Pharmacological Management of Acute Spinal Cord Injury

Alok Sharma*

**Introduction**

Medical care for acute spinal cord injury has advanced greatly in the last 50 years. Significant advances in recent years, including an effective drug therapy (e.g. methylprednisolone) for acute spinal cord injury and better imaging techniques for diagnosing spinal damage, have improved the chances of recovery of patients with spinal cord injuries.

The potential for pharmacological intervention to either preserve or recover neurological function after spinal cord injuries exists because most traumatic injuries do not involve actual physical transection of the cord, but rather the spinal cord is damaged as a result of a contusive, compressive or stretch injury.

Typically, residual white matter containing portions of the ascending sensory and descending motor tracts remains intact, allowing the possibility of neurological recovery. However, during the first minutes and hours following injury, a secondary degenerative process is initiated by the primary mechanical injury that is proportional to the magnitude of the initial insult.

Nevertheless, the initial anatomical continuity of the injured spinal cord in the majority of cases has lead to the notion that pharmacological treatments, which interrupt the secondary cascade, if applied early, can improve the spinal cord tissue survival, and thus preserve the necessary anatomic substrate for functional recovery to take place.

**Therapeutic Strategy for Medical Management**

Therapeutic strategy for the medical management of acute spinal cord injury should be based on the following factors:

- Scientific rationale.
- Experimental and clinical evidence from existing literature.
- Logic and common sense.
- Safety.
- Availability.

**Pharmacological Agents Available**

A variety of promising substances have been tested in animal models of acute spinal cord injury, but few have had potential application to human spinal cord injury patients. Four pharmacological agents have been studied: two corticosteroids (methylprednisolone and tirilazad mesylate), naloxone and GM-1 ganglioside. Methylprednisolone and GM-1 ganglioside have been studied extensively in acute spinal cord injuries; whereas, other two agents, tirilazad mesylate and naloxone, have been studied less extensively and as yet have unclear efficacy in the management of acute spinal cord injuries. Although there are no prospective, randomized, double-blind, multicenter, controlled studies, dexamethasone has been used for many years, where methylprednisolone is not available. There is no class 1 evidence for the use of dexamethasone in the treatment of acute spinal cord injuries.

**GM-1 Ganglioside**

In a small study of 37 patients, Geisler et al. showed that GM-1 ganglioside was better than placebo. This study was criticized due to an inadequate sample size. In 1992, a multicenter GM-1 ganglioside acute spinal cord injury study was initiated. It was a prospective, double-blind, randomized and stratified trial and enrolled 797 patients. Patients were randomized into three initial study groups: placebo, low-dose GM-1 (300 mg loading dose and then 100 mg/day for 56 days) and high-dose GM-1 (600 mg loading dose and then 200 mg/day for 56 days). Placebo or GM-1 was administered at the end of the 23-h methylprednisolone infusion.

At the study conclusion, 37 patients were judged ineligible, leaving 760 patients for primary efficacy analysis. The authors found no significant difference in mortality between treatment groups. The authors did not identify a higher proportion of patients with marked recovery in motor function at 26 weeks when they compared GM-1-treated patients to the placebo-treated group in their primary efficacy analysis.

![The available medical evidence does not support a significant clinical benefit from the administration of GM-1 ganglioside in the treatment of patients after acute spinal cord injury.]

**Methylprednisolone**

The randomized trials of methylprednisolone in the treatment of acute spinal cord injury provide evidence for a significant improvement in motor function recovery if administered within 8 h of injury.

**Pathophysiology of Spinal Cord Injury and Rationale for Methylprednisolone**

Primary injury of the spinal cord refers to the initial mechanical damage due to local deformation of the spine. Direct compression and damage of neural elements and blood vessels by fractured and displaced bone fragments or disc material occur after mechanical trauma.

The secondary mechanism is initiated by the primary injury. The secondary mechanism includes a cascade of biochemical and cellular processes, such as electrolyte abnormalities, marked depletion of the high-energy phosphate reserves, formation of free radicals, vascular ischemia, tissue edema, lactic acidosis, posttraumatic inflammatory reaction and apoptosis or genetically programmed cell death.

Experimental evidence suggests that Methylprednisolone reverts or reverses all the effects that are described above.
1. **Concept of Idling Neurons**

Idling neurons are those that are still alive, but their function is compromised. Penumbras (between the dead cells and the normal cells) are structures that are not dead but are dysfunctional. If the treatment is effective, the penumbra becomes normal. If the treatment is not effective, penumbra becomes part of dead cells and neurological deficit remains.

2. **Clinical Evidence**

Tables 1 and 2 provide the snapshots of clinical trials with methylprednisolone in acute spinal cord injury.

### Table 1: Clinical trials in favor of methylprednisolone

<table>
<thead>
<tr>
<th>Study</th>
<th>Description of study</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Bracken et al., 1984</td>
<td>Multicenter, double-blind randomized trial comparing methylprednisolone (1000 mg/day vs. 100 mg/day for 11 day) in treatment of 330 acute spinal cord injury patients (NASCIS I study)</td>
<td>No difference in results overall but in those who received methylprednisolone within 8 h there was a benefit to the higher dose group</td>
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<tr>
<td>Bracken et al., 1990</td>
<td>Multicenter, randomized, double-blind, placebo-controlled trial comparing methylprednisolone with naloxone and placebo in treatment of 487 acute spinal cord injury patients (NASCIS II study)</td>
<td>Significant improvement in motor change scores and sensation change scores at 6 month post-injury for patients treated with methylprednisolone compared to naloxone</td>
</tr>
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<td>Bracken et al., 1997</td>
<td>Methylprednisolone administered for 48 h and tirilazad mesylate administered for 48 h in the treatment of 499 acute spinal cord injury patients (NASCIS III study)</td>
<td>48-h methylprednisolone administered patients had improved motor recovery at 6 weeks and 6 months compared with 24-h methylprednisolone administered and 48-h administered tirilazad mesylate</td>
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<td>Otani et al., 1994</td>
<td>158 Patients, methylprednisolone group and control group with no placebo</td>
<td>Analysis of patients treated within the 8 h window show that high-dose methylprednisolone resulted in greater motor recovery at 6 weeks, 6 months and 1 year</td>
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<td>Pettersson et al., 1998</td>
<td>40 Whiplash injury patients, methylprednisolone 30 mg/kg followed by 5.4 mg/kg/h for 23 h compared to controls</td>
<td>Methylprednisolone patients were found to have fewer disabling symptoms, fewer sick days and a healthier sick leave profile at 6 months post-injury</td>
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Methylprednisolone prevents
- Lipid peroxidation.
- Posttraumatic ischemia.
- Destruction of neuronal and microvascular membranes.

Inhibition of lipid peroxidation results in
- Preservation of spinal blood flow.
- Preservation of metabolism.
- Reduced damage from high levels of extracellular calcium and excitotoxicity.
- Reduced protease-mediated damage to neuro-filament proteins.
- Preserved Na and K homeostasis.

It is known that the central nervous system is the only tissue that is incapable of regeneration. Therefore, therapeutic strategies should be aimed at increasing the ability of neuronal cells to survive the adverse conditions that exist following injury/damage.

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### Idling neurons

<table>
<thead>
<tr>
<th>Core Area</th>
<th>Normal Viable Cells</th>
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<tr>
<td>Cellular structures are irreversibly damaged</td>
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<table>
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<tr>
<th>Penumbra</th>
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<td>Cellular structures are viable but nonfunction</td>
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</table>
Table 2: Clinical trials not in favor of methylprednisolone

<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Galandiuk et al., 1993</td>
<td>Prospective assessment of 15 patients from 1990 to 1993 with No difference in neurological outcome between two sets of retrospective review of 17 patients from 1987 to 1990 to assess patients differences in treatment outcome with methylprednisolone compared with treatment without corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Gerhart et al., 1995</td>
<td>Concurrent cohort comparison study (population-based) of No differences in neurological outcome 363 acute spinal cord injury patients managed from 1990 to 1991 and 1993. In all, 188 patients managed with NASCIS II methylprednisolone compared with 90 patients with no methylprednisolone</td>
<td>Overall, methylprednisolone improves neurological recovery</td>
</tr>
<tr>
<td>George et al., 1995</td>
<td>Retrospective review of 145 acute spinal cord injury patients, No difference in mortality or neurological outcome between 80 treated with methylprednisolone compared with 65 who did not receive methylprednisolone</td>
<td>Overall, methylprednisolone improves neurological recovery</td>
</tr>
<tr>
<td>Gerhart et al., 1995</td>
<td>Retrospective review with historical control of 231 acute Methylprednisolone-treated patients had significant increases spinal cord injury patients, 91 excluded. Comparison of in pneumonia medical complications among 93 methylprednisolone patients compared with 47 who received no methylprednisolone</td>
<td>Overall, methylprednisolone improves neurological recovery</td>
</tr>
<tr>
<td>Poynton et al., 1997</td>
<td>Case-Control analysis of 71 consecutive acute spinal cord injury No difference on outcome admissions, 63 available for 13 months to 57 months follow up. About 38 patients were treated with methylprednisolone compared with 25 referred &gt;8 h after injury who received no methylprednisolone</td>
<td>Overall, methylprednisolone improves neurological recovery</td>
</tr>
<tr>
<td>Pointillart et al., 2000</td>
<td>Multicenter, prospective, randomized clinical trial of 106 acute No significant difference in neurological outcome SCI patients treated with methylprednisolone, nimodipine, neither or both</td>
<td>Overall, methylprednisolone improves neurological recovery</td>
</tr>
<tr>
<td>Matsumoto et al., 2001</td>
<td>Prospective randomized, double-blind study comparing Methylprednisolone patients had higher incidence of incidence of medical complications among 46 acute spinal complications cord injury patients, 23 treated with methylprednisolone, 23 with placebo</td>
<td>Overall, methylprednisolone improves neurological recovery</td>
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Overall, methylprednisolone improves neurological recovery (motor function, sensation to pinprick and touch) by 20%.

The authors concluded that patients with acute spinal cord injury who receive methylprednisolone within 3 h of injury should be maintained on the 24 MP regimen. When methylprednisolone is administered 3–8 h after injury, they recommended the 48-h methylprednisolone regimen.

The primary NASCIS II report clearly stated that no benefit of methylprednisolone was observed in the total study group. In the prior analysis of patients treated relatively quickly after the injury (within 8 h, which was the modal time from injury to initiating therapy, and the only dichotomy analyzed), patients treated with methylprednisolone recovered significantly better than placebo-treated patients. Examination of effect of a drug as a function of time to injury was a major hypothesis in the design of both NASCIS II and III.

Clarification on Some of the Points Raised Against NASCIS Study

Weakness in the Control Group

The comparison of placebo-treated patients before vs. after 8 h is not a randomized comparison, and there is no reason to expect that these patients would be similar. The time taken to initiate therapy was largely a function of how quickly patients were admitted to hospital and there are many reasons why this may vary by severity of injury. The only valid comparisons for analysis are the ones reported, that is, comparison of treatment (which was randomized) within early and late time periods.

Combined Improvement was due to the Differences in Changes in the Patients with Incomplete Lesions

Statistically significant improvement in methylpred-
Harmonisation of Technical Requirements for Registration of the initial investigators.

NASCIS II and III, there is a concern regarding analyses not these complex datasets in an unbiased manner. Since NASCIS biostatistical and clinical expertise to understand and analyze use of the data and demonstrate that they have the technical, and groups, who submit a proposal describing their intended Primary Data have Still not been Made Public the world.

In NASCIS III, there is a Randomization Imbalance

In NASCIS III, an imbalance at randomization was reported, which allowed somewhat more severely injured patients to tirilazad mesylate. There was also a nonsignificant baseline difference in the two tirilazad mesylate groups.

Baseline neurological function was controlled in all statistical analyses and, as expected, the multivariate analysis of the two methylprednisolone groups showed reduced improvement differences when the baseline differences were taken into account. These controlled analysis form the primary published results.

Numbers, Tables and Figures have been Inconsistently Defined

The NASCIS III report shows severity of injury of all patients in the trial. Overall, for motor function, 35.2% were quadriplegic; 31.0% paraplegic; 13.4% quadriparietic and 4.0% paraparetic; and 14.4% normal, although all normal motor responses had some sensory loss. After accounting for trial exclusion criteria (gunshot wounds, etc.), the study population reflects the pattern of spinal injury seen in hospital emergency departments. Both NASCIS II and III showed efficacy of methylprednisolone in severely injured patients, defined as having complete neurological injury. Experimental Study on the Efficacy of Methylprednisolone in enhancing neurore generation and provided the rationale for the use of methylprednisolone in enhancing neuroregeneration. The weight of the evidence from cat and other models using methylprednisolone in enhancing neuroregeneration and other therapies are not being conducted. Currently, primary evidence of efficacy and safety from three trials and secondary evidence from the trials of related clinical conditions and animal studies, as reported in the Cochrane review, support the use at this time.

Animal and Human Studies: Differences

Animal studies serve two roles in developing scientific evidence: they prompt the testing of therapies in humans after successful trial in animals, and they provide a biological plausibility to the human evidence once it has been gathered. The weight of the evidence from cat and other models using methylprednisolone in enhancing neuroregeneration and other therapies are not being conducted. Currently, primary evidence of efficacy and safety from three trials and secondary evidence from the trials of related clinical conditions and animal studies, as reported in the Cochrane review, support the use at this time.

Experimental Evidence

Experimental Study on the Efficacy of Methylprednisolone and Dexamethasone in the Treatment of Acute Spinal Cord Injury in Rats

Sharma et al. studied the effect of methylprednisolone sodium succinate in comparison with dexamethasone in experimentally induced acute spinal cord compression in 50 Wister albino rats (250–350 g). The rats were divided into group A (control) and group B; group B was subdivided into B1, B2, B3, where methylprednisolone was given after 1, 8 and 24 h and Pharmaceuticals for Human Use (ICH)/FDA guidelines. The ICH/FDA guidelines were published in 1996, but they enshrined principles and practices that have been evolving for many years. The NASCIS reports, even the earlier ones, meet both the spirit and intent of the recommendations.
B4, where dexamethasone was given after 1 h of spinal cord injury respectively.

This study inferred that methylprednisolone is potent in promoting recovery post-trauma, especially if given in right dose and at the right time (i.e. at the earliest time after trauma).

| Table: Methylprednisolone is more effective than dexamethasone in promoting clinical and histological recovery and reducing edema when given earliest after trauma, and these results are statistically significant (at 8 and 24 h). |

An experimental study to evaluate and compare the neuroprotective effect of hypothermia, naloxone, methylprednisolone and combination of hypothermia and methylprednisolone in spinal cord injury in rat.

Sharma et al. evaluated and compared the neuroprotective effect of hypothermia, naloxone, methylprednisolone and combination of hypothermia and methylprednisolone in acute compressive spinal cord injury in rat model. Immunized and conditioned 50 Wister albino rats of either sex, ranging in weight from 250 to 350 g, were used for the study. The rats were divided into following groups:

- **Group A**: Control – those undergoing only spinal cord compression.
- **Group B**: Those undergoing spinal cord compression, followed by treatment with either of the three modalities. Group B1: Treated with naloxone.
- **Group B2**: Treated with local hypothermia.
- **Group B3**: Treated with methylprednisolone.
- **Group C**: Treated with combination hypothermia and methylprednisolone.

Combination of methylprednisolone and hypo-thermia is more effective in promoting clinical and histopathological recovery as compared with any single drug. Methylprednisolone, hypothermia and naloxone, all three modalities of treatment, are effective in promoting clinical and histopathological recovery. But methylprednisolone has shown maximum efficacy, which is statistically significant compared to other two.

The study recommends early decompression of spinal cord injury with local application of hypothermia and to start methylprednisolone as early as possible.

### Role of Methylprednisolone in Elective Spinal Surgery

- While an elective surgery has been performed on the spine (particularly the cervical and dorsal spine), it is worthwhile to start with methylprednisolone as a bolus dose at the start of surgery and continuing it as a maintenance dose throughout the duration of surgery.
- After completing the surgery, ice cold saline is used to irrigate the dura for a few minutes. This not only helps in homeostasis, but is also neuroprotective and likely to reduce any post-operative neurological deficits.

### Complications

#### Respiratory Complications

The incidence of respiratory complications is higher with methylprednisolone, particularly in unconscious patients on ventilatory support. Prior to the CRASH trial, several centers used methylprednisolone for the head injury. It was found that in these patients, it was difficult to wean off the ventilator. The CRASH trial showed a 3% increase in the mortality in the methylprednisolone group, which forced investigators to terminate the trial. Respiratory complication is a very serious problem; one must put the patient on higher ventilator, good physiotherapy and good ventilation.

### Gastrointestinal Complications

According to gastroenterologists, monotherapy with methylprednisolone does not increase the incidence of gastrointestinal bleeding. Moreover, NASCIS trials did not show any significant increase in gastrointestinal bleeding with methylprednisolone. Also, typical stress ulcer prophylactic agents, such as histamine-2 receptor antagonists and proton pump inhibitors, were not used widely at the time of NASCIS. Number of newer agents are coming up for the better management of gastrointestinal complications.

### Future Hope

- 4-Aminopyridine (chronic spinal cord injury)
- Neotrofin
- GM-1
- Guanosine derivatives
- Activated macrophages
- Alternating current stimulation
- Fetal neural transplantation
- Olfactory ensheathing glial cells
- Transplantation of stem cells

### Key Points

- High-dose methylprednisolone is an option in patients with an acute spinal cord injury. Even a minimal improvement in sensory and motor functions can lead to better overall functional outcomes.
- Routine use of adequate fluid resuscitation, stress ulcer prophylaxis and avoidance of hyperglycemia can limit the complications and result in better treatment outcomes.

### References

7. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results


