately evaluated for patients treated within 8 hours of injury.

Rationale for Recommendation

This question differs from Part 1 as it focuses on the efficacy and safety of MPSS administered within 8 hours of injury. The outcomes ranked as most critical for decision making were change in motor and sensory scores and risk of major complications. The strength of evidence for findings related to these outcomes was moderate; across 3 randomized controlled trials and 1 prospective cohort study, there was no serious risk of bias, no serious inconsistency or indirectness, and undetected publication bias. There, however, was a serious risk of imprecision, which resulted in a downgrade in the overall quality of the evidence. The GDG unanimously agreed that the overall certainty of evidence was moderate.

There was discussion surrounding whether an analysis was planned a priori to evaluate the effect of timing of MPSS administration. Using criteria suggested by Oxman and Guyatt,²⁸ the methodologists confirmed that the subgroup analyses were valid based on GRADE criteria: (1) was the subgroup variable specified at baseline; (2) was the difference statistically significant; (3) did the hypothesis precede rather than follow the analysis; (4) was the subgroup analysis one of a smaller number of hypotheses tested; (5) was the difference suggested by comparisons within rather than between studies; (6) was the difference consistent across studies; and (7) is there indirect evidence that supports the hypothesized difference? In the study by Bracken et al, 2 subgroup hypotheses were tested, one related to the timing of MPSS administration and the other to the severity of injury.⁵ The subgroups were specified prior to randomization as “early” or “late” administration of MPSS relative to the time of injury; however, the exact cutoff (8 hours) was not selected at baseline, but chosen after data collection based on the median time from injury to treatment. Subsequent studies used this 8-hour cut point in their analyses,

which allowed for data pooling and meta-analysis.²⁴⁻²⁶ There was a statistically significant difference in motor scores between patients receiving MPSS within 8 hours of injury and those treated after 8 hours of injury. In addition, the point estimates were similar in the studies by Bracken et al⁵ and Otani et al,²⁴ and the confidence limits of the estimate reported by Pointillart et al²⁵ nearly overlapped the entire confidence intervals reported in the other 2 studies. Finally, indirect evidence from a number of preclinical SCI studies have demonstrated the potential for MPSS, when administered early postinjury, to improve neurobehavioral outcomes and/or reduce the extent of neural tissue cavitation by attenuating membrane lipid peroxidation.¹⁻³

The GDG unanimously agreed that there was probably no important uncertainty or variability about how much stakeholders value the main outcomes. Clinicians, patients, and payers would similarly value improved motor and sensory scores and reduced risk of major complications.

The anticipated desirable effects were improved motor scores, pinprick sensation, and light touch. Pooled results at 6- or 12-month follow-up indicate a modest improvement in mean motor scores in the MPSS group compared with the control group (Effect size: 3 randomized controlled trials: 3.88, 95% CI = 0.50 to 7.27, $P = .02$; 3 randomized controlled trials + 1 prospective cohort = 3.21, 95% CI = 0.10 to 6.33, $P = .04$). It is difficult to determine whether these changes represent clinically important improvements as the minimum clinically important differences of neurological outcomes have yet to be established; however, even a small difference can substantially improve a patient’s quality of life. The GDG were either uncertain or believed the desirable effects were probably not large (no = 1; probably no = 8; uncertain = 10; probably yes = 3).

The anticipated undesirable effects of MPSS include complications such as death, wound infection, gastrointestinal hemorrhage, sepsis, urinary tract infection, pneumonia, and decubiti. Based on the evidence, there is no statistically significant difference between treatment groups in the pooled risk of any of these complications. There was a weak trend for increased risk of pulmonary embolism in the MPSS group; however, the clinical impact of this complication on long-term outcomes is largely unknown. Furthermore, the risk of complications was not separately evaluated for patients treated within 8 hours of injury. The GDG unanimously agreed that the undesirable anticipated effects are probably small. The GDG group were either uncertain or believed that the desirable effects (motor recovery) are probably large relative to the undesirable effects (complications/mortality) (probably no = 1; uncertain = 11; probably yes = 9; yes = 2). There was substantial discussion throughout the course of voting; specifically, the GDG agreed to define a “large effect” as a clinically important change. This discussion may partially explain the discrepancy between the voting results for the size of the anticipated desirable effects and the relative size of anticipated desirable to undesirable effects.

In the absence of literature, the GDG used their clinical expertise to discuss the resources required to administer MPSS to patients with SCI. The GDG unanimously agreed that the resources required are probably small as MPSS is an off-patent drug with low associated costs. Unfortunately, there were no studies evaluating the cost-effectiveness of MPSS in patients with SCI; however, the GDG believed that the incremental cost is probably small relative to the net motor benefits.

The GDG unanimously believed that a recommendation for MPSS within 8 hours of injury would reduce health inequities since this drug is available at most health centers and is inexpensive. The option of administering MPSS within 8 hours of injury is probably acceptable to key stakeholders as there is potential for small to modest improvements in neurologic recovery at no increased risk of death or other complications. Given that even small improvements in motor function can translate to substantial gains in quality of life, both patients and clinicians would find this option acceptable. Finally, the GDG agreed that this option is probably feasible to implement as there are limited foreseeable barriers from a cost and process standpoint (probably no = 1; probably yes = 15; yes = 2; varies = 5). Potential barriers include establishing a diagnosis of SCI and administering the drug within 8 hours of injury.

Considering all these factors, the GDG voted that the desirable consequences probably outweigh the undesirable consequences in most settings ($n = 15/21$); this led to the formation of a weak recommendation that a 24-hour infusion of high-dose MPSS be considered as a treatment option for adult patients who present within 8 hours of traumatic SCI ($n = 17/19$). Although the effect size for motor recovery is small (3-4 motor points), this change may be important in certain patients where even small motor improvements may have important functional consequences.

Part 3. The Use of 48-Hour High-Dose Methylprednisolone Sodium Succinate in Patients With Spinal Cord Injury

Population Description: Patients with acute SCI

Key Question: Should a 48-hour infusion of high-dose MPSS be administered to adult patients with acute SCI?

Recommendation 3: We suggest not offering a 48-hour infusion of high-dose MPSS to adult patients with acute SCI.

Quality of Evidence: No included studies

Strength of Recommendation: Weak

Evidence Summary

There were no studies included in the systematic review (reported elsewhere in this issue) that addressed the efficacy of a 48-hour high-dose infusion of MPSS relative to placebo or no treatment. NASCIS III, however, compared a 24-hour versus 48-hour infusion of high-dose MPSS.⁸ Based on the results from this study, there was a significantly higher incidence of

severe pneumonia ($P = .02$) in the 48-hour group compared with the 24-hour group. Furthermore, there was an increased incidence of severe sepsis in the 48-hour group; however, the difference between the 24-hour and 48-hour groups was within the limits of chance for this outcome ($P = .07$). In summary, there may be an increased incidence of severe pneumonia and sepsis when the duration of infusion increases from 24 hours to 48 hours.

Rational for Recommendation

The outcomes ranked as most critical for decision making were change in motor and sensory scores and risk of major complications. There were no included studies that addressed the efficacy and safety of a 48-hour high-dose infusion of MPSS relative to placebo or no treatment. The evidence for this recommendation was therefore indirect and derived from the NASCIS III study, which compared the safety of a 24-hour and 48-hour infusion of high-dose MPSS.⁸

The GDG unanimously agreed that there was probably no important uncertainty or variability about how much stakeholders value the main outcomes. Clinicians, patients, and payers would similarly value improved motor and sensory scores and reduced risk of major complications.

In the absence of evidence, the GDG unanimously agreed that it was uncertain whether the anticipated desirable and undesirable effects of a 48-hour infusion of high-dose MPSS were large/small. In the NASCIS III study, however, there was a significantly higher incidence of severe pneumonia and severe sepsis in the 48-hour cohort compared with the 24-hour cohort.⁸

In the absence of literature, the GDG used their clinical expertise to discuss the resources required to administer MPSS to patients with SCI. The GDG unanimously agreed that the resources required are probably small as MPSS is an off-patent drug with low associated costs. Unfortunately, there were no studies evaluating the cost-effectiveness of MPSS in patients with SCI; as a result, the cost-benefit ratio is uncertain.

The GDG unanimously believed that a recommendation for MPSS in patients with SCI would reduce health inequities since this drug is available at most health centers and is inexpensive. The option of administering a 48-hour infusion of high-dose MPSS is probably not acceptable to key stakeholders as there is no evidence to support its efficacy. Furthermore, a 48-hour infusion may be associated with increased infectious complications. Finally, the GDG unanimously agreed that this option is probably feasible to implement. There are limited foreseeable barriers from a cost and process standpoint, although this may be variable across different institutions.

Considering all these factors, the GDG voted that the undesirable consequences probably outweigh the desirable consequences in most settings ($n = 19/24$); this led to the formation of a weak recommendation against the use of a 48-hour infusion of high-dose MPSS to adult patients with SCI ($n = 15/24$). Although this treatment is feasible to implement and is unlikely

to increase health inequities, these factors are mitigated by the lack of demonstrated efficacy and potential for harm.

Further Justification for Changes in Recommendations

As indicated previously, this guideline aimed to consolidate the recommendations from the 2002 and 2013 AANS/CNS guidelines. The discrepancies between our recommendations and those proposed in 2002 and 2013 are largely a result of the group comparisons we made; specifically, we distinguished between a 24-hour versus 48-hour infusion of MPSS as well as between administration within and after 8 hours of injury. Similar to the AANS/CNS guidelines, our systematic review indicated that, across all patients, MPSS does not confer any clinical benefit compared with no pharmacological treatment.¹³ In patients treated within 8 hours of injury, however, our meta-analysis supported a near 4-point difference in motor scores between groups (favoring MPSS). In terms of safety, our systematic review only indicated a significant difference in risk of complications between patients treated with a 24-hour versus a 48-hour infusion. In contrast, there were no observed differences in harmful side effects between a 24-hour MPSS group and a control group. In fact, a study by Wilson et al indicated that treatment with MPSS was associated with a reduced risk of experiencing one or more complications; this finding, however, was based on very low level evidence.

The systematic review by Hurlbert reported a higher incidence of gastrointestinal hemorrhage, wound infection, and pulmonary embolism in patients treated with MPSS compared with controls.¹³ Although none of these findings were reported as statistically significant, the authors acknowledged that none of these comparisons were properly powered to avoid Type II error. A number of studies were excluded in our systematic review that were included in the one published by Hurlbert; differences in inclusion criteria may partly explain the discrepancies in results between these 2 reviews and, consequently, differences in recommendations. Our review targeted either randomized controlled trials or observational studies that controlled for baseline severity score. We are confident that the studies synthesized in our meta-analysis truly reflect the highest quality of evidence published on this topic. Although some of the comparisons were not properly powered to detect a difference between treatment groups, this limitation was reflected by downgrading the overall strength of evidence for imprecision.

Evidence Gaps and Future Research Recommendations

Given that MPSS has the longest track record for use, and has been the subject of the greatest study and controversy in the context of SCI, we included an evaluation of this drug in these guidelines. That said, we acknowledge that there are a number of new putative neuroprotective agents in the translational pipeline that have shown promise in preclinical and early phase

clinical studies. At present, however, there is inadequate evidence to justify any recommendation with respect to these emerging treatments. Future studies evaluating the efficacy of these agents alone, and in combination with MPSS, would be of interest. Given the fact that several large, high-quality randomized controlled trials evaluating MPSS in SCI have been completed, it would be difficult to justify the initiation of another similar study, especially in the face of limited resources and the aforementioned therapies that have yet to be formally tested in large clinical studies.

Implementation Considerations

It is expected that this guideline will influence clinical practice and facilitate evidence-based decision making. Dissemination of the knowledge from this guideline is of critical importance and will be accomplished at multiple levels:

- Presentation at international spine surgery, critical care, neurology, anesthesiology, and vascular medicine conferences
- Scientific and educational courses in symposium format
- Webinar dissemination of information to a broad audience in an interactive format
- Publication of a focus issue in a peer-reviewed journal
- Submission to the National Guideline Clearinghouse
- AOSpine International Spinal Cord Injury Knowledge Forum

Potential barriers to implementation include the following:

1. *Clinical uptake by surgeons:* The use of MPSS in the setting of traumatic SCI is one of the most contentious issues in the field. Many clinicians are opposed to the routine use of MPSS, even within 8 hours of injury, due to perceived increased risks of complications and mortality. As a result, the decision to administer MPSS in the acute phase of SCI may remain in the hands of individual surgeons.
2. Given that SCI occurs in geographically isolated regions, successful administration of MPSS within 8 hours of injury may be dependent on location of injury (ie, where the injury occurred) and the local transport and prehospital systems in place. Furthermore, timely treatment with MPSS may require administration at the site of injury or en route to a trauma center by first responders, which may pose additional logistical challenges.

Internal Appraisal and External Review of This Guideline

Vice-chairs of the GDG conducted an internal appraisal of the final guideline using Appraisal of Guidelines for Research & Evaluation II (AGREE II) standards.²⁹ A multidisciplinary group of stakeholders, including patients, were invited to

externally review the final draft prior to publication. Additional details of these processes and a summary of conflicts of interest for external reviewers are found in the accompanying methods paper.

Plans for Updating

The guidelines will be reviewed by the primary sponsor and the Vice-Chairs at 3 years to a maximum of 5 years following publication. The guideline will be updated when new evidence suggests the need to modify our recommendations. An earlier update will be considered if there are changes in (1) the evidence related to harms and benefits; (2) outcomes that would be considered important for decision making; (3) ranking of current critical and important outcomes; and (4) available interventions and resources.³⁰

Authors' Note

Guideline Development Committee Members: Co-Chair: Michael G. Fehlings, MD, PhD, Neurosurgery; Co-Chair: James Harrop, MD, Neurosurgery; Vice Chair: Jefferson R. Wilson, MD, PhD, Neurosurgery; Vice Chair: Anthony Burns, MD, Physical Medicine/Rehabilitation; General Member of Leadership Group: Brian Kwon, MD, PhD, Orthopedic Surgery; Systematic Review Coordinator: Lindsay Tetreault, PhD, Research.

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Declaration of Conflicting Interests

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Supplemental Material

The supplemental material is available in the online version of the article.

References

1. Braughler J, Hall E. Effects of multi-dose methylprednisolone sodium succinate administration on injured cat spinal cord neurofilament degradation and energy metabolism. *J Neurosurg.* 1984;61:290-295. doi:10.3171/jns.1984.61.2.0290.
2. Hall ED, Braughler JM. Glucocorticoid mechanisms in acute spinal cord injury: a review and therapeutic rationale. *Surg Neurol.* 1982;18:320-327.
3. Hall ED, Braughler JM. Effects of intravenous methylprednisolone on spinal cord lipid peroxidation and Na⁺⁺K⁺-ATPase activity. Dose-response analysis during 1st hour after contusion injury in the cat. *J Neurosurg.* 1982;57:247-253. doi:10.3171/jns.1982.57.2.0247.
4. Akhtar AZ, Pippin JJ, Sandusky CB. Animal studies in spinal cord injury: a systematic review of methylprednisolone. *Altern Lab Anim.* 2009;37:43-62.
5. Bracken MB, Shepard MJ, Collins WF Jr, et al. 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. doi:10.3171/jns.1992.76.1.0023.
6. Bracken MB, Shepard MJ, Collins WF, et al. 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. doi:10.1056/NEJM199005173222001.
7. Bracken MB, Shepard MJ, Hellenbrand KG, et al. Methylprednisolone and neurological function 1 year after spinal cord injury. Results of the National Acute Spinal Cord Injury Study. *J Neurosurg.* 1985;63:704-713. doi:10.3171/jns.1985.63.5.0704.
8. Bracken MB, Shepard MJ, Holford TR, 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;277:1597-1604.
9. Eck JC, Nachtigall D, Humphreys SC, Hodges SD. Questionnaire survey of spine surgeons on the use of methylprednisolone for acute spinal cord injury. *Spine (Phila Pa 1976).* 2006;31:E250-E253. doi:10.1097/01.brs.0000214886.21265.8c.
10. Hurlbert RJ. Methylprednisolone for the treatment of acute spinal cord injury: point. *Neurosurgery.* 2014;61(suppl 1):32-35.
11. Fehlings MG, Wilson JR, Cho N. Methylprednisolone for the treatment of acute spinal cord injury: counterpoint. *Neurosurgery.* 2014;61(suppl 1):36-42.
12. Hurlbert R. Methylprednisolone for acute spinal cord injury: an inappropriate standard of care. *J Neurosurg Spine.* 2000;93:1-7.
13. Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. *Neurosurgery.* 2013;72(suppl 2):93-105. doi:10.1227/NEU.0b013e31827765c6.
14. Hadley M, Walters B, Grabb P, et al. Pharmacological therapy after acute cervical spinal cord injury. *Neurosurgery.* 2002;50:563-572.
15. Anonymous. Pharmacological therapy after acute cervical spinal cord injury. *Neurosurgery.* 2002;50(suppl 3):S63-S72.

16. Shiffman RN, Michel G. Toward improved guideline quality: using the COGS statement with GEM. *Stud Health Technol Inform.* 2004;107:159-163.
17. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med.* 2003;139:493-498.
18. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64:401-406.
19. Agency for Healthcare Research and Quality. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (AHRQ Publication No. 10(14)-EHC063-EF). Rockville, MD: Agency for Healthcare Research and Quality; 2013.
20. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol.* 2013;66:719-725. doi:10.1016/j.jclinepi.2012.03.013.
21. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol.* 2013;66:726-735. doi:10.1016/j.jclinepi.2013.02.003.
22. Schunemann HJ, Oxman AD, Akl EA, et al. Moving from evidence to developing recommendations in guidelines: article 11 in integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. *Proc Am Thorac Soc.* 2012;9:282-292. doi:10.1513/pats.201208-064ST.
23. Wu JC, Ko CC, Yen YS, et al. Epidemiology of cervical spondyloitic myelopathy and its risk of causing spinal cord injury: a national cohort study. *Neurosurg Focus.* 2013;35:E10. doi:10.3171/2013.4.FOCUS13122.
24. 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 [in Japanese]. *Sekitsui Sekizui J.* 1994;7:633-647.
25. Pointillart V, Petitjean ME, Wiart L, et al. Pharmacological therapy of spinal cord injury during the acute phase. *Spinal Cord.* 2000;38:71-76.
26. Evaniew N, Noonan V, Fallah N, et al. 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. *J Neurotrauma.* 2015;32:1674-1683. doi:10.1089/neu.2015.3963.
27. Wilson JR, Arnold PM, Singh A, Kalsi-Ryan S, Fehlings MG. Clinical prediction model for acute inpatient complications after traumatic cervical spinal cord injury: a subanalysis from the surgical timing in Acute Spinal Cord Injury Study. *J Neurosurg Spine.* 2012;17:46-51.
28. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. *Ann Intern Med.* 1992;116:78-84.
29. Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. *CMAJ.* 2010;182:E472-E478. doi:10.1503/cmaj.091716.
30. Shekelle P, Woolf S, Grimshaw JM, Schünemann HJ, Eccles MP. Developing clinical practice guidelines: reviewing, reporting, and publishing guidelines; updating guidelines; and the emerging issues of enhancing guideline implementability and accounting for comorbid conditions in guideline development. *Implement Sci.* 2012;7:62.