Strategies of Medical Intervention in the Management of Acute Spinal Cord Injury

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Study Design. Literature review.

Objective. The purpose of this paper is to review clinical treatment strategies and future developments in the treatment of acute spinal cord injury.

Summary of Background Data. The treatment of acute spinal cord injury continues to be supportive. The search for specialized pharmacologic agents to prevent secondary injury and promote repair or regeneration remains heated.

Methods. Medline search from 1996 to present limited to clinical research and basic science review articles in the English Language.

Results. Steroids continue to be administered in the clinical setting of acute spinal cord injury primarily out of peer pressure and fear of litigation. Basic science experiments suggest that modulation of post-traumatic inflammation may provide the best opportunity to arrest the secondary injury cascade. Protein kinase and metalloproteinase inhibition are promising treatment strategies. Regeneration techniques are concentrating on cell transplantation and manipulating glial receptors and protein production. Clinical investigations are limited to Phase III trials on a very select few of these drugs.

Conclusions. While many advances in the basic science of spinal cord injury provide optimism for future treatments, clinical science lags. At present, there are no pharmacologic strategies of proven benefit. Although steroids continue to be given to patients with spinal cord injury in many institutions, evidence of deleterious effects continues to accumulate. Current standard of care management includes support of arterial oxygenation and spinal cord perfusion pressure.

Key words: trauma, medical management, therapy, paraplegia, quadriplegia. **Spine 2006;31:S16–S21**

The devastating consequences of traumatic spinal cord injury (SCI) continue to haunt the corridors of medical science now into the 21st century. Few conditions cause such degree of permanent disability in previously high functioning individuals who after injury remain fully cognitive and become faced with the Herculean challenges of reintegration into society. Whether it is by walking, riding, jumping, or flying, it is the individual engaged in enjoying life that most frequently becomes afflicted by this tragic condition in the span of a heartbeat or two.

The consequences of SCI are as permanent as they are sudden and devastating. Despite a rich tradition of medical successes in the last 100 years spanning the discovery of insulin to gene splicing technology, the progress in the treatment of acute SCI has been painstakingly slow. However, a better understanding of the pathophysiology underlying SCI has emerged which currently guides research efforts and clinical treatment strategies (Table 1). Structural damage that occurs in the spinal cord after injury is broadly categorized into primary and secondary mechanisms. Primary cell death happens at the time of injury. It is due to direct mechanical forces such as shear, laceration, distraction, and compression applied to the spinal cord causing structural disruption of neuronal, glial, and vascular structures with immediate indiscriminate cell death.

Within minutes of primary injury, a subsequent cascade of biochemical events is initiated, leading to delayed or secondary cell death that evolves over a period of days to weeks. A variety of complex chemical pathways are likely involved including hypoxia, ischemia, intracellular and extracellular ionic shifts, lipid peroxidation, free radical production, excitotoxicity, eicosanoid production, neutral protease activation, prostaglandin production, and programmed cell death or apoptosis. The end result is that, days or weeks after SCI, a population of neuronal and glial support cells die that otherwise survived the initial injury.

The distinction between primary and secondary injury is not well defined, as it is likely that even primary injury evolves over a period of time. Furthermore, the amount that secondary injury contributes to the overall neurologic deficit resulting from SCI is not known. Atomic absorption spectroscopy suggests that it may account for only 10% of the total pathology after SCI.[1] However, preservation of even a small amount of functional neuronal tissue may allow independent ambulation. Animal studies suggest that as little as 10% of long tract integrity may be all that is necessary for locomotion to occur.[2]

Quite clearly, the only treatment for primary injury at this time is prevention. Medical strategies for the treatment of acute SCI are directed at ameliorating the degree of secondary injury that follows the initial injury, and are referred to as neuroprotective treatments. The promise of a cure for SCI rests with regeneration strategies that aim to restore disrupted spinal cord tissue, such as through cell transplantation. The purpose of this paper is to review current clinical and basic science research to provide an overview to the clinician of where the science

Table 1. Strategies of Medical Intervention in the Treatment of Acute SCI With Clinical Evidence or Nearing Clinical Trial

Treatment Strategy	Mechanism	Clinical Status
Primary injury: regeneration		
Stem cell transplantation	Implantation of pluripotential progenitor cells that differentiate into functional neuronal and glial tissues	Phase I (feasibility and safety)
Gene therapy	Reprogramming surviving cells to adopt a regenerative profile	None
Electrical stimulation	Manipulation of nerve growth and guidance along electrical gradients	Phase I (feasibility and safety)
Secondary injury: neuroprotection		
Support of oxygenation and spinal cord perfusion pressure	Reduction of the ischemic penumbra surrounding the zone of primary necrosis	Class III clinical evidence: recommended treatment
Methylprednisolone	Free radical scavenger and inhibition of lipid peroxidation	Class I clinical evidence controversial: treatment option
GM-1 ganglioside	Anti-excitotoxic properties, reduced apoptosis	Class I clinical evidence: no sustained effects
Minocycline	Pro- and anti-inflammatory properties, inhibition of free radical production, reduced apoptosis	Phase I (feasibility and safety)
Cethrin	Rho inhibition, which causes down-regulation of growth inhibitor production	Phase I (feasibility and safety)
Activated macrophage implantation	Cytokine secretion, antigen-presenting activity	Phase I (feasibility and safety)

of SCI treatment is now and take a glimpse at what the future holds.

■ Methods

Clinical publications reporting on medical management of acute SCI were identified from a Medline search indexed by key words "spinal cord injury" and "treatment" limited to 1996 and later. Basic science evidence was restricted to initiatives nearing clinical applications.

■ Results

A total of 346 publications were identified from a Medline search of acute spinal cord injuries from 1996 to the present, limited to human studies written in English. Titles and abstracts were examined, appropriate content selected, and manuscripts reviewed. The overview is presented in two sections: clinical evidence and basic science initiatives.

Clinical Evidence

Support of Spinal Cord Perfusion Pressure

Despite a number of exciting treatments being developed in the basic science arena, clinical applications of pharmaceutical agents for acute SCI remain relatively limited. By far the most important considerations for medical management remain arterial oxygenation and blood pressure support. It is well established that both hypoxia and ischemia compound traumatic central nervous system (CNS) injury in both animals and humans. Hypotension similarly aggravates SCI by reducing spinal cord blood flow and perfusion.[3–11] Although no Class I or II evidence exists, Class III clinical evidence suggests that optimizing spinal cord perfusion may improve clinical outcome. In 1976, Zach et al published his observations that 117 patients with acute SCI recovered more function than expected when treated with a combination of dexamethasone, rheomacrodex, and hydergine.[12] Delayed admission and resulting delays in volume support

were associated with less recovery. Similar results were echoed by Levi et al who reported improved clinical outcome with hemodynamic support.[13,14] Tator et al found improved recovery in 144 SCI patients given standardized care including volume augmentation.[15] More recently, Vale et al noted that of 77 patients with acute SCI, 92% of their incomplete cervical cord injured patients, and 88% of their incomplete thoracic cord injuries regained the ability to walk, leading them to conclude that early volume resuscitation and blood pressure augmentation optimizes the potential for neurologic recovery.[16] The compelling nature of these animal and human studies has resulted in SCI treatment guidelines that recommend avoidance of systolic blood pressure < 90 mm Hg and maintenance of mean arterial blood pressure between 85 and 90 mm Hg for the first week in patients with acute injury.[17]

Steroids

Methylprednisolone has enjoyed widespread use in the setting of acute SCI since the publication of the preliminary NASCIS II results in 1990.[18] However, the results of the first NASCIS trial were actually published in 1984.[19] A total of 330 patients were randomized to receive either 25 mg or 250 mg of methylprednisolone sodium succinate (MPSS) every 6 hours for 10 days after a 100-mg bolus. No differences in clinical improvement were observed between the two groups, but only 54% were available for follow-up at 6 months. However, the high-dose group demonstrated a significantly higher incidence of wound infection ($P = 0.01$) and a trend toward more sepsis, pulmonary emboli, and death that did not reach statistical significance.

Four years later, both the medical community and popular press welcomed high-dose steroids for the treatment of acute SCI based on the preliminary NASCIS II results. Long-term (1 year) follow-up data were made available in 1992.[20] This prospective, randomized, dou-

ble-blind, controlled, multicenter trial examined the difference between high-dose MPSS, naloxone, and a placebo given through a 24-hour period after SCI. From 10 centers, 487 patients were successfully randomized with 95% follow-up at 1 year. No differences were observed in neurologic outcomes between the three groups. Twice as many pulmonary emboli and wound infections were seen in the steroid group compared with controls, but this did not reach statistical significance.

In *post hoc* analyses, patients treated with MPSS within 8 hours of their SCI showed a statistically significant improvement in motor and sensory scores at 6 months, but this effect persisted for motor scores only at 1 year. While a mean improvement of 5 points on the motor grading scale was reported for total right-sided scores, when distributed over 2 or 3 muscle groups, an improvement of 1 to 2 points in an individual muscle, particularly one of Grade 0 strength, becomes of questionable functional significance.[21] In addition, the rationale behind the arbitrary *post hoc* 8-hour cutoff has never been clarified.[22] As expected under the conditions of negative primary hypotheses, additional *post hoc* analyses suggested that patients receiving MPSS after 8 hours did more poorly than controls.[23]

Tirilazad mesylate was developed as a pharmaceutical agent to improve on the membrane stabilizing and free radical scavenging activities of methylprednisolone. It was brought to clinical trial for SCI in the NASCIS III study.[23,24] A total of 499 patients were randomized to one of three treatment groups from 16 centers across North America: 24-hour MP, 48-hour MP, or 48-hour tirilazad mesylate. There were no differences between any of the groups with respect to primary outcome measures such as motor, sensory, or FIM scores at the 1-year endpoint. However, *post hoc* analyses once again showed a potentially interesting observation. Patients treated with the 48-hour MP protocol between 3 and 8 hours after injury had slightly better motor scores than the 24 hour MP group at 6 weeks and 6 months. At 1 year, the difference in raw motor scores between the two groups was 1 point. The change from baseline (admission) motor scores was 14 points for the 24 hour group and 19 points for the 48 hour group ($P = 0.054$). Sensory scores were no different between the groups.

Adverse side effects associated with methylprednisolone administration were also encountered. Severe pneumonia afflicted twice as many patients, while severe sepsis was contracted by four times as many patients in the 48-hour MP group compared with the 24-hour group. Six times as many patients died from respiratory complications in the 48-hour MP group ($P = 0.056$).

Other clinical studies have been published attempting to define the effects of MP on SCI. These have been reviewed in detail previously.[25] Only two other Class I clinical trials have been performed in a prospective randomized manner, neither with the power of the NASCIS studies. In both, the primary outcome measures proved no different between treatment and control groups.[26,27]

However, harmful side effects associated with the administration of methylprednisolone at NASCIS II and III doses continue to be reported including myopathy.[28] The CRASH trial, in which MP was randomly given to 10,008 head injured patients in doses comparable to the NASCIS III 48 hour protocol, was closed before reaching its target population of 20,000 because interim analyses showed the relative risk of death to be 1.18 for the MP-treated patients compared with controls ($P = 0.0001$).[29] These results suggest that, for every 30 patients treated with 48-hour MP, one will die because of the drug.

Over the past 10 years, a lively debate has ensued in the literature over whether or not steroids should be used at all in SCI. Many authors have tried to further distill and objectify the results of the NASCIS studies, most with unfavorable conclusions.[21,30–33] Unfortunately, the data from NASICS II and III (NIH funded studies) have never been released for independent review. The AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves Guidelines committee reviewed all available evidence and concluded that " . . . methylprednisolone for either 24 or 48 hours is . . . an option in the treatment of patients with acute spinal cord injuries that should be undertaken only with the knowledge that the evidence suggesting harmful side effects is more consistent than any suggestion of 'clinical benefit'."[34] Despite these considerations, many physicians continue to prescribe methylprednisolone for acute SCI even today. However, when the reasons for such behavior are examined, more than 70% do so because of the perception that everyone else does or out of fear for litigation, while only 17% of treating physicians prescribe steroids because they believe them to be efficacious (Figure 1).[35]

GM-1 Ganglioside

The only other medication to be formally tested through clinical trial for use in SCI is GM-1 ganglioside (Sygen). It
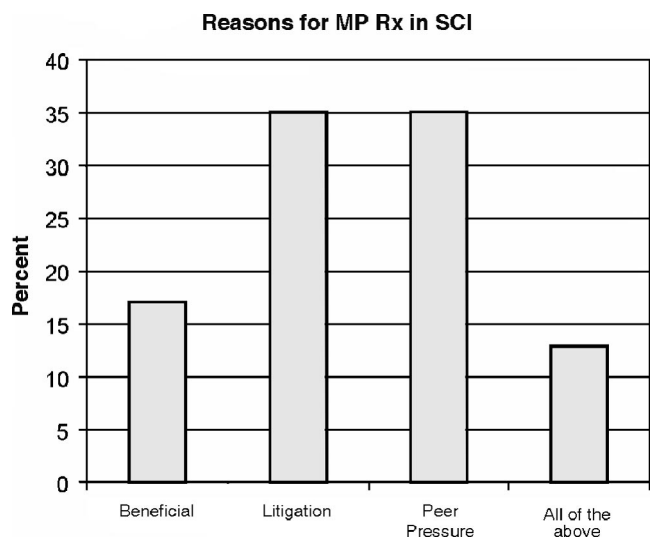

Figure 1. Results of 60 spinal surgeons surveyed about their reasons for methylprednisolone administration in SCI. Modified from Hurlbert RJ, Moulton R. Why do you prescribe methylprednisolone for acute spinal cord injury? *Can J Neurol Sci* 2002;29:236–9.

is a compound normally found in cell membranes of CNS tissue in mammals and is thought to have antiexcitotoxic activity, promote neuritic sprouting, potentiate the effects of nerve growth factor, and prevent apoptosis. Initial results for functional recovery in SCI patients were very promising in those who received this drug compared with those receiving placebo.[36] However, in a much larger multicenter study, these results could not be reproduced during long-term follow-up.[37] Consequently, despite basic science and clinical evidence of neuroprotection activity, GM-1 ganglioside is not used in routine clinical practice to treat SCI at this time.

Basic Science Initiatives Nearing Clinical Trial

Cellular Bridges: Transplantation and Regeneration

Transplantation of progenitor or stem cells into the injured spinal cord continues to hold promise for future clinical regeneration strategies. Glial progenitor cells introduced into injured rodent spinal cords successfully differentiate into oligodendrocytes, myelinating surviving axons, enhancing conduction velocity, and improving function.[38–40] Neural differentiated embryonic stem cells survive transplantation into injured spinal cords and differentiate into astrocytes, oligodendrocytes, and neurons promoting functional recovery as well.[41]

Human embryonic stem cells can be amplified and differentiated into human oligodendrocytes that functionally integrate into the mouse spinal cord after transplantation.[42] Fetal stem cells have also been transplanted into primates 9 days after contusive midcervical SCI and have been shown to differentiate into neurons, astrocytes, and oligodendrocytes.[43] Histologic and behavioral outcomes were improved after 8 weeks compared with placebo treated animals.

Endogenous progenitor cells can be isolated from the human adult nervous system, propagated, and transplanted.[44–46] Although host-donor incompatibilities are avoided, this technique has so far been limited by the invasive nature of the CNS biopsy necessary to obtain the cells and the time required to expand the cell population before transplantation. Human olfactory ensheathing cells may also provide a source of progenitor cells for transplantation and repair. They have been shown to improve functional outcome in SCI animal studies.[47] However, the potential for clinical use is limited because of the relatively small number of cells available for harvesting, their resistance to *in vitro* culturing techniques, and their dependence on olfactory fibroblasts to propagate.[48]

As part of a Phase I clinical trial, porcine oligodendrocyte progenitors have been transplanted into patients with spinal cord injuries demonstrating safety but not efficacy.[49] Phase I testing for human embryonic stem cell transplantation in patients with SCI is expected within the next year or two.[50] However, these trials are not without their risks, particularly of undesirable regeneration producing pain and tumor formation.[51]

Electric field gradients have been studied extensively in animals as a means of influencing and guiding nerve growth after injury and in improving cell survival with mixed results. This technology has been recently applied to human SCI patients in a Phase I feasibility study.[52] Ten ASIA Grade A patients underwent implantation of oscillating field generators within 18 days of injury. The devices were well tolerated and no serious adverse events encountered. One-year follow-up suggested significant improvement in both motor and sensory scores. Additional studies are being planned.

Neuroprotection

Neuroprotective strategies are directed at preserving additional neuronal and glial loss (*i.e.*, secondary injury) following the primary or initial injury. As with maintenance of spinal cord perfusion pressure, methylprednisolone, and GM ganglioside, neuroprotective agents target some part of the post-traumatic biochemical cascade that occurs before homeostasis within the CNS is again reached. Inflammation that occurs following SCI has become fertile ground for research into neuroprotective strategies. In most instances, the premise is that certain aspects of inflammation are detrimental to the surviving neurons, their axons, and the supporting glia. Monoclonal antibodies targeted against the surface antigens of neutrophils, monocytes, macrophages, and even lymphocytes not only reduce the zone of injury following SCI but can improve neurologic outcome as well.[53,54] Modulation of chemokines released from these cells after SCI also appears to be helpful in ameliorating secondary injury.[55] Delivery of these agents (and others such as nerve growth factors) through genetically engineered cells may allow these treatments to be delivered locally, avoiding systemic side effects from higher intravascular doses.[56]

Minocycline is an antibiotic in the tetracycline family that is a metalloproteinase inhibitor with anti-inflammatory properties. It has been shown effective in reducing lesion size and improving neurologic function in mice and rats.[57–60] The mechanisms are likely multiple and involve regulation of growth factor bioavailability, anti- and pro-inflammatory properties, cellular signal transduction, and mediation of apoptosis.[61] A Phase II pilot study is presently underway investigating feasibility for a larger clinical trial at the University of Calgary.

The GTPase ras homology protein (Rho) is part of a biochemical pathway mediating growth inhibitors embedded in CNS myelin and the glial scar. Repulsive guidance molecules such as semaphorins and repulsive clotting factors make use of this pathway.[62–64] Rho inhibition promotes axonal regeneration, reduces secondary injury, and increases functional recovery in experimental SCI.[65–67] A multicenter clinical Phase 1 safety and tolerance study is currently underway, examining the effects of a Rho inhibitor (Cethrin) after SCI (Bioaxone Corp., Montreal, Quebec, Canada). The drug

is applied directly to the dura through surgical implantation following SCI.

Partial motor recovery has been observed in rats with complete spinal cord transections treated with local injection of macrophages activated by *ex vivo* incubation with peripheral nerve or autologous skin.[68] Macrophages activated in this way are thought to develop neuroprotective profiles such as the ability to secrete cytokines and undertake antigen-presenting activity. Results of a Phase I safety study in which autologous macrophages were implanted on the caudal border of the injured spinal cord in 8 motor and sensory complete patients have recently been published.[69] No serious adverse events were attributable to the study intervention and three patients improved to ASIA C status. A multicenter Phase II trial is currently underway.

■ Conclusion

The most important principles to follow in the treatment of patients with acute spinal cord injury are oxygenation, blood pressure support through volume replacement (and if necessary inotropes), and immobilization. Current basic science and clinical literature suggests that mean arterial pressures be kept around 85 mm Hg in the acute postinjury phase. Methylprednisolone administration for either 24 or 48 hours is still practiced in many centers but in the absence of either compelling or reproducible clinical evidence, in most cases because of peer pressure or for fear of litigation. Harmful side effects from the doses used in SCI have been described in multiple independent publications. Many new basic science initiatives hold promise for future treatments in SCI, both through neuroprotection and regeneration. A few are nearing formal clinical trial status. However, before embracing these agents as treatment options it is important that their beneficial or harmful effects be carefully documented. At present, there are no pharmacologic strategies of proven benefit.

■ Key Points

● The mainstay of medical management for acute spinal cord injury is oxygenation and blood pressure support in cases where the mean arterial pressure falls below 85 mm Hg.

● Administration of methylprednisolone for 24 or 48 hours for patients within 8 hours of injury is still practiced in many institutions. However, the evidence for efficacy is weak while the evidence for significant complications is well documented.

● Future treatment strategies in neuroprotection and regeneration are promising and nearing clinical trial. However, clinical evidence must be meticulously obtained, thoroughly analyzed, and carefully weighed before adopting any of these interventions as standard therapies.

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