METHYLPREDNISOLONE IN ACUTE SPINAL CORD INJURY

SUMMARY

The administration of methylprednisolone (MP) for patients with acute spinal cord injury (ASCI) has been highly controversial. MP can confer neuroprotective effects to patients by mitigating the secondary response to ASCI. However, there are significant risks associated with MP administration. Initial support for MP use was based on the results of the National Spinal Cord Injury Study (NASCIS) trials, which reported improved long-term functional outcomes in ASCI patients treated with high doses of MP (1-4). Although widely considered to have valid study designs, these trials have faced scrutiny due to questionable data quality, statistical analysis, interpretations, and conclusions. Further investigation reveals no class I or class II evidence of a beneficial effect of MP (5,6). Current guidelines advise against the use of MP for ASCI.

RECOMMENDATIONS

- **Level 1**
  - **Methylprednisolone should NOT be used for the treatment of acute spinal cord injury.**
- **Level 2**
  - **None**
- **Level 3**
  - **None**

INTRODUCTION

Acute spinal cord injury (ASCI) is a devastating condition affecting approximately 40 million people worldwide each year (7). These injuries most-commonly occur in men aged 20-35, and are often the result of motor vehicle collisions, falls, violence, or recreational mishaps. Thirty to sixty percent of these patients do not survive to hospital, and, of those who do, 17-33% percent do not survive the first year (8). Acute respiratory failure is the most common cause of death among those who reach the hospital. Survivors generally require prolonged or repeated hospitalizations for complications or rehabilitation related to their injury.

The pathophysiology of ASCI involves a primary injury to the spinal cord that then triggers a secondary response, which in turn perpetuates the first. The primary injury is the result of direct mechanical forces, such as impact and compression. Within minutes, a complex cascade of cellular and molecular forces results in a secondary injury characterized by ischemia, edema, neurogenic shock, hemorrhage, vasospasm, thrombosis, electrolyte derangements, neurotransmitter accumulation, arachidonic acid release, free radical formation, inflammation, lipid peroxidation, and apoptosis. Apart from prevention,

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.

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there is little that can be done to treat the primary injury. Therefore, research efforts have focused on ameliorating the secondary response and reducing the extent of permanent paralysis. Several interventions and pharmacological therapies have been evaluated. The most-commonly tested has been MP, a corticosteroid that confers a variety of neuroprotective effects by inhibiting elements of the secondary response such as lipid peroxidation, free radical formation, ischemia, and inflammation.

The National Acute Spinal Cord Injury Study (NASCIS) group was founded in 1977 (7). The most highly-cited and debated trials have come from this group. A series of three studies in the 1980s and 1990s showed improved long-term neurological outcomes in ASCI patients treated with high-dose MP. This led to the adoption of MP therapy as the standard of care for ASCI, a standard that is still upheld in many centers throughout the world today. This conclusion, however, has been subject to considerable debate over the past decade, and it has been overshadowed by studies showing a significant risk of complications due to MP therapy. MP can no longer be safely recommended for the treatment of ASCI. It is worth noting that MP is not FDA-approved for this use.

LITERATURE REVIEW

NASCIS

The NASCIS trials were all prospective, randomized, double-blind, multi-center studies. In 1984, NASCIS 1 evaluated two MP regimens in 330 patients: 1) 100 mg bolus followed by 25 mg every six hours for ten days, and 2) 1000 mg bolus followed by 250 mg every six hours for ten days. At six weeks, six months, and one year post-injury, no significant differences were found between the two regimens in neurological protection conferred. However, the incidence of wound infections was significantly higher in the high-dose group (p=0.01) (1,2).

NASCIS 2, published in 1990, randomized 487 ASCI patients to one of three arms: 1) MP 30 mg/kg bolus followed by 5.4 mg/kg/hr for 23 hours, 2) naloxone 5.4 mg/kg bolus followed by 4.5 mg/kg/hr for 23 hours, and 3) placebo (3). No significant differences in motor or sensory improvement were seen at one year, and there were no significant differences in complications. In a *post-hoc* analysis of patients who were treated within eight hours of injury, there was a significant improvement in motor function among those given MP compared to placebo (p=0.03). This improvement was recorded as a five-point increase on a fifty-point scale, but it is not clear that this point difference was clinically significant. Unfortunately, these positive results have not been reproduced in other studies, and the original data has not been made available for re-analysis by other researchers despite repeated calls for its release (including calls from the study investigators themselves). The cut-off point of eight hours was based on the fact that the median time to treatment was about eight hours (7).

The final trial, NASCIS 3, was published in 1997 and evaluated 499 patients who were given a loading dose of MP 30 mg/kg within eight hours of injury and then randomized into one of three arms: 1) MP 5.4 mg/kg/hr for 23 hours, 2) MP 5.4 mg/kg/hr for 48 hours, and 3) tirilazad mesylate 2.5 mg/kg every six hours for 48 hours (4). There were no significant differences in neurological recovery among the three groups. As in the NASCIS 2 trial, the only significant result was found after a *post-hoc* analysis of a subset of patients. Among patients who received the bolus dose of MP more than three hours after the injury (but still less than eight hours), group 2 patients (MP for 48 hours) had greater (albeit clinically insignificant) motor improvement than group 1 patients (MP for 24 hours) at six weeks (p=0.04) and six months (p=0.01) follow-up. This difference became less significant at one year (p=0.053). Again, the three-hour cutoff was based on the median time to treatment, within the eight-hour window (7).

MP therapy in patients with ASCI

Recently, several systematic reviews have been published regarding the use of MP in patients with ASCI. These constitute class I evidence and form the basis of the Level I recommendation in this guideline.

The current CNS/AANS guideline on the management of acute cervical spine and spinal cord injuries (March 2013) is a systematic review of 27 studies (5,6). Only studies conducted on humans and published in English were included, and the quality of evidence ranged from class I to class III. However, this document provides a clear summary of the available literature to date. It reveals that there is no

class I nor class II evidence showing a benefit of MP for ASCI patients. Although there is class III evidence of some beneficial effects of MP, none of these effects have been proven to be clinically meaningful.

In 2013, a systematic review of civilian gunshot injuries to the spine showed no added benefit of steroids in the restoration of motor and sensory function (9). This review is limited by heterogeneity among the studies.

In 2009, Botelho, et al. performed a systematic review of randomized controlled trials comparing MP with placebo (10). Two studies were reviewed, and no significant differences were found in either motor or sensory function after treatment with MP.

A Cochrane review published in 2012 looked at eight randomized controlled trials of steroid treatment, in any language (7). The patient population included those with ASCI as well as whiplash and lumbar disc disease, due to the "possibility of spinal cord injury with these conditions" (7). The study concluded that there is increased motor recovery among patients treated with high-dose MP within eight hours, and that the risk of infections is not significantly increased. However, three of the eight trials evaluated were conducted by the author of the review, raising the possibility of a conflict of interest.

A retrospective cohort study in 2011 compared patients with ASCI who received any MP to those who did not (11). The primary endpoint was change in neurological function from ICU admission to ICU discharge. No significant differences in neurological outcome were found between the two study groups.

Complications

The current CNS/AANS guidelines reveal class I evidence showing that administration of MP is significantly associated with wound infection, hyperglycemia (requiring insulin), and gastrointestinal (GI) hemorrhage. In addition, the review describes class II evidence indicating that patients treated with MP have a significantly higher risk of infection (wound, urinary tract, respiratory tract) and steroid-induced myopathy. Lastly, there is class III evidence that a significant association exists between MP treatment and pneumonia, respiratory failure, peptic ulcer disease, gastrointestinal hemorrhage, and hyperglycemia (requiring insulin) (5).

A retrospective case-control study in 2014 describes the association between MP for ASCI and GI hemorrhage (12). ASCI alone is a significant risk factor for GI bleeding, and GI hemorrhage is the third most common cause of death in paraplegic and quadriplegic patients, after the acute injury phase. All of the ASCI patients in this study had undergone surgery for their injury. The first cohort of patients received MP as per the NASCIS 2 trial (n=216) and the second group of patients did not receive any MP (n=134). Of the 350 patients, six developed overt GI bleeding, confirmed by upper endoscopy to be secondary to bleeding ulcers in the stomach and duodenum. All six of these patients had complete cervical spine injuries. In a subgroup analysis of patient with cervical spine injuries, there was a significant difference in the incidence of GI hemorrhage between those who received steroids and those who did not ($p=0.04$). Two of the six patients died, yielding a mortality of 33% once the bleed was diagnosed. The average time to onset of the GI hemorrhage was sixteen days from the day of injury.

Another retrospective case control study from 2014 compared ASCI patients who received high-dose MP with those who did not receive any MP (13). The goal of the study was to evaluate complications associated with the administration of MP for ASCI. Overall, there was a significantly higher risk of complications in the MP group ($p=0.001$), especially with regards to GI bleeding ($p<0.001$). There were no significant differences in in-hospital mortality.

A retrospective cohort study from 2011, comparing patients receiving MP to those not receiving steroids, also found a significantly higher incidence of complications in the MP group (11). Specifically, the MP group had more hyperglycemia (OR 5.67, 95% CI 1.85-17.31) and GI hemorrhage (OR 19.16, 95% CI 1.64-223.3).

Dimar et al. conducted a retrospective database review in 2010 to identify risk factors for the development of a complication among patients with thoracolumbar spine injuries who undergo surgical stabilization (14). Multivariate logistic regression revealed three factors predictive of a major complication: American Spinal Injury Association (ASIA) score, Charlson Comorbidity Index (CCI), and administration of high-dose steroids (dosage based on the NASCIS 2 and 3 protocols).

In 2014, a case report was published of a woman who developed ASCI following elective cervical laminectomy for cervical stenosis (15). Post-operatively, she received two separate courses of intravenous steroids, after which she developed secondary adrenal insufficiency. This case is the fourth such instance reported in the literature of adrenal insufficiency following the administration of steroids for ASCI, and it highlights the severity of the complications associated with MP.

Practice patterns and usage of MP for the treatment of ASCI

Despite a lack of concrete scientific data to support the notion that MP offers any significant long-term benefits for patients with ACSI, and the ample evidence of the contrary, physicians continue to prescribe this medication. Some physicians genuinely believe in the benefits of MP for ASCI patients. Others feel a need to do everything possible for these patients, and, for some, doing something is better than doing nothing. Still other physicians fear that failure to institute high-dose steroid therapy to ASCI patients can become grounds for litigation. These attitudes have led to inappropriate application of the NASCIS recommendations to some patients. For example, although the NASCIS trials excluded patients with penetrating trauma to the spinal cord, misapplication of the data has resulted in patients with stab or gunshot wounds to the spinal cord receiving high-dose steroid therapy. Several surveys of various groups of physicians corroborate these facts.

In 2014, members of the US-based Cervical Spine Research Society were surveyed regarding their use of steroids for ASCI (16). Results were compared to a similar survey from 2006. Although there was a significant decrease in the number of surgeons using high-dose steroids in 2014 as compared with 2006, about half still used steroids to treat ASCI. Among these surgeons, 26% believed that steroids improved neurological recovery, 19% used steroids because of institutional protocol, and 26% gave them for medicolegal reasons. Neurosurgeons were less likely to prescribe steroids than orthopedic spine surgeons. Surprisingly, over half of the surgeons surveyed (71%) had firsthand experience with complications from steroid use. All of the surgeons recognized certain contraindications to the administration of steroids for ASCI: sepsis, GI bleed, and presentation >8 hours after injury.

Members of the Polish Society of Spinal Surgery were similarly surveyed (17). 73% of these surgeons treated ASCI patients with steroids. About one third believed in its effectiveness, 30% were adhering to institutional policy, and 37% feared litigation.

In the Czech Republic, a 2011 survey found that MP is used in all regional centers of emergency medical service (18). In spinal surgery centers, where ASCI patients are treated, 16% administer MP due to a belief in its efficacy, 21% for both efficacy and medicolegal reasons, and 63% give patients steroids for medicolegal reasons only.

In Germany, of all trauma, orthopedic, and neurosurgical departments that treat ASCI, 55% use MP (19). Ten percent of these centers use MP according to one of the protocols of the NASCIS 1 study, which has been outdated for many years. Reasons for administering MP are similar to other countries: effectiveness, common practice, and medicolegal concerns.

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Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Author: Seema Mittal Patel, MD, MPH
Editor: Michael L. Cheatham, MD
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Please direct any questions or concerns to: webmaster@surgicalcriticalcare.net