The Current Role of Steroids in Acute Spinal Cord Injury

Mohamad Bydon, Joseph Lin, Mohamed Macki, Ziya L. Gokaslan, Ali Bydon

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


Department of Neurosurgery and Spinal Outcomes Laboratory, Johns Hopkins Hospital, Baltimore, Maryland, USA

To whom correspondence should be addressed:
Ali Bydon, M.D.
[E-mail: abydon1@jhmi.edu]

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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.