The Current Role of Steroids in Acute Spinal Cord Injury

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Key words
- Acute spinal cord injury
- ASCI
- ASIA classification system
- Methylprednisolone
- Steroids

Abbreviations and Acronyms
ASCI: Acute spinal cord injury
ASIA: American Spinal Injury Association
MP: Methylprednisolone
MRI: Magnetic resonance imaging
NASCIS: National Acute Spinal Cord Injury Study


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■ BACKGROUND: **Acute spinal cord injury (ASCI) is a catastrophic event that can profoundly affect the trajectory of a patient's life. Debate continues over the pharmacologic management of ASCI, specifically, the widespread but controversial use of the steroid methylprednisolone (MP). Treatment efforts are impeded because of limitations in understanding of the pathobiology of ASCI and the difficulty in proving the efficacy of therapies.**

■ METHODS: **This review presents the pathophysiology of ASCI and the laboratory and clinical findings on the use of MP.**

■ RESULTS: **The use of MP remains a contentious issue in part because of the catastrophic nature of ASCI, the paucity of treatment options, and the legal ramifications. Although historical data on the use of MP in ASCI have been challenged, more recent studies have been used both to support and to oppose treatment of ASCI with steroids.**

■ CONCLUSIONS: **ASCI is a devastating event with a complex aftermath of secondary damaging processes that worsen the initial injury. Although the results of NASCIS (National Acute Spinal Cord Injury Study) II and III trials led to the widespread adoption of a high-dose MP regimen for patients treated within 8 hours of injury, subsequent studies have called into question the validity of NASCIS conclusions. Further evidence of the ineffectiveness of the MP protocol has led to declining confidence in the treatment over the last decade. At the present time, high-dose MP cannot be recommended as a standard of care, but it remains an option until supplanted by future evidence-based therapies.**

INTRODUCTION

Acute spinal cord injury (ASCI) is a catastrophic event that can profoundly affect the trajectory of a patient's life, with wide-reaching social and economic effects (79). Loss of independence, paralysis or paresis, and other detriments to quality of life cause significant morbidity and mortality through pneumonia, cardiovascular disease, and suicide (90). Accompanying injuries are present in 78.5% of cases (20). Advances in emergency care and rehabilitation have led to improvements in projected life expectancy for these patients to 70% of normal for patients with tetraplegic ASCI, 84% of normal for patients with paraplegic ASCI, and 92% of normal for ASCI patients with incomplete lesions. Regardless of such advances, the immediate medical management of ASCI is far from optimal (26, 90).

Approximately 2.6% of patients at major trauma centers present with ASCI (20). Approximately 10,000–12,000 such injuries occur in the United States each year (7, 28, 41). Estimates for annual incidence of ASCI range from 11.5–53.4 per 1 million in developed countries; adjustment to account for patients who die before reaching the hospital places the figure at 71 per 1 million (20, 28, 80). This injury is particularly distressing because patients are more likely to be young. There is a male-to-female ratio of 3:1 to 4:1, and the peak incidence is between the ages of 10 and 40 years, although the average age has been increasing (28, 80). Motor vehicle accidents, where the patient is in the vehicle, a pedestrian, or a bicyclist, account for approximately 50% of ASCI cases (28, 80, 85). Work accidents, falls, violence, and recreational injuries account for the remainder of cases (28, 80, 85). Alcohol is found to play a role in the injuring incident in >25% of cases (28, 80, 85). Injuries are concentrated in the cervical spine: 55%–65% of ASCIs occur from C1 to C7-T1, with the remainder distributed through the rest of the spine (20, 28, 80). Pediatric patients account for 0.7%–9.5% of ASCI; they have higher cervical level injury (C1-C4) and have a poorer prognosis associated with younger age (18, 41, 43, 78). Spinal cord injury without radiologic abnormality is particularly possible in younger pediatric patients and infants because of the greater elasticity of the spinal column (18, 41, 43, 69, 78). These injuries are often associated with sports-related injuries or child abuse and are associated with a worse prognosis for neurologic outcome (18, 41, 43, 69, 78).

Outcome is often poor for ASCI. An estimated one third to two thirds of patients die before reaching the hospital (20, 24, 28, 52, 80, 85, 90). Of patients who arrive at the hospital, 4.4%–21.4% die during the initial hospital admission, and another 13% die within 1 year (20, 24, 28, 52, 80, 85, 90). Respiratory complication is the most common cause of death after admission (24, 52). Using the American

Spinal Injury Association (ASIA) classification system for neurologic injury in ASCI, 45% of patients have complete impairment with no motor or sensory function through S4-S5 (grade A), 15% have incomplete impairment with sensory but no motor function below the injury level (grade B), 10% have incomplete impairment with sensory function and muscle grade <3 below the injury level (grade C), 30% have incomplete impairment with sensory function and muscle grade of ≥3 below the injury level (grade D), and 10% have no impairment (grade E) (62, 80). Improvement in impairment grading is seen during initial hospital stay in 36% of patients, and 11% see continued improvements within 2 years; however, neurologic gains are usually limited to only 1 ASIA grade (21, 39). Older age, higher cervical level, Glasgow Coma Scale score on arrival, ASIA grade, and multiple trauma are the most important predictors of hospital morbidity and mortality (24, 27, 80).

Despite the poor long-term medical prognosis including respiratory, cardiovascular, renal, and psychological problems coupled with loss of neurologic functions, 60%–75% of survivors of ASCI report good or excellent quality of life even after decades of living with impairment (39, 89). However, measuring quality of life for these individuals remains difficult to standardize (29). There is a pressing need to improve care for these injuries. Debate continues over the pharmacologic management of ASCI, in particular, the widespread but controversial use of the steroid methylprednisolone (MP), a potent glucocorticoid. Treatment efforts are curtailed because of limitations in understanding of the pathobiology of ASCI and the difficulty in proving the efficacy of therapies. Finally, prevention remains the most important factor in mediating these injuries (90).

PATHOPHYSIOLOGY OF ASCI

ASCI is characterized by primary mechanical insult from initial impact and compression, followed by secondary cellular and molecular damage that begins minutes after injury and lasts days. Primary injury typically involves severe contusion or compression of the spinal cord and rarely transection (50). The primary lesion can deteriorate further through secondary processes. Evidence has emerged regarding the main mechanisms of secondary injury, including inflammation, edema, ischemia, hemorrhage, electrolyte imbalance, arachidonic acid release, glutamate excitotoxicity, apoptosis, and lipid peroxidation leading to membrane lysis (14, 22, 55, 59, 80, 84, 86). These secondary insults lead to cell death, gradually causing expansion of the primary lesion and cavitation of the injured spinal cord tissue (14, 19, 33, 36, 50, 84).

Because these secondary mechanisms are delayed after the initial trauma, treatment during the acute time period has the potential to prevent or reduce neurologic deficits resultant from secondary injury. However, onset can be very rapid; of the processes thought to be most damaging, ischemia occurs within minutes, and lipid peroxidation and inflammation occur within hours, compounding the initial mechanical trauma (4, 21, 22, 84, 86). Surgery to decompress the spinal cord and stabilize the vertebral column can be important to prevent further mechanical injury, but it most likely cannot halt secondary processes (32). Potential interventions to limit secondary injury are under investigation in animal models, including erythropoietin, systemic hypothermia, nonsteroidal antiinflammatory drugs, progesterone, estrogen, and G_{M1} ganglioside; the last mentioned has progressed to human trials (46, 54). More recent advances notwithstanding, the most common pharmacologic treatment to mediate secondary damage in ASCI is MP, which is believed to act by inhibition of lipid peroxidation, inflammation, and ischemia (16, 21). The risks and benefits of limiting these processes are complicated and not well understood in patients with ASCI, adding to the debate over MP (30, 49).

TREATMENT WITH MP

The earliest example of steroid-based treatment for ASCI came from Ducker and Hamit in 1969 (31). A body of evidence for improved neurologic outcomes after MP treatment in ASCI was provided by NASCIS (National Acute Spinal Cord Injury Study) I in 1984, NASCIS II in 1990, and NASCIS III in 1997 (8, 9, 12). Based on NASCIS findings, a high-dose MP protocol calls for an intravenous 30 mg/kg bolus followed by an intravenous 5.4 mg/kg/hour maintenance infusion up to either 24 hours after trauma (if begun within 3 hours of injury) or 48 hours after trauma (if begun within 3–8 hours). MP is not used after 8 hours posttrauma or for penetrating ASCI, and its efficacy is unproven in pediatric patients and patients with injuries to the cauda equina (9, 12, 21, 68).

Although controversial, this protocol has become a widely used treatment. A survey of trauma services in the United Kingdom in 2006 found that about 68% administer MP for ASCI (38). Delegates at the European Cervical Spine Research Society meeting were surveyed, and 75% reported using MP, although 68% used it with concerns about its risks (67). In a 2006 survey of North American spine surgeons, 90.5% reported using MP for ASCI; however, only 24.1% were confident in its effect on clinical outcomes (34). Although it is commonly used, MP remains a controversial treatment because both clinical impact and safety have been heavily disputed (60, 65).

LABORATORY FINDINGS RELATED TO MP

Much of the groundwork in animal studies supporting MP argues that it inhibits secondary injury after ASCI. In 1979, Hall and Baker (42) showed that MP acutely enhanced cat spinal reflex transmission by increasing synaptic discharge; these authors argued that MP represented a possible treatment for central nervous system injuries. In 1981, Means et al. (63) found in cats that treatment with MP after spinal cord injury resulted in significantly greater recovery of neurologic function ($P < 0.001$) and significantly smaller lesion volume ($P < 0.004$) compared with no treatment. Braughler and Hall (15, 17) reported that MP in cat spinal tissue both acutely strengthened Na^+,K^+-ATPase activity (thought to be depressed in secondary damage from spinal cord trauma) and prevented increases in lactate and decreases in pyruvate, indicating that secondary ischemia was avoided. Hall and Braughler in 1982 (16) and Anderson et al. in 1985 (1) showed that MP in cat spinal tissue reduced lipid peroxidation after spinal cord trauma, another important mechanism of secondary damage. More recently, the role of apoptosis in ASCI has emerged. In 1998, Emery et al. (35) observed apoptosis in 14 of 15 patients with ASCI. In 1999, Ray et al. (76) demonstrated that MP helped limit apoptosis in rat spinal cords after trauma.

Modulation of the inflammatory response to ASCI has been promising but complicated. In 1995, Bartholdi and Schwab (3) found that although MP inhibits early infiltration by neutrophils and macrophages in rats, the steroid does not limit or slow secondary cell death. Because glucocorticoids are known to suppress inflammation, some investigators have suggested that the clinical effect of MP may rest on this function alone (2). Donnelly and Popovitch (30) and Jones et al. (49) emphasized that pharmacologic intervention on inflammation must take into account both the beneficial and the harmful effects of inflammatory processes.

Some animal studies downplay the effectiveness of MP. Lee et al. (57) found that MP limited death of oligodendrocytes but not neurons after ASCI in a rat model. Koyanagi and Tator (51) treated rats with MP after ASCI and found no improvement in spinal cord blood flow relative to control. Rabchevsky et al. (74) found that MP had no effect on lesion volume or recovery of motor function in rats. Merola et al. (64) reported mixed results in rats, with MP reducing edema but failing to halt necrosis. Rabinowitz et al. (75) found that MP had no effect on neurologic recovery in dogs with ASCI, and MP alone was less effective than surgical decompression. However, overall, the literature from laboratory results is suggestive of potential benefits from MP treatment in animals, warranting its study in humans.

CLINICAL FINDINGS RELATED TO MP

Evidence on the effect of MP in patients with ASCI has not been definitive. Support for the clinical use of MP comes primarily from NASCIS II and III. In 1984 and 1985, Bracken et al. (8, 11) reported on NASCIS I, a multicenter, double-blind, randomized trial. From 1979–1981, 330 patients were randomly assigned to either a low-dose (100 mg bolus for 10 days) or a high-dose (1000 mg bolus for 10 days) MP protocol. The authors found no significant difference between the 2 groups at 6 weeks, 6 months, and 1 year of follow-up; they did find an increased risk of infection with high-dose MP. However, they noted the need for a placebo comparison to test the effect of MP, leaving the door open to further investigation.

In 1990 and 1992, Bracken et al. (9, 10) reported on NASCIS II, a multicenter, double-blind, randomized, placebo-controlled trial. Suspecting that the earlier dosage of MP was too low owing to evidence from animal studies (16, 17), the authors adapted their earlier protocol to use a bolus of 30 mg/kg followed by infusion of 5.4 mg/kg/hour for 23 hours. They treated 162 patients using this regimen with MP; 154 patients using this regimen with naloxone, another candidate drug; and 171 patients with a placebo. Naloxone was not found to have significant effects. After 6 months of follow-up, the authors found that among patients treated within 8 hours of injury, the patients receiving MP ($n = 62$) had improved neurologic functions compared with patients receiving placebo ($n = 65$), with significant increases in touch sensation ($P = 0.030$), pinprick sensation ($P = 0.016$), and muscle strength ($P = 0.033$) (9). After 1 year of follow-up, improvement in motor function remained ($P = 0.030$), but no significant advantage persisted in sensory function. Mortality and major morbidity were similar between the 3 arms (10).

In 1997 and 1998, Bracken et al. (12, 13) reported on NASCIS III, a multicenter, double-blind, randomized trial. They treated 166 patients using the existing 24-hour MP protocol; 167 patients with an extended 48-hour MP protocol, lengthening the infusion; and 166 patients with tirilazad instead of MP for 48 hours. There was no significant difference between the 3 protocols for patients treated within 3 hours of injury. The authors found that in patients who began treatment 3–8 hours after trauma, the 48-hour MP protocol delivered significantly greater recovery of motor function compared with the 24-hour MP protocol after 6 weeks ($P = 0.04$) and 6 months ($P = 0.01$) of follow-up. Additionally, functional independence measures were found to be higher after 6 months for patients in the 48-hour MP protocol in total score ($P = 0.08$), self-care ($P = 0.03$), and sphincter control ($P = 0.01$). However, patients in the 48-hour MP protocol had an increased risk of severe sepsis ($P = 0.07$) and pneumonia ($P = 0.02$) (12). After 1 year of follow-up, the authors continued to observe greater recovery of motor function for patients in the 48-hour MP protocol versus the 24-hour MP protocol ($P = 0.053$). However, the differences in functional independence measures were no longer significant, and the 48-hour MP protocol was associated with higher risk of urinary tract infection ($P = 0.01$) (13). The authors did not use a placebo group for comparison.

Combined, NASCIS II and III formed the basis for the MP protocol currently in widespread use for ASCI. However, the validity of the NASCIS findings has been disputed. Nesathurai (68) was one of the earliest authors to raise doubts about the NASCIS trials, commenting in 1998 that in NASCIS II, comparison of the overall treatment group and placebo group produced no significant difference in outcome, an important limitation to the value of subgroup analysis. Given the arbitrary selection of the 8-hour time limit, Nesathurai argued that the NASCIS authors had analyzed every discrete window of opportunity (timeframe) for a significant finding; such a method would yield a false-positive result with $P < 0.05$ one out of 20 times by the definition of the P value. NASCIS II had 78 such potential subgroups, and NASCIS III had 36; such post hoc findings were not robust. In addition, Nesathurai (68) noted that although the data may be neurologically significant, they may not have been functionally significant in terms of self-care, mobility, and quality of life. In 2000, Coleman et al. (25) reported more statistical issues. Among other findings, these authors reanalyzed the NASCIS III results by adjusting for an excess of patients with minor injuries (and minimal amount of recovery), negating the statistical significance of the original findings.

Also in 2000, Hurlbert (44) called into question the arbitrary 8-hour time frame in NASCIS II owing to the lack of physiologic basis. Additionally, Hurlbert noted the inappropriate exclusion of noncompliant patients (a statistical fallacy that introduces bias) in the reporting of NASCIS III results and the loss of $P < 0.05$ significance after 1 year of follow-up. Hurlbert (45) followed up in 2001 with a literature review, concluding that the primary outcomes of NASCIS II and III were not significant and that MP should not be recommended for use in the treatment of ASCI. In concurrence with Hurlbert, Short et al. (81) called into question the NASCIS II results. The authors noted that other prospective studies had failed to validate NASCIS II, while raising concerns about the safety of MP given certain findings of increased mortality in animal studies. A more recent review of NASCIS II and III by Sayer et al.

in 2006 (79) again raised doubts about the NASCIS findings, reasoning that they were most likely due to selective subgrouping or statistical artifacts. Additional data from NASCIS II revealed no benefit from MP for patients with complete ASCI. Sayer et al. (79) also noted that the primary finding of NASCIS II arose from an analysis of patients treated before 8 hours ($n = 127$), who accounted for only 44% of the overall study population ($n = 487$).

Novel evidence arguing against the use of MP has been accumulating. Poynton et al. (71) retrospectively reviewed 71 patients, 63 of whom were followed up after 29.6 months on average, and found no significant effect of corticosteroids on neurologic recovery. Gerndt et al. (40) retrospectively reviewed 140 patients with ASCI, 93 of whom were treated using the NASCIS-recommended protocol. Although MP treatment was associated with 2.6 times higher rates of pneumonia, more days on the ventilator, and longer intensive care unit stays, there was no difference in mortality. Pointillart et al. (70) reported a prospective, randomized trial of 106 patients; 100 patients were available for follow-up after 1 year. Patients were treated with MP, nimodipine, both MP and nimodipine, or neither MP nor nimodipine. The authors observed no benefit to neurologic recovery from any medication but did find a higher rate of hyperglycemia ($P < 0.05$) among patients treated with MP. In 2001, Matsumoto et al. (61) reported a double-blind, randomized, placebo-controlled trial of MP in 46 patients with cervical ASCI. Patients treated with MP had significantly more pulmonary ($P = 0.009$) and gastrointestinal ($P = 0.036$) complications and were more likely to have pulmonary complications if >60 years old ($P = 0.029$). However, overall, there was no significant difference in total complication rates between the 2 groups.

In 2002, Qian et al. (72) noted that the dose of MP in the NASCIS-recommended protocol was higher than any other indication and speculated that such high levels of MP could cause acute corticosteroid myopathy, severe sepsis, and pneumonia. The authors argued that myopathy would cause temporary muscle weakness that would resolve within the NASCIS follow-up time frame, creating a false appearance of improved recovery for patients treated with MP. Qian et al. (73) followed up with a prospective cohort study published in 2005, in which they found signs of acute corticosteroid myopathy in muscle biopsy specimens of 4 of 5 patients with ASCI treated with the MP protocol and zero of 3 patients with ASCI not treated with MP.

In 2008, Suberviola et al. (83) retrospectively reviewed 82 patients with ASCI; 59 patients had been treated with MP. They observed an increased risk of respiratory tract infection ($P = 0.02$), overall infection ($P = 0.004$), and hyperglycemia (odds ratio, 17.0; 95% confidence interval, 4.52–66.3) and found no significant improvement in neurologic recovery. In 2009, Ito et al. (48) reported a prospective cohort study of 79 patients with cervical ASCI in which 38 patients received MP and 41 did not. The authors found no significant difference in neurologic improvement after 3 months of follow-up but did find significantly greater rates of infectious complications (respiratory tract, urinary tract, and wound) in the patients treated with MP ($P = 0.028$).

Although the literature criticizing the NASCIS trials is significant, there are several studies that continue to support the use of MP. In 2006, Tsutsumi et al. (87) retrospectively studied 70 patients with cervical ASCI; 37 patients received MP within 8 hours of injury using the NASCIS II protocol (dose maintenance to 24 hours posttrauma), and 33 did not receive MP. The authors found no advantage to MP treatment for patients with complete injuries (ASIA grade A). However, for patients with incomplete injuries, MP treatment was associated with greater improvement in motor score at 6 months of follow-up ($P = 0.0049$). No significant relationship between MP and complication rate was found. Based on these results, Tsutsumi et al. (87) recommended the adoption of the NASCIS II protocol but not the extended NASCIS III protocol.

An alternative theory of MP efficacy through hemorrhage control has also arisen. In 2007, Leypold et al. (58) retrospectively studied magnetic resonance imaging (MRI) of 82 patients with ASCI; 48 of the patients were treated with MP. The authors found that MP treatment correlated with decreased size of intramedullary hemorrhage ($P = 0.04$) but not edema. This effect could potentially limit secondary damage in ASCI; Miyanji et al. (66) correlated intramedullary hemorrhage on MRI with ASIA motor scoring of 100 patients (mean follow-up, 7.3 months; $P < 0.001$). However, Boldin et al. (6) performed a prospective cohort study of 29 patients with cervical ASCI who underwent surgery and observed that MRI findings of edema size (but not hemorrhage) were predictive of worse neurologic recovery in a dose-response fashion. Further studies are needed to assess the effect of MP on hemorrhage, edema, and overall neurologic outcome.

DISCUSSION

The use of MP remains a contentious issue, in part because of the catastrophic nature of ASCI, the paucity of treatment options, and the legal ramifications. The current, widely used MP protocol is an unsatisfactory medical answer to the problem of ASCI. The evidence supporting use of MP in animal studies was promising, but clinical trials have produced mixed results. The NASCIS findings were limited to minor increments in motor function across many muscle groups (9, 12). Given the serious methodologic flaws that have been identified (25, 44, 65, 68, 71, 79, 81), the NASCIS recommendations cannot be accepted as proven.

Adaptation of the delivery of MP may provide safe and effective treatment. Extensive lymphocytopenia in rat organs has been observed after MP treatment of ASCI, histologically explaining the infectious complications associated with MP (53). Avoiding this global steroid effect may be key to shifting risk-benefit considerations. Chvatal et al. (23) developed a topical MP vehicle using nanoparticles embedded in agarose hydrogel that provided local reduction of lesion volume in a rat model of ASCI, while potentially avoiding systemic exposure to MP. This method has yet to reach human trials. Although MP is not a definitive treatment for ASCI at this time, there may be a role for MP in treating ASCI through improved indications and techniques.

Therapy for ASCI may arise through entirely different drugs. MP is a blunt instrument to suppress inflammation. A more nuanced approach may be necessary given the inflammatory mix of injury, neuroprotection, and repair (5, 30, 49). A rational modulator of immune function could prove effective by limiting the damages caused by inflammation, while

preserving or enhancing its advantageous effects both locally and systemically (30). A nonsteroidal pharmacologic approach may be necessary to address other secondary damage mechanisms in ASCI. Given limitations to currently studied candidate drugs for the management of secondary injury, research into the regeneration of ASCI by novel therapies, such as stem cell transplantation, may prove fruitful (47). Extensive guidelines for future trials have been published by the International Campaign for Cures of Spinal Cord Injury Paralysis, establishing a useful and rigorous standard by which definitive investigations can proceed (37, 56, 82, 88). However, until a therapy is supported with robust, reproducible evidence, a definitive standard of care for ASCI remains lacking.

Given this vacuum, the status of MP as placeholder treatment for ASCI explains its continued popularity in practice despite its questionable standing in research. There is limited evidence supporting the use of MP, but there is no other treatment with any evidence behind it. As Rozet (77) opined, when asked "to give or not to give," giving the only option available may be, after all, the only option.

CONCLUSIONS

ASCI is a devastating event with a complex aftermath of secondary damaging processes that worsen the initial injury. In animal models, MP has been shown to moderate some of the implicated mechanisms of secondary injury, motivating its study in humans. Results of NASCIS II and III led to widespread adoption of a high-dose MP regimen for patients treated within 8 hours of injury, providing the first pharmacologic therapy for ASCI. However, the NASCIS analysis was flawed, and subsequent studies have called into question the validity of its conclusions. Further evidence of the ineffectiveness of the MP protocol and its association with complications has led to declining confidence in the treatment over the last decade. At the present time, it cannot be recommended as a standard of care, but it remains an option until supplanted by future evidence-based therapies.

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