

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

# METHYLPREDNISOLONE IN ACUTE SPINAL CORD INJURY

## SUMMARY

Acute spinal cord injury (ASCI) is pathophysiologically characterized by an initial mechanical or “primary” injury that is followed by a series of “secondary” injury events including ischemia, calcium- and sodium-mediated cell injury, excitotoxic cell death, inflammation, edema, and apoptosis or genetically programmed cell death (1). Methylprednisolone sodium succinate (MPSS) possesses a variety of neuroprotective effects including inhibition of lipid peroxidation, calcium influx, ischemia, and antiinflammatory effects, but at the risk of increased infection (1,2, 15,18-20,22,25-26). The National Spinal Cord Injury Study (NASCIS) trials have previously reported improved long-term functional outcome in ASCI patients treated with high doses of MPSS (3-6). Although widely considered to possess valid study designs; the data quality, statistical analysis, interpretation, and conclusions of these studies remain highly controversial (1,7-11,23). Until a more convincing body of evidence can be provided, the routine use of MPSS following ASCI should be avoided until the benefits can be proven to outweigh the risks.

## RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Methylprednisolone should not be used for the routine treatment of blunt ASCI.**
  - **Methylprednisolone should not be used for the routine treatment of penetrating ASCI.**
- **Level 3**
  - **Concurrent stress ulcer and hyperglycemia prophylaxis should be instituted during steroid administration.**

## INTRODUCTION

Acute spinal cord injury (ASCI) is a devastating disease affecting an estimated 10,000-15,000 patients in the United States each year (12,13). Typically a result of motor vehicle crashes or recreational mishaps, 46% of ASCI patients will not survive their first year post-injury (12). The most important factors predicting survival following ASCI include age, level of injury, and neurologic grade (12). Those who do survive require prolonged or repeated hospital admissions for complications or rehabilitation related to their injury. Given that the median age of patients sustaining ASCI is 27 years, there is significant potential for long-term morbidity and loss of productivity. As a result, the economic impact of ASCI is enormous with the cost of managing ASCI in the United States estimated at \$4 to \$5 billion dollars per year (12-14).

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## EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

## LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

ASCI may occur as a result of either primary or secondary injury. Primary ASCI is commonly a combination of the initial injury (due to fracture, dislocation, missile injury, acutely ruptured disc, etc...) as well as subsequent persisting compression. Secondary ASCI may occur due to multiple causes including ischemia, edema, vasospasm, thrombosis, electrolyte derangements, neurotransmitter accumulation, arachidonic acid release and free radical formation, and apoptosis (1).

Methylprednisolone sodium succinate (MPSS) possesses a variety of neuroprotective effects including inhibition of lipid peroxidation, calcium influx, ischemia, and anti-inflammatory effects (1,2). The ability to inhibit secondary injury to the traumatized spinal cord is appealing. Beginning in the mid-1980's, the National Spinal Cord Injury Study (NASCIS) trials began reporting improved long-term functional outcome in ASCI patients treated with high-dose MPSS (3,4). The subsequent NASCIS-2 and NASCIS-3 trials resulted in MPSS therapy being widely considered a "standard of care" for ASCI (5,6,24,27).

Although widely considered to possess valid study designs, the data quality, statistical analysis, interpretation, and conclusions of these studies remain highly controversial (1,7-11,23). Although conducted as prospective, randomized controlled studies, the primary outcome analysis of the NASCIS-2 and NASCIS-3 trials were both negative with the modest beneficial effects being proven only through post hoc analyses excluding >70% of the patients. Proponents argue that even small improvements in motor recovery have the potential to be amplified into meaningful improvements in quality of life (7). It is notable that the findings of NASCIS-2 and -3 have never been independently confirmed. Of further concern has been the reluctance of the NASCIS investigators to release the original data for independent review so that the above concerns can be addressed. Other studies have raised issues regarding the safety of such therapy in light of the questionable results and known complications of high-dose steroids. In the most recent clinical practice guideline from the consortium for spinal cord medicine, they state that there is no clinical evidence "to definitively recommend the use of any neuroprotective pharmacologic agent, including steroids" for treating ASCI to improve function (8-11,15-20,27).

## **LITERATURE REVIEW**

The mechanisms and potential for long-term outcome of ASCI following blunt vs. penetrating trauma are distinctly different. For this reason, the existing literature will be divided into that which pertains to blunt and that which addresses penetrating ASCI.

### Blunt Spinal Cord Injury

Because of the implications of lipid peroxidation as a major factor in the deterioration of central nervous system function after trauma, the use of parenteral corticosteroids, such as MPSS, as a means of inhibiting free radical injury and maximizing post injury neurologic status has been widely evaluated. The most highly cited and debated trials come from the multi-center NASCIS group. The original findings of NASCIS-2 received significant coverage in the press and support from the National Institutes of Health (NIH). As a result, the recommendations of the NASCIS-2 trial and subsequent NASCIS-3 trial have been previously considered a "standard of care" (24). Failure to institute high-dose steroid therapy has been feared by many physicians as grounds for litigation leading to inappropriate application of the NASCIS trial recommendations in some patients. As clinical experience with the NASCIS recommendations has evolved, the potentially significant complications of high-dose steroid therapy have become evident and have been the focus of a number of clinical trials (2,15,18-20,22,25-26). Because the immunosuppressive and anti-inflammatory effects of corticosteroids are reversible, one would anticipate that complications related to this therapy would be most apparent within the first few weeks of administration. The NASCIS-2 trial, however, did not begin documenting complications until 6 weeks after injury. In addition, patients with "other life-threatening morbidities" were excluded from the NASCIS-2 trial focusing instead upon patients with largely isolated spinal injuries. In addition, a significant percentage of the NASCIS-3 trial patients were enrolled with "normal motor function". Both the NASCIS-II and NASCIS-III trials have been questioned for their use of statistical analysis (11,23). As a result, concerns have been raised as to whether or not the NASCIS trial results were a result of statistical error.

#### NASCIS 2 Criticisms:

- Overall analysis was negative
- Positive effects were limited to an underpowered post hoc analysis of patients receiving steroids within 8 hours of injury
- Control group outcome was worse than that of published historical controls
- Effect sizes were small
- Functional importance of purported benefit is unclear and not statistical at 1 year
- Effect on long tract function is unclear
- Significant concerns regarding effect of MPSS on wound healing and sepsis

#### NASCIS 3 Criticisms

- Overall analysis was negative
- Lack of a placebo group
- Positive effects were limited to post hoc analysis of patients receiving steroids between 0-3 and 3-8 hours post-injury
- There was only modest improvement ( $p=0.08$ ) on a single component of the Functional Independence Measure (FIM) scale
- There was an increased incidence of sepsis and pneumonia with 48-hour steroid treatment

A review of the various trials published regarding the use of MPSS in blunt spinal cord injury are listed at the end of this guideline.

#### Penetrating Spinal Cord Injury

It is intuitive that penetrating injuries that transect the spinal cord cannot be salvaged with any pharmacological agent (19). As a result, the long-term prognosis for functional recovery following penetrating trauma to the spinal cord is worse than that for blunt injury. Although the NASCIS trials excluded patients with penetrating trauma to the spinal cord, misapplication of the NASCIS trial data and fear of litigation has resulted in many patients with stab or gunshot wounds to the spinal cord receiving high-dose steroid therapy. Several trials have retrospectively evaluated the outcome of patients with penetrating spinal cord injury (16,19,20). These studies have consistently found no benefit to high-dose methylprednisolone in patients with penetrating spinal cord injuries, and have identified an increased incidence of infectious and gastrointestinal complications (20).

#### **SUMMARY**

MPSS in the treatment of ACSI is a highly controversial topic. Despite a lack of concrete scientific data to support that MPSS offers any significant long-term benefit for the treatment of patients with ACSI, physicians continued to prescribe this medication based upon the questionable results of the NASCIS trials. Recent evidence-based medicine guidelines, however, no longer include MPSS as a “standard of care” and even warn against its use. Until a more convincing body of evidence can be provided, the routine use of MPSS following ACSI should be avoided until the benefits can be proven to outweigh the risks.

### Blunt Spinal Cord Injury

Author	Year	Evidence	Findings
Galandiuk (15)	1993	Class III	Combined prospective/retrospective case-control study of 32 spine trauma patients. The 14 patients with ASCI received MPSS according to the NASCIS II protocol. Length of stay and incidence of clinical infection were both increased in the MPSS patients, although the differences did not achieve statistical significance due to the small sample size. T helper/suppressor cell ratio and serum IgG levels were both lower in the MPSS patients.
Gerndt (2)	1997	Class III	Retrospective case-control review of 140 patients of which 93 received MPSS according to the NASCIS II protocol. Ventilator days and ICU days were both significantly increased and rehabilitation days decreased in the MPSS patients. There was a 4-fold increase in the incidence of acute pneumonia in the MPSS patients. Mortality was not impacted by use of MPSS.
Bracken (3,4) NASCIS-1	1984	Class II	Prospective, randomized, double-blind multi-center trial of MPSS in 330 patients with ASCI. Patients were randomized to one of two arms: 1) 100-mg bolus followed by 25 mg q 6 hours for 10 days OR 2) 1000-mg bolus followed by 250 mg q 6 hours for 10 days. No significant difference in any of the primary neurologic outcome measures was detected. There was an almost 4-fold increase in wound infections in the high-dose group (p=0.01). There were trends towards increased sepsis, pulmonary embolus, and death in the high-dose group.
Bracken (5) NASCIS-2	1990	Class II	Prospective, randomized, double-blind multi-center trial of MPSS in 487 patients with ASCI. Patients were randomized to one of three arms: 1) MPSS 30 mg/kg bolus followed by 5.4 mg · kg <sup>-1</sup> · hr <sup>-1</sup> infusion for 23 hours, 2) naloxone 5.4 mg/kg bolus followed by 4.5 mg · kg <sup>-1</sup> · hr <sup>-1</sup> infusion for 23 hours, OR 3) a placebo infusion. All primary outcome measures, including neurologic outcome and mortality, did not differ between the three groups. <i>Post hoc</i> subgroup analysis of fewer than 50% of those enrolled identified improved neurologic function in patients treated with MPSS within 8 hours of injury. Patients who received MPSS more than 8 hours after injury demonstrated worse neurologic function than did the placebo group (p=0.08). There were increases in wound infection, gastrointestinal bleeding, and pulmonary embolus in patients who received MPSS although these differences were not statistically significant.
Otani (21)	1994	Class II	Prospective, randomized, non-blinded multi-center trial of MPSS in 158 patients with ASCI (published in Japanese). Patients were randomized to one of two arms: 1) MPSS 30 mg/kg bolus followed by 5.4 mg · kg <sup>-1</sup> · hr <sup>-1</sup> infusion for 23 hours, OR 2) routine medical management. MPSS was administered within 8 hours of injury. 26% of patients were excluded from analysis for protocol violations. Neurologic outcome did not differ between the two groups. Serious study design and analysis flaws raise concerns regarding the validity of these data.
Prendergast (16)	1994	Class III	Retrospective review of 54 patients with ASCI (23 blunt, 31 penetrating). 29 patients received MPSS while 25 did not. Among patients with blunt ASCI, neurologic outcome did not differ between those who did and did not receive MPSS.

George (17)	1995	Class III	Retrospective review of 130 patients with ASCI. 75 patients received MPSS while 55 did not. MPSS was administered per the NASCIS-2 protocol. No difference in mortality or discharge FIM score was identified. Discharge mobility was worse in the MPSS group ( $p < 0.05$ ).
Bracken (6) NASCIS-3	1997	Class II	Prospective, randomized, double-blind multi-center trial of MPSS in 499 patients with ASCI. All patients were administered MPSS 30 mg/kg and then randomized to one of three arms: 1) MPSS 5.4 mg · kg <sup>-1</sup> · hr <sup>-1</sup> infusion for 23 hours, 2) MPSS 5.4 mg · kg <sup>-1</sup> · hr <sup>-1</sup> infusion for 47 hours, OR 3) tirilizad mesylate 2.5 mg/kg bolus q 6 hours for 48 hours. Treatment was initiated within 8 hours of injury in all patients. Randomization did not result in equal patient groups as 25% of Group 1 patients had normal motor function while only 14% of Group 2 patients had normal motor function ( $p = 0.012$ ). Patients who received tirilizad demonstrated significantly worse motor function than did patients who received MPSS. Among the MPSS groups, all primary outcome measures were not different. <i>Post hoc</i> subgroup analysis identified that patients who received their MPSS bolus more than 3 hours post-injury demonstrated significantly greater motor function if they received 48 hours of MPSS rather than 24 hours. This excludes almost 70% of the study patients from further analysis. Although improved motor and sensory scores were seen in the MPSS groups at 6 weeks and 6 months post-injury, no differences in motor or sensory function were detectable at 1 year. There was a 2-fold increase in severe pneumonia ( $p = 0.02$ ), a 4-fold increase in severe sepsis ( $p = 0.07$ ), and a 6-fold increase in mortality ( $p = 0.056$ ) due to respiratory complications in the 48 hour MPSS patients when compared to 24 hour MPSS patients.
Pointillart (18)	2000	Class I	Prospective, randomized trial of MPSS in 106 patients with ASCI. Patients were randomized to one of four arms: 1) MPSS 30 mg/kg bolus followed by 5.4 mg · kg <sup>-1</sup> · hr <sup>-1</sup> infusion for 23 hours, 2) nimodipine 0.015 mg · kg <sup>-1</sup> · hr <sup>-1</sup> for 2 hours followed by 0.03 mg · kg <sup>-1</sup> · hr <sup>-1</sup> infusion for 7 days, 3) both agents, OR 4) neither medication. Although neurologic outcome was improved in all four groups at 1 year, no significant differences existed between groups. The incidence of infectious complications was higher (66% vs. 45%) in patients who received MPSS.
Matsumoto (22)	2001	Class I	Prospective, randomized, double-blind trial of MPSS vs. placebo in 46 patients with ASCI. MPSS was administered according to the NASCIS-2 protocol. 23 patients received MPSS and 23 patients did not. Pulmonary and gastrointestinal complications were both significantly more common in the MPSS group.
Tsutsumi (25)	2006	Class III	Restrospective review of patients admitted for ASCI. The authors showed statistical improvement only in incomplete ASCI at six months. The subgroup was small however (19 v 8) and demonstrated no information whether the improvement was of any functional significance.
Suberviola (26)	2008	Class II	Restrospective review of patients admitted to the ICU with ASCI. There were 59 patients within the MPSS group and 23 in the no MPSS group. MPSS was administered as per NASCIS protocol. The MPSS group had lower ISS score and still showed lack of improvement at time of ICU discharge but had increased ICU stay, hyperglycemia, and increased pulmonary infection.

### Penetrating Spinal Cord Injury

Author	Year	Evidence	Findings
Prendergast (16)	1994	Class III	Retrospective review of 54 patients with ASCI (23 blunt, 31 penetrating). 29 patients received MPSS while 25 did not. Penetrating ASCI patients who received MPSS demonstrated worse motor function (up to 2 months post-injury) than did those not receiving steroids.
Levy (19)	1996	Class III	Retrospective review of 252 patients with penetrating ASCI of which 55 received MPSS. Motor function was not improved by administration of MPSS. Number of complications was not increased by MPSS.
Heary (20)	1997	Class III	Retrospective review of 254 penetrating ASCI patients of which 61 received steroids (MPSS or dexamethasone). Steroid administration did not improve motor function, but did increase infectious, gastrointestinal, and pancreatic complications.

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