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# Neuroprotection During the Acute Phase of Spinal Cord Injury

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## Key Points

Secondary injuries amplify the degree of damage obtained from a primary injury and leave individuals with worse injuries than what was incurred from the initial trauma.

Neuroprotection is a recent area of medical research investigating pharmaceuticals that counteract the vascular and biochemical repercussions of secondary injury.

Methylprednisolone is not effective for neurological recovery during the acute phase post SCI, and there is conflicting evidence whether its use is associated with the development of medical complications.

Dexamethasone is not effective for neurological recovery during the acute phase post SCI and may be associated with the development of medical complications.

Progesterone and vitamin D is not effective for neurological recovery during the acute phase post SCI.

Naloxone is not effective for neurological recovery during the acute phase post SCI.

Tirilazad mesylate is no more effective than methylprednisolone for neurological recovery during the acute phase post SCI.

Nimodipine is not effective for neurological recovery during the acute phase post SCI.

There is conflicting evidence regarding the effectiveness of erythropoietin for neurological recovery during the acute phase post SCI.

There is conflicting evidence regarding the effectiveness of GM-1 ganglioside for neurological recovery during the acute phase post SCI.

Granulocyte-colony stimulating factor may be effective for neurological recovery during the acute phase post SCI.

Thyrotropin-releasing hormone may be effective for neurological recovery during the acute phase post SCI in individuals with incomplete injuries.

Gacyclidine is not effective for neurological recovery during the acute phase post SCI.

Cethrin® is a safe and tolerable drug, but its effect on neurological recovery remains unknown during the acute phase post SCI.

Minocycline is not effective for neurological recovery during the acute phase post SCI.

Riluzole may be effective for neurological recovery during the acute phase post SCI.

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# 1 Executive Summary

Despite promising results from preclinical and early phase clinical trials, the neuroprotective properties of pharmacotherapeutic candidates have been difficult to demonstrate when scaled to later phase clinical trials. This could be attributable to several factors. First, there is high variability in the potential for patient recovery, as individuals with cervical injuries tend to recover more neurological function than those with thoracic injuries (S. Casha et al., 2012; Fehlings et al., 2011). Likewise, patients with incomplete injuries tend to recover more so than those with complete injuries (M. B. Bracken et al., 1997; Pitts, Ross, Chase, & Faden, 1995; Tsutsumi, Ueta, Shiba, Yamamoto, & Takagishi, 2006). Recovery also varies depending on age (Burns, Golding, Rolle, Graziani, & Ditunno, 1997; Leypold, Flanders, Schwartz, & Burns, 2007; Pollard & Apple, 2003) and whether or not the SCI is penetrating as opposed to non-penetrating (Heary et al., 1997; Levy et al., 1996). Accommodating for these differences through sub-group analysis is hindered with statistical robustness of smaller sample sizes. Second, there has currently been no consensus regarding a method for selecting agents suitable for translation to humans based on preclinical performance. Tator et al. (C. H. Tator et al., 2012) suggested that preclinical data should be assessed based on 1) the animal/injury model(s) used; 2) timing of therapy; 3) evidence of beneficial effects of therapy; 4) reproducibility/replication and publication of results; 5) safety/toxicity of the agent; and 6) other factors such as preclinical lab environments. That human injuries are variable in their etiology and are often accompanied by other injuries makes them less straight-forward to treat compared to SCI in well controlled animal models (Sharif-Alhoseini M, 2014). Lastly, the efficacy of the drug also depends on the time when it was administered. Although timing of therapy is reported in the preclinical literature, it does not currently reflect feasible timing for treatment in humans (C. H. Tator et al., 2012; Wilson & Fehlings, 2014).

Along with six criteria proposed by Tator et al. (C. H. Tator et al., 2012), only one other publication by Kwon et al. (Kwon et al., 2009) addressing preclinical grading criteria to determine translatability to human trials proposes an objective scoring system to select the most promising candidates for translation. Continued development and validation of a preclinical scoring system involving worldwide experts in preclinical and clinical SCI is the next step towards selecting the next most promising pharmacotherapy for translation to humans (C. H. Tator et al., 2012).

In the interim, there is currently no pharmaceutical therapy recognized as the standard of care for neuroprotection during acute SCI. To date, EPO, G-CSF, TRH, and riluzole must be considered carefully due to the small study sample sizes used to investigate these pharmaceutical agents. Alternative study design methods might also be considered to mitigate for the large sample sizes required in a relatively small and heterogenous patient population to reach statistical significance (Tanadini et al., 2014) for a potential pharmacotherapeutic agent to be proven effective as a neuroprotectant in acute SCI.

## 2 Methods

A key word literature search for scientific articles published from January 1, 2014 to September 1, 2019 investigating acute neuroprotective management following spinal cord injury (SCI) was conducted using the following online databases: MEDLINE, CINAHL, Scopus, EMBASE and Cochrane Library. Population key words (i.e., spinal cord injury, paraplegia, tetraplegia, and quadriplegia) and neuroprotection key words (i.e., steroids, methylprednisolone, prednisolone, dexamethasone, GM-1 ganglioside, monosialotetrahexosyl ganglioside, corticosteroid, aminosteroid, nonglucocorticoid steroid, tirilazad, tirilazad mesylate, naloxone) were used in combination. The search was limited to English publications that were either journal articles, reviews or systematic reviews (excluding case reports) with at least three adults ( $\geq 18$  years) with SCI. More than 50% of participants included in the study had to have a SCI, unless the results were stratified. Animal and pediatric studies, and case reports were omitted. It should be noted that articles were considered suitable for inclusion in this module if all, or the majority of, participants in each study were within approximately 3 months post SCI.

## 3 Introduction

SCI commonly results in permanent loss of partial or full sensation and movement below the level of injury and can therefore be physically and emotionally devastating for patients and their caregivers. The estimated incidence of SCI in Canada is about 4,000 each year (41 per million) (Noonan et al., 2012), with young men being the most common demographic experiencing these accidents (Kirshblum, Groah, McKinley, Gittler, & Stiens, 2002). However, more recently, the Canadian demographic has reported a shift to older adults as a result of falls in the elderly overtaking motor vehicle accidents as the most common cause of injury (Pickett, Campos-Benitez, Keller, & Duggal, 2006). Regions in Russia, Sweden and Norway also reflect the increasing contribution of falls as the most common etiology of injury (Singh, Tetreault, Kalsi-Ryan, Nouri, & Fehlings, 2014). Although many individuals may never fully recover sensation and movement, patient outcomes have drastically improved with advances in pre-hospital care, emergency care, acute trauma care, surgical interventions, and rehabilitation. Common treatments that have contributed to the decrease in mortality and increase in acute recovery include treating neurogenic shock, hemodynamic resuscitation, spine stabilization, surgery, prophylactics, and pharmaceuticals for neuroprotection to minimize injury. The use of pharmaceuticals for neuroprotection has been the subject of excitement and debate since the 1970s and continues to gain research interest over time. In this module, only the evidence that exists for pharmaceutical agents used during the acute phase of SCI will be reviewed; other research avenues of neuroprotection such as stem cell transplants (M Kan, A Ling, & Lu, 2010), autologous bone marrow transplantation (Chhabra et al., 2016) and macrophage therapy (Kigerl & Popovich, 2006; Lammertse et al., 2012) will be omitted.

### 3.1 Phases of Injury

There are two acute phases of SCI, namely primary (at the moment of injury and immediately thereafter) and secondary (i.e. minutes to weeks or months post injury). The initial mechanical

insult to the spinal cord is considered to be the primary injury; currently, damage incurred from this trauma cannot be reversed with pharmaceuticals. The primary injury is the strongest predictor of overall prognosis (Oyinbo, 2011). Within minutes after the initial insult, physiological and molecular changes occur that amplify the injury and enlarge the lesion site; these subsequent reactions are referred to as secondary injuries.

The primary injury is manifested by neuron death at the impact site and hemorrhaging. Secondary injuries also include continued neuron death and hemorrhaging, but also extend to encompass edema and inflammation, vascular alterations (e.g., neurogenic shock, ischemia), and biochemical reactions (e.g., production of toxic reactive oxygen species and neurotransmitters). The majority of the secondary injury is determined within days to a week and is the time frame during which neuroprotective strategies should be initiated. Secondary injuries continue to mount for weeks to months after injury (Fleming et al., 2006) and can substantially worsen the injury sustained from the initial trauma.

Traditionally, the medical care of those impacted by SCI focused on keeping the patient alive and later addressing complications (e.g., spasticity, pain, bladder dysfunction) that arose from the initial injury. Recently, efforts have been placed on protecting neurons from additional damage caused by secondary injuries (Sadowsky, Volshteyn, Schultz, & McDonald, 2002), and also on comprehensive and intensive rehabilitation. This concept of 'neuroprotection' has initiated medical research to develop pharmaceuticals that target the imminent vascular and biochemical reactions that occur after SCI.

## 3.2 Overview of Secondary Injuries

There are at least 25 well-established secondary injury mechanisms that can occur within minutes, weeks and months following a SCI (Oyinbo, 2011). Of these, the mechanisms that are most targeted for pharmaceutical intervention are reviewed below.

### 3.2.1 Inflammation

Inflammation occurs within the first minutes of a SCI and can persist for weeks or even months. It is predominantly caused by immune cells releasing reactive oxygen species and pro-inflammatory cytokines. The presence of immune cells can initially be advantageous because they remove cellular debris that resulted from the original injury in an effort to make room for new neurons to grow. Excessive and/or chronic inflammation, however, can lead to exacerbation and damage of surrounding healthy tissue (Allison & Ditor, 2015).

### 3.2.2 Vascular Secondary Injuries: Hemorrhage and Ischemia

SCI leads to local haemorrhaging and associated cell death, especially in the grey matter. Capillaries and venules at the injury site can experience a sudden reduction in blood flow and this ischemia can continue to worsen over several hours post injury. Ischemia is arguably the biggest determinant of the degree of secondary injury, as it often extends beyond the spinal cord and negatively affects perfusion and oxygenation in surrounding tissues, causing permanent damage (Amar & Levy, 1999). Hemorrhage can promote ischemia (Wallace, Tator, & Frazee,

1986); in turn ischemia can promote edema of the spinal cord (Charles H Tator, 1998) and production of reactive oxygen species (Lewen, Matz, & Chan, 2000).

### 3.2.3 Excitotoxicity

An additional biochemical outcome of secondary injury is an increase in cellular levels of calcium ions. To pass an electrical signal between neurons, neurotransmitters must be released from one synapse and bind to receptors on the neighbouring synapse. This release of neurotransmitters is regulated by calcium ions moving through calcium channels. The N-methyl-D-aspartate (NMDA) receptor is a calcium channel that, when open, allows electrical signals to transfer between neurons in the spinal cord. The receptor is only open when it is bound with glutamate (Guzman-Lenis, Navarro, & Casas, 2009). The initial spinal cord trauma and subsequent ischemia produce an accumulation of glutamate around the injury site (Amar & Levy, 1999). Excitotoxicity occurs when excessive glutamate causes overstimulation of the NMDA receptor, allowing high levels of calcium ions into the neighbouring cells. The influx of calcium activates a series of destructive enzymes, including phospholipases that go on to damage the phospholipid cell membrane and proteases thereby destroying proteins. Over time, neuron cells become damaged and die. Other negative effects of excitotoxicity include edema of the spinal cord and the production of reactive oxygen species (Grossman et al., 2014).

### 3.2.4 Lipid Peroxidation

During secondary injury, toxic oxygen free radicals are produced from excitotoxicity, mitochondrial dysfunction and the oxidative stress resulting from ischemia. These reactive oxygen species, as well as other free radicals created from the injury, react with proteins and lipids in nerve cells (Christie et al., 2008). Lipid peroxidation is a major cause of secondary nerve damage because the phospholipid membranes of neurons become oxidized and rupture (Kavanagh & Kam, 2001).

### 3.2.5 Apoptosis

Apoptosis of neurons seems to be largely a result of high calcium levels in the cells during excitotoxicity, as well as the interaction with reactive oxygen species and inflammation. Taken together, these processes can activate signaling cascades leading to programmed cell death of nerve cells and surrounding tissue cells (Oyinbo, 2011).

### 3.2.6 Axon Demyelination and Degeneration

Neurons that survive the initial mechanical injury are still at risk of death from axon demyelination for many weeks post SCI (Liu et al., 1997). The initial injury as well as subsequent inflammation (Waxman, 1989) and excitotoxicity (S Casha, Yu, & Fehlings, 2001) destroys the surviving neurons' oligodendrocytes, which are critical to neuron protection because they are the glial cells that form the myelin sheath around axons in the central nervous system. Demyelination leaves axons unprotected and vulnerable to degeneration and apoptosis from reactive oxygen species and inflammatory cytokines.



### 3.2.7 Neurogenic Shock

An intact spinal cord is required for proper autonomic nervous system (ANS) function and thus cardiovascular stability. The ANS is comprised of two opposing systems, the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), which interact to regulate various functions including heart rate (HR), blood pressure (BP) and vagal tone. Changes in cardiovascular function are lesion-dependent, with high-level injuries (T6 or above) contributing to significant SNS dysfunction and resulting in the greatest degree of cardiovascular impairment following SCI. During the acute phase of SCI, individuals typically present with neurogenic shock, a condition predominantly characterized by the simultaneous presence of bradycardia (HR of less than 60 beats per minute) and arterial hypotension (systolic BP below 90 mmHg and diastolic BP below 60 mmHg; (Furlan & Fehlings, 2008; Krassioukov, 2009; Popa et al., 2010). Hypotension from neurogenic shock can be especially dangerous when it contributes to ischemia. In this case, there is not enough blood (and therefore oxygen) being delivered to the spinal cord or vital organs and tissues, and the affected cells become damaged or destroyed. Neurogenic shock can persist for weeks and is typically counteracted with established treatments for hypotension, bradycardia, and hypothermia (Mack, 2013). For more information on SNS disruption and resulting cardiovascular dysfunction, refer to the Cardiovascular Complications during the Acute Phase of Spinal Cord Injury module in SCIRE version 5.0.

Table 1. Overview of Common Secondary Injuries and Pharmaceutical Agents

Secondary Injury	Description	Pharmaceutical Agent/Treatment Used to Counteract Injury
Inflammation	Swelling at the injury site. Dead cells attract inflammatory cells such as macrophages, neutrophils, and microglia, which in turn release pro-inflammatory cytokines at the site of injury.	<ul style="list-style-type: none"> <li>• Methylprednisolone</li> <li>• Dexamethasone</li> <li>• Minocycline</li> <li>• Erythropoietin</li> <li>• Granulocyte-colony stimulating factor</li> <li>• Cethrin®</li> </ul>
Hemorrhage	Initial injury results in bleeding within the grey matter, which leads to hemorrhagic death of afflicted cells.	<ul style="list-style-type: none"> <li>• Methylprednisolone</li> </ul>
Ischemia	Blood flow is restricted from the spinal cord and surrounding tissues. Hypoxia results in cell death.	<ul style="list-style-type: none"> <li>• Methylprednisolone</li> <li>• Naloxone</li> <li>• Nimodipine</li> <li>• Erythropoietin</li> <li>• Thyrotropin-releasing hormone</li> </ul>
Edema	Swelling and fluid build-up around the spinal cord. Can be the result of initial trauma, ischemia, and excitotoxicity.	<ul style="list-style-type: none"> <li>• Methylprednisolone</li> <li>• Riluzole</li> </ul>
Excitotoxicity	Neuronal damage caused by overstimulation, produced by high levels of calcium ions and glutamate.	<ul style="list-style-type: none"> <li>• Riluzole</li> <li>• Minocycline</li> <li>• Erythropoietin</li> <li>• GM-1 ganglioside</li> </ul>

		<ul style="list-style-type: none"> <li>• Thyrotropin-releasing hormone</li> </ul>
Lipid peroxidation	Reactive oxygen species steal electrons from neuron cell membranes, resulting in membrane lysis and cell death.	<ul style="list-style-type: none"> <li>• Methylprednisolone</li> <li>• Tirilazad mesylate</li> <li>• Erythropoietin</li> <li>• Minocycline</li> <li>• Riluzole</li> </ul>
Apoptosis	Programmed cell death of neurons due to presence of cytokines and reactive oxygen species.	<ul style="list-style-type: none"> <li>• Methylprednisolone</li> <li>• Erythropoietin</li> <li>• GM-1 ganglioside</li> <li>• Granulocyte-colony stimulating factor</li> <li>• Minocycline</li> </ul>
Axon demyelination	Damaged oligodendrocytes cause demyelination of neurons. Exposed axons are susceptible to damage from reactive oxygen species.	<ul style="list-style-type: none"> <li>• Granulocyte-colony stimulating factor</li> <li>• GM-1 ganglioside</li> <li>• Cethrin®</li> <li>• Erythropoietin</li> </ul>
Neurogenic shock	Normal sympathetic nervous system functioning is disrupted, leading to hypotension and bradycardia.	<ul style="list-style-type: none"> <li>• Established treatments for bradycardia, hypotension, and hypothermia</li> </ul>

## Conclusion

### Key Points

Secondary injuries amplify the degree of damage obtained from a primary injury and leave individuals with worse injuries than what was incurred from the initial trauma.

Neuroprotection is a recent area of medical research investigating pharmaceuticals that counteract the vascular and biochemical repercussions of secondary injury.

## 4 Pharmaceutical Agents for Neuroprotection During Acute SCI

Over time, advances in our understanding of the molecular pathways that signal abnormally during secondary injury, in combination with our knowledge of axon protection and repair, have led to novel pharmaceutical interventions to treat acute SCI. Pharmacological experimentation for acute SCI in animal models began in the late 1960s (Ducker & Hamit, 1969) and human trials began in the 1980s (Michael B Bracken et al., 1984). Drugs currently under investigation include those used to treat other neurological disorders as well as some synthesized exclusively for SCI.

To date, there have been a number of trials in humans for pharmaceuticals to investigate their efficacy in acute SCI which will be described in the sections below.

## 4.1 Steroids

To date, there have been two steroids used for neuroprotection in acute SCI: dexamethasone and methylprednisolone (MP). These pharmaceutical agents are both glucocorticoid steroids, which are known for their strong anti-inflammatory properties (Barnes, 2006). Limited information on the role of dexamethasone for acute SCI exists, but the mechanism of action for MP is beginning to be better understood. MP has long been used to treat brain edema, although the dose administered for SCI is much higher (Heary et al., 1997). It has been reported that, in addition to its anti-inflammatory properties, the main role for this drug at high doses is to act as an antioxidant to scavenge reactive oxygen species (Edward D Hall, 1992; B. H. Lee et al., 2005). Furthermore, MP is thought to inhibit lipid peroxidation (Edward D Hall, 2003) and reduce cell apoptosis (Vaquero, Zurita, Oya, Aguayo, & Bonilla, 2006). The high doses administered very early after injury are necessary because the absorption into the spinal tissues rapidly decreases over time. Determining the appropriate MP dosage is complex due to its biphasic dose response curve whereby potential benefits at low doses transition to toxic effects at higher doses (Edward D Hall & Springer, 2004).

Before testing for the efficacy of pharmacological treatments in acute SCI existed, dexamethasone was occasionally prescribed (Heary et al., 1997). Promise in animal models for MP resulted in the first randomized controlled trial (RCT) of any pharmacological agent for treating acute SCI (Michael B Bracken et al., 1984). The National Acute Spinal Cord Injury Study (NASCIS) conducted a trial comparing high and low dose MP. The results of this study suggested that patients who received high dose MP had no neurological improvement but significant increases in medical complications compared to those who received low dose MP. Following the release of this study, further RCTs and retrospective studies were launched to further understand the neuroprotective effectiveness of steroids during acute SCI.

Table 2. Steroids for Neuroprotection in Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<a href="#">Aminmansour et al. (2016)</a> Iran RCT PEDro= 9 N <sub>initial</sub> = 32, N <sub>final</sub> = 32	<b>Population:</b> Progesterone + Vitamin D group: Mean age= 41.88±13.6yr; Gender: male= 56.2%, female= 43.8%; Level of injury: cervical, thoracic, lumbar; Severity of injury: Incomplete. Placebo group: Mean age= 45.2±13.7yr; Gender: male= 50%, female= 50%; Level of injury: cervical, thoracic,	1. Progesterone + vitamin D group performed significantly better than placebos on ASIA motor scores for all extremities at 6 months (p<0.05). No significant differences between groups seen at other time points. 2. Progesterone + vitamin D group performed significantly better than placebos on ASIA sensory scores for

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	lumbar; Severity of injury: Incomplete. <b>Treatment:</b> Patients were first administered methylprednisolone per standard protocol. Patients were then randomly assigned to receive progesterone (0.5 mg/kg) twice daily and vitamin D3 (5ug/kg) twice daily or placebo for up to 5 days. <b>Outcome Measures:</b> Assessed baseline, 6 days, 3 and 6 months post-injury. ASIA motor and sensory scores <b>Chronicity:</b> Individuals were studied within 8 hr of sustaining injury.	right upper, left lower, and right lower at 6 months ( $p < 0.05$ ). No significant differences between groups seen at other time points.
<a href="#">Costa et al.</a> 2015 Italy RCT PEDro= 7 N <sub>initial</sub> = 19, N <sub>final</sub> = 19	<b>Population:</b> Mean age= 27.67y Gender: male= 94.7%, female= 5.3%; Level of injury: cervical, thoracic; Severity of injury: AIS A or B <b>Treatment:</b> Participants were randomized to receive either methylprednisolone or erythropoietin treatment groups for 48 hours. <b>Outcome Measures:</b> ASIA motor and sensory, MAS, Penn Score, VAS, SCIM. Evaluated at baseline, day 3, 7, 14, 30, 60, and 90. <b>Chronicity:</b> Screened and enrolled within 8 hours of sustaining injury.	1. No between-groups difference on ASIA motor and sensory, MAS, Penn score, VAS or SCIM ( $p > 0.05$ ) at day 90.
<a href="#">Pointillart et al.</a> (2000) (English translation of Petitjean et al. (1998)) France RCT PEDro=6 N=106	<b>Population:</b> Age range=20-47 yr; Gender: male=90%, female=10%; Level of injury: not specified; Severity of injury: complete=45%, incomplete=55%. <b>Treatment:</b> Patients were randomly assigned to one of four groups: methylprednisolone (MP), nimodipine, MP + nimodipine, or no treatment. The dosages of nimodipine were 0.15 mg/kg/h over 2 hr followed by 0.03 mg/kg/h for 7 days. The dosages of MP followed	1. After one year, there were no significant differences in neurological recovery based on ASIA scores among the four groups ( $p > 0.05$ ). 2. Patients who received MP had significantly higher rates of hyperglycemia compared to those who received nimodipine and those who received no medication ( $p < 0.05$ ). 3. The authors noted that patients with incomplete injuries experienced

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>National Acute Spinal Cord Injury Study (NASCIS) II guidelines and were 30 mg/kg over 1 hr followed by 5.4 mg/kg/h for 23 hr.</p> <p><b>Outcome Measures:</b> The following after 1 year: neurological function based on ASIA score (motor and sensory), adverse event outcomes.</p> <p><b>Chronicity:</b> Individuals were hospitalized within 8 hr of sustaining injury.</p>	<p>significantly more neurological recovery than patients with complete injuries (<math>p &lt; 0.0001</math>).</p>
<p><a href="#">Petterson &amp; Toolanen</a> (1998)                      Sweden                      RCT                      PEDro=8                      N=40</p>	<p><b>Population:</b> Mean age=35 yr; Gender: male=55%, female=45%; Level of injury: not specified; Severity of injury: complete=0%, incomplete=100%.</p> <p><b>Treatment:</b> Patients treated for whiplash injuries received either methylprednisolone (MP) according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines or placebo.</p> <p><b>Outcome Measures:</b> The following after 6 months: degree of disabling symptoms, total number of sick days from work, sick-leave profile 6 months after injury.</p> <p><b>Chronicity:</b> Individuals were administered treatment within 8 hr of sustaining injury.</p>	<ol style="list-style-type: none"> <li>1. Patients who received MP had significantly fewer disabling symptoms than patients who received placebo (<math>p = 0.047</math>).</li> <li>2. Patients who received MP had significantly fewer sick days (<math>p = 0.01</math>) and a significantly lower sick-leave profile (<math>p = 0.003</math>) than patients who received placebo.</li> </ol>
<p><a href="#">Bracken et al.</a> (1997)                      USA                      RCT                      PEDro=7                      N=499</p>	<p><b>Population:</b> Mean age: not specified; Gender: male=85%, female=15%; Level of injury: not specified; Severity of injury: complete=50%, incomplete=50%;</p> <p><b>Treatment:</b> Patients were randomly assigned to receive either methylprednisolone (MP) for 24 hr (5.4 mg/kg), MP for 48 hr (5.4 mg/kg), or tirilazad mesylate for 48 hr (2.5 mg/kg). All treatment groups initially received a bolus of MP (30 mg/kg). All patients received the study drug within 8 hr of injury. The 24 hr MP group</p>	<p><b>Overall Analyses:</b></p> <ol style="list-style-type: none"> <li>1. Compared to patients that received 24 hr MP, there was no significant difference in motor function recovery in patients that received 48 hr MP at 6 weeks (<math>p = 0.09</math>) and 6 months (<math>p = 0.07</math>) post injury. After 6 months, more patients who received 48 hr MP improved at least one motor function 'category' compared to those who received 24 hr MP, but this difference was not significant (<math>p = 0.6</math>).</li> <li>2. There were no significant differences in sensory function (pinprick, light</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>served as the reference; there was no placebo group.</p> <p><b>Outcome Measures:</b> The following after 6 weeks and 6 months: motor function, sensory function (pinprick, light touch, deep pain), adverse event outcomes.</p> <p>The following after 6 months: Functional Independence Measure (FIM).</p> <p><b>Chronicity:</b> Individuals received the study treatment within 8 hr of sustaining injury.</p>	<p>touch, deep pain) among patients who received any of the treatments at 6 weeks or 6 months post injury (<math>p&gt;0.05</math> in all cases).</p> <p>3. Overall FIM scores at 6 months did not differ significantly between patients who received 24 hr MP and patients who received 48 hr MP (<math>p=0.08</math>); however, patients who received 48 hr MP gained significantly more sphincter control (<math>p=0.01</math>) and self-care (<math>p=0.03</math>) compared to those receiving 24 hr MP.</p> <p>4. Patients who received 48 hr MP experienced significantly more severe pneumonia than patients who received 24 hr MP or tirilazad mesylate after 6 weeks (<math>p=0.02</math>).</p> <p><b>Analyses of Time to Loading Dose (within 3-8 hr vs &gt;8 hr):</b></p> <p>5. Patients who received treatments within 3 hr showed no significant differences in neurological recovery in all three treatment groups (<math>p&gt;0.05</math>).</p> <p>6. Patients who initiated any MP treatment within 3-8 hr gained significantly more motor function after 6 months than those who initiated any MP treatment after 8 hr (<math>p=0.03</math>).</p> <p>7. Among patients who started treatment between 3-8 hr, patients who received 48 hr MP within 3-8 hr improved significantly more motor function than those receiving 24 hr MP at 6 weeks (<math>p=0.04</math>) and 6 months (<math>p=0.01</math>) post injury.</p> <p><b>Analyses of Severity of the Injury (complete vs. incomplete):</b></p> <p>8. Patients with incomplete injuries (receiving either 24 hr or 48 hr MP) recovered more motor function than patients with complete injuries after</p>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		6 weeks and 6 months compared to baseline measurements, but these differences were not significant ( $p \geq 0.05$ in all cases).
<p><a href="#">Bracken et al.</a> (1998)                      (One year follow up to Bracken et al. (1997))                      N=431</p>	<p><b>Outcome Measures:</b> The following after 1 year: motor function, sensory function (pinprick and light touch), Functional Independence Measure (FIM).</p>	<p><b>Initial Analysis:</b></p> <ol style="list-style-type: none"> <li>1. Patients receiving 48 hr MP did not differ from patients receiving 24 hr MP with regards to motor function improvement after 1 year (<math>p=0.232</math>).</li> <li>2. Patients who received 48 hr MP and 48 hr tirilazad mesylate experienced more deaths from pneumonia, respiratory distress syndrome, and respiratory failure compared to patients who received 24 hr MP, however this difference was not significant (<math>p=0.056</math>).</li> <li>3. There were no significant differences in FIM scores across any of the treatment groups one year later (<math>p &gt; 0.05</math>).</li> </ol> <p><b>Analyses of patients treated within 3 hr compared to patients treated between 3-8 hr:</b></p> <ol style="list-style-type: none"> <li>4. Patients who received any treatment within 3 hr did not differ in motor function after one year (<math>p &gt; 0.05</math>).</li> <li>5. Patients who received 24 hr MP within 3-8 hr experienced diminished motor function after one year. Patients who received 48 hr MP within 3-8 hr did not experience significant improvement in their motor function (<math>p=0.053</math>).</li> </ol> <p><b>Analyses of Severity of the Injury (complete vs. incomplete):</b></p> <ol style="list-style-type: none"> <li>6. The authors note that patients with incomplete injuries experienced more motor function recovery than patients with complete injuries (data not shown).</li> </ol>
<p><a href="#">Bracken et al.</a> (1990)                      USA</p>	<p><b>Population:</b> Mean age: not specified; Gender: not specified; Level of injury: not specified;</p>	<p><b>Overall Analysis:</b></p> <ol style="list-style-type: none"> <li>1. There were no significant improvements in motor function or sensory function in patients who</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
RCT PEDro=10 N=487	<p>Severity of injury: complete=60%, incomplete=40%.</p> <p><b>Treatment:</b> Patients were randomly allocated to receive either methylprednisolone (MP; 62.5 mg/mL), naloxone (25 mg/mL) or placebo. Both drugs were administered as a 15 minute loading dose followed by a 23 hr maintenance dose.</p> <p><b>Outcome Measures:</b> Motor function, sensory function (pinprick and light touch), adverse events. Outcomes were assessed at 6 weeks and 6 months.</p> <p><b>Chronicity:</b> Individuals were randomized to study groups within 12 hr of sustaining injury.</p>	<p>received either MP or naloxone compared to patients who received placebo 6 weeks and 6 months after injury (<math>p&gt;0.05</math>).</p> <p>2. There were no significant differences in adverse event outcomes during hospitalization between those who received MP, those who received naloxone, and those who received placebo (<math>p&gt;0.05</math>).</p> <p><b>Analyses of Time to Loading Dose (<math>\leq 8</math> h vs <math>&gt;8</math> h):</b></p> <p>3. Patients treated with MP within 8 hr had a significant improvement in motor function (<math>p=0.048</math>) and sensory touch function (<math>p=0.034</math>) 6 weeks later compared to those treated with placebo. No significant differences were seen with regards to pinprick sensory function (<math>p&gt;0.05</math>).</p> <p>4. Patients treated with MP within 8 hr had a significant improvement in motor function (<math>p=0.033</math>), pinprick scores (<math>p=0.016</math>) and touch (<math>p=0.030</math>) 6 months later compared to those treated with placebo.</p> <p>5. Patients treated with MP after 8 hr had no improvements in motor function or sensory function 6 weeks or 6 months after injury (<math>p&gt;0.05</math>) compared to those treated with placebo.</p> <p><b>Analyses by Injury Severity:</b></p> <p>6. Patients with complete injuries treated with MP had significant improvement in motor function 6 weeks after injury (<math>p=0.021</math>) compared to those treated with placebo. There were no significant improvements in sensory function.</p> <p>7. Patients with incomplete injuries treated with MP had no significant improvements in motor or sensory function 6 months after injury</p>



Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		<p>compared to those treated with placebo (<math>p&gt;0.05</math>).</p> <p>8. Patients with complete injuries treated with MP had significant improvement in motor function (<math>p=0.019</math>), pinprick sensation (<math>p=0.028</math>), and touch sensation (<math>p=0.050</math>) 6 months after injury compared to those treated with placebo.</p> <p>9. Patients with incomplete injuries treated with MP had significant improvement in motor function 6 months after injury (<math>p=0.018</math>) compared to those treated with placebo. There were no significant improvements in sensory function.</p>
<p><a href="#">Bracken et al.</a> (1992) (One year follow up to Bracken et al. (1990)) N=427</p>	<p><b>Outcome Measures:</b> The following after 1 year: motor function, and sensory function (response to pinprick and touch sensation)</p>	<ol style="list-style-type: none"> <li>1. Treatment with (30 mg/kg bolus and 5.4 mg/kg/hr for 23 hours) of MP is indicated for acute spinal cord trauma, but only if it can be started within 8 hours of injury.</li> <li>2. At 1 year, pneumonia occurred in 1.4% of naloxone-treated patients compared with 3.3% for placebo (<math>p=0.04</math>).</li> <li>3. Among all randomized patients more than 8 hours postinjury, those receiving either MP (<math>p=0.080</math>) or naloxone (<math>p=0.100</math>) recovered less motor function than those given placebo.</li> </ol>
<p><a href="#">Wu et al.</a> (2011) Taiwan Case Control N=32</p>	<p><b>Population:</b> Mean age=41.7 yr; Gender: male=84%, female=16%; Level of injury: cervical-lumbar; Severity of injury: complete=9%, incomplete=91%.</p> <p><b>Treatment:</b> Patients either received methylprednisolone (MP) within 8 hr post injury or delayed MP treatment (<math>\geq 8</math> hr of sustaining injury).</p> <p><b>Outcome Measures:</b> The following after questionnaire follow up (time span 3-69 months post injury):</p>	<ol style="list-style-type: none"> <li>1. Patients who received MP after 8 hr experienced slightly greater pain and an increased prevalence of neuropathic pain, but these differences were not significant (<math>p=0.155</math> and <math>p=0.141</math>, respectively).</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	severity of pain and presence of neuropathic pain. <b>Chronicity:</b> The time period since injury ranged from 3-69 months.	
<a href="#">Ito et al.</a> (2009) Japan Case control N=79	<b>Population:</b> Mean age: not specified; Gender: male=80%, female=20%; Level of injury: cervical; Severity of injury: complete=27%, incomplete=73%, AIS A-D. <b>Treatment:</b> Patients were either given methylprednisolone sodium succinate (MPSS) according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines (2003-July 2005) or no MPSS (August 2005-2007). <b>Outcome Measures:</b> The following after 3 months: neurological recovery using the ASIA motor score and ASIA impairment score at 3 months post injury, and complications. <b>Chronicity:</b> Individuals received treatment within 8 hr of sustaining injury.	<b>Overall Analyses</b> 1. There were no significant differences in neurologic improvement between patients who received MPSS and patients who did not receive MPSS according to the AIS ( $p>0.05$ ). 2. There were no significant differences in motor function between patients who received MPSS and patients who did not receive MPSS according to the ASIA motor score ( $p>0.05$ ). 3. Patients who received MPSS experienced significantly more total infections ( $p=0.028$ ) and pneumonia ( $p=0.019$ ) than patients who did not receive MPSS. <b>Analyses of Severity of Injury and Type of Injury:</b> 4. Among patients with complete injuries, there were no significant differences in motor function between those who received MPSS and those who did not receive MPSS according to the ASIA motor score ( $p>0.05$ ). 5. Among patients with incomplete injuries, there were no significant differences in motor function between those who received MPSS and those who did not receive MPSS according to the ASIA motor score ( $p>0.05$ ). 6. Among patients without fractures, there were no significant differences in neurologic improvement ( $p>0.05$ ) or motor function ( $p>0.05$ ) between those who received MPSS and those who did not receive MPSS according to the AIS and motor score.
<a href="#">Zhuang et al.</a> (2008)	<b>Population:</b> Mean age=43.4 yr; Gender: male=77%, female=23%;	1. Among patients with complete injuries, there were no significant

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China Pre-Post Test N=43	<p>Level of injury: cervical-lumbar; Severity of injury: complete=28%, incomplete=72%.</p> <p><b>Treatment:</b> All patients received methylprednisolone (MP) 30 mg/kg for 15 minutes and 5.4 mg/kg/h for 23 hr after a 45 minute interval, according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines.</p> <p><b>Outcome Measures:</b> The following after MP treatment compared to before MP treatment (time period not specified): sensory function (acupuncture sense and light touch) and motor function.</p> <p><b>Chronicity:</b> Individuals received treatment within 8 hr of sustaining injury.</p>	<p>differences in sensory function or motor function after MP treatment compared to before MP treatment (<math>p&gt;0.05</math>).</p> <p>2. Among patients with incomplete injuries, there was a significant decline in motor score after MP treatment compared to before MP treatment (<math>p&lt;0.01</math>). There were no significant differences in sensory function after MP treatment compared to before MP treatment (<math>p&gt;0.05</math>).</p>
<a href="#">Suberviola et al.</a> (2008) Spain Case Control N=82	<p><b>Population:</b> Mean age: not specified; Gender: male=84%, female=16%; Level of injury: cervical and non-cervical; Severity of injury: complete=54%, incomplete=46%.</p> <p><b>Treatment:</b> Patients either received methylprednisolone (MP) 30 mg/kg for 15 minutes and 5.4 mg/kg/h for 23 hr after a 45 minute interval, according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines or no MP.</p> <p><b>Outcome Measures:</b> The following after intensive care unit discharge: mortality, neurological function using the Frankel scale, adverse event outcomes.</p> <p><b>Chronicity:</b> Individuals were hospitalized within 8 hr of sustaining injury.</p>	<ol style="list-style-type: none"> <li>1. There were no significant differences in mortality between patients who received MP and patients who did not (OR=0.48, 95% CI: 0.08-3.64).</li> <li>2. There were no significant differences in neurological function using the Frankel scale between patients who received MP and patients who did not (OR=1.09; 95% CI: 0.35-3.66).</li> <li>3. Patients who received MP experienced significantly more overall infections (<math>p=0.004</math>), more respiratory infections (<math>p=0.02</math>), and more early-onset hyperglycemia (<math>p&lt;0.01</math>) than patients receiving no MP.</li> </ol>
<a href="#">Leypold et al.</a> (2007) USA Case Control N=82	<p><b>Population:</b> Mean age: not specified; Gender: male=80%, female=20%; Level of injury: cervical; Severity of injury: complete=100%, incomplete=0%, AIS A.</p>	<ol style="list-style-type: none"> <li>1. There were no significant differences in terms of the presence of spinal cord hemorrhages between patients who received MP and patients who did not (<math>p&gt;0.05</math>).</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p><b>Treatment:</b> Patients were treated with methylprednisolone (MP) bolus 30 mg/kg plus 5.4 mg/kg/h for 24 hr, according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines (1987-1993), or were given no MP (1998-2002; historical controls).</p> <p><b>Outcome Measures:</b> The following within 3 days of injury using MRI: presence/absence of intramedullary hemorrhage, length of intramedullary hemorrhage, length of spinal cord edema.</p> <p><b>Chronicity:</b> Individuals received treatment within 8 hr of sustaining injury.</p>	<ol style="list-style-type: none"> <li>2. Patients who received MP had significantly shorter mean length of intramedullary hemorrhage compared to the control group (<math>p=0.04</math>).</li> <li>3. There were no significant differences in the length of spinal cord edema in either group (<math>p&gt;0.05</math>).</li> <li>4. The authors note that younger patients were more likely than older patients to manifest edema and hemorrhage.</li> </ol>
<p><a href="#">Lee et al.</a> (2007)                      China                      Case Control                      N=138</p>	<p><b>Population:</b> Mean age=48.5 yr; Gender: male=68%, female=32%; Level of injury: C2-C7; Severity of injury: complete=69%, incomplete=31%.</p> <p><b>Treatment:</b> Patients either received methylprednisolone (MP; according to National Acute Spinal Cord Injury Study (NASCIS) II and III guidelines) or received no MP. Some patients also received surgery.</p> <p><b>Outcome Measures:</b> The following at follow-up examination (unspecified date): neurological function using the Frankel scale, adverse event outcomes.</p> <p><b>Chronicity:</b> The mean interval between injury and transfer and injury and transport was 6.9 hr and 23 minutes, respectively.</p>	<ol style="list-style-type: none"> <li>1. 11 (69%) of 16 complete SCI patients treated with surgery and MP improved by one Frankel score (no statistical analyses reported)*.</li> <li>2. 21 (68%) of 31 incomplete SCI patients treated with surgery and MP improved by one Frankel score (no statistical analyses reported)*.</li> <li>3. Steroid complications were noted in 14 (87.5%) of 16 patients with complete injuries and 8 (28.6%) of 28 patients with incomplete injuries and 2 (14.3%) of 14 patients with mild spinal cord contusion (no statistical analyses reported).</li> </ol> <p>*Patients not stratified by those receiving MP only vs. MP plus surgery, or those receiving MP according to NASCIS II vs. NASCIS III (for those who did not receive MP).</p>
<p><a href="#">Tsutsumi et al.</a> (2006)                      Japan                      Case Control                      N=70</p>	<p><b>Population:</b> Age range=13-86 yr; Gender: male=86%, female=14%; Level of injury: cervical; Severity of injury: complete=61%, incomplete=39%, AIS A-D.</p> <p><b>Treatment:</b> Patients received methylprednisolone (MP)</p>	<p><b>Overall Analyses:</b></p> <ol style="list-style-type: none"> <li>1. Patients who received MP experienced significantly more motor improvement than patients who did not receive MP after 6 weeks (<math>p=0.0033</math>) and 6 months (<math>p=0.0007</math>).</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines or no MP.</p> <p><b>Outcome Measures:</b> The following after 6 weeks and 6 months: neurological recovery using the ASIA motor scale, improvement in myotomal level.</p> <p>The following within 6 weeks: adverse event outcomes.</p> <p><b>Chronicity:</b> Individuals were admitted to hospital within 7 days after sustaining injury.</p>	<p>2. There were no significant differences with regard to myotomal level between patients who received MP and patients who did not at 6 weeks (<math>p=0.6456</math>) and 6 months (<math>p=0.1966</math>).</p> <p>3. There were no significant differences between patients who received MP and those who did not with regards to medical complications (<math>p&gt;0.05</math>).</p> <p><b>Analyses of Severity of the Injury (complete vs. incomplete):</b></p> <p>4. Among patients with incomplete injuries, those treated with MP experienced significantly more motor improvement after 6 weeks (<math>p=0.0195</math>) and 6 months (<math>p=0.0049</math>).</p> <p>5. Among patients with complete injuries, there were no significant differences in motor improvement between groups after 6 weeks (<math>p&gt;0.05</math>) and six months (<math>p&gt;0.05</math>).</p>
<p><a href="#">Rasool et al.</a> 2004                      India                      Prospective                      Controlled Trial                      N=48</p>	<p><b>Population:</b> Mean age: not specified; Gender: male=80%, female=20%; Level of injury: cervical; Severity of injury: complete=20%, incomplete=80%.</p> <p><b>Treatment:</b> Patients received methylprednisolone (MP) according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines or no MP (control group).</p> <p><b>Outcome Measures:</b> The following after 6 weeks and 6 months: neurological function using the ASIA scale (both motor and sensory function).</p> <p><b>Chronicity:</b> Individuals who presented to hospital within 8 hr of sustaining injury received treatment. Those who presented later than 8 hr post injury were placed in the control group.</p>	<p>1. Patients who received MP gained significantly more motor recovery than patients who did not receive MP after 6 weeks (<math>p&lt;0.001</math>).</p> <p>2. Patients who received MP gained significantly more sensory recovery with regard to pinprick (<math>p&lt;0.001</math>) and light touch (<math>p&lt;0.001</math>) scores than patients who did not receive MP after 6 weeks.</p> <p>3. Patients who received MP gained significantly more motor recovery than patients who did not receive MP after 6 months (<math>p&lt;0.001</math>).</p> <p>4. Patients who received MP gained significantly more sensory recovery with regard to pinprick (<math>p&lt;0.001</math>) and light touch (<math>p&lt;0.001</math>) scores than patients who did not receive MP after 6 months.</p>
<p><a href="#">Pollard &amp; Apple</a> (2003)</p>	<p><b>Population:</b> Mean age: not specified; Gender: not specified;</p>	<p>1. Patients who received MP did not significantly differ in neurological</p>

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USA Case Control N=412	<p>Level of injury: cervical; Severity of injury: complete=0%, incomplete=100%.</p> <p><b>Treatment:</b> Patients received methylprednisolone (MP) according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines or did not receive MP.</p> <p><b>Outcome Measures:</b> The following after discharge from rehabilitation: neurological function using the ASIA scale.</p> <p><b>Chronicity:</b> Individuals were admitted to hospital within 90 days of injury.</p>	<p>function compared to patients who did not receive MP (<math>p&gt;0.05</math>).</p> <p>2. Patients aged younger than 18 experienced significantly more neurological recovery than patients in any other age group (<math>p=0.002</math>).</p>
<p><a href="#">Poynton et al. (1997)</a>                      Ireland                      Case Control                      N<sub>initial</sub>=71, N<sub>final</sub>=63</p>	<p><b>Population:</b> Age range=17-76 yr; Gender: not specified; Level of injury: not specified; Severity of injury: complete=58%, incomplete=42%.</p> <p><b>Treatment:</b> Patients admitted before 8 hr of injury received methylprednisolone (MP) 30 mg/kg for 15 minutes and 5.4 mg/kg/h for 23 hr after a 45 minute interval according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines; patients admitted after 8 hr of injury received no MP.</p> <p><b>Outcome Measures:</b> The following at a follow-up examination (mean=29.6 months): neurological function using ASIA motor and sensory scores.</p> <p><b>Chronicity:</b> Individuals who presented to hospital within 8 hr of sustaining injury received treatment. Those who presented later than 8 hr post injury did not receive treatment.</p>	<ol style="list-style-type: none"> <li>1. There were no significant improvements in neurological function between patients who received MP and patients who did not (<math>p&gt;0.05</math>).</li> <li>2. The authors note that there were no complications attributed to the administration of MP.</li> <li>3. The authors note that neurological recovery was most likely in patients with incomplete injuries instead of complete injuries, and in patients who were tetraplegic versus paraplegic.</li> </ol>
<p><a href="#">Heary et al. (1997)</a>                      USA                      Case Control                      N=254</p>	<p><b>Population:</b> Mean age=26 yr; Gender: male=91%, female=9%; Level of injury: cervical-lumbar;</p>	<ol style="list-style-type: none"> <li>1. There were no significant differences in Frankel score improvement between patients who received</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>Severity of injury: complete=75%, incomplete=25%.</p> <p><b>Treatment:</b> Patients with gunshot wounds to the spine either received methylprednisolone (MP; according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines), dexamethasone (initial dose of 10-100 mg), or no steroids.</p> <p><b>Outcome Measures:</b> The following at follow-up examination (unspecified date): Frankel score, AIS score, adverse event outcomes.</p> <p><b>Chronicity:</b> Thirty-one patients received MP within 8 hr of injury. Of patients initially treated at an outside hospital (n=119), 95% were transferred to the study hospital within 48 hr of injury.</p>	<p>steroids and patients who did not receive steroids (<math>p&gt;0.05</math>).</p> <ol style="list-style-type: none"> <li>2. Patients who received MP did not experience a significant improvement in neurological recovery based on the ASIA score compared to patients who did not receive steroids (<math>p=0.41</math>).</li> <li>3. Patients who received dexamethasone did not experience a significant improvement in neurological recovery based on the ASIA score compared to patients who did not receive steroids (<math>p=0.077</math>).</li> <li>4. Patients who received dexamethasone experienced significantly more gastrointestinal complications compared to patients who did not receive steroids (<math>p=0.021</math>).</li> <li>5. Patients who received MP experienced significantly more episodes of pancreatitis compared to patients who did not receive steroids (<math>p=0.04</math>).</li> </ol>
<p><a href="#">Merry et al.</a> (1996)                      USA                      Case Control                      N<sub>initial</sub>=19, N<sub>final</sub>=15</p>	<p><b>Population:</b> Mean age=50 yr; Gender: male=53%, female=47%; Level of injury: cervical-lumbar; Severity of injury: complete=0%, incomplete=100%.</p> <p><b>Treatment:</b> Patients with incomplete SCI received steroids (either methylprednisolone (MP), dexamethasone or both) or no steroids. Treatments differed with regards to duration, combination, and protocol among patients.</p> <p><b>Outcome Measures:</b> The following at hospital discharge: neurological function using Frankel scale, adverse event outcomes.</p> <p>The following at last clinic visit (mean=14.4 months): neurological function using Frankel scale.</p>	<ol style="list-style-type: none"> <li>1. Comparing discharge from hospital to admission to hospital, most patients (11/15) improved by at least one Frankel grade*. The authors did not differentiate steroid patients from non-steroid patients.</li> <li>2. Comparing most recent clinic visit to discharge from hospital, few patients (5/15) improved by at least one Frankel grade*. The authors did not differentiate steroid patients from non-steroid patients.</li> <li>3. The authors noted hospital complications occurred in 11 of the 14 patients who received steroids and all 3 of the patients who died had received steroids*.</li> </ol> <p>*No statistical analyses were performed.</p>

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	<p><b>Chronicity:</b> Four of 6 patients treated before May 1990 were administered steroid treatment on average 7 hr post injury. Eight of 13 patients treated after May 1990 received steroid treatment on average 4 hr post injury. One patient received treatment 41 hr post injury.</p>	
<p><a href="#">Levy et al.</a> (1996)                      USA                      Case Control                      N=236</p>	<p><b>Population:</b> Mean age=25.6 yr; Gender: male=94%, female=6%; Level of injury: cervical-lumbar; Severity of injury: complete=55%, incomplete=45%.</p> <p><b>Treatment:</b> Patients with penetrating gunshot wounds either received methylprednisolone (MP) according to National Acute Spinal Cord Injury Study (NASCIS) II within 8 hr of admission or did not receive MP.</p> <p><b>Outcome Measures:</b> The following at discharge from rehabilitation compared to admission to rehabilitation: neurological function based on the Frankel scale, autonomy after injury, ability to ambulate.</p> <p>The following during hospital stay: adverse event outcomes.</p> <p><b>Chronicity:</b> Individuals received steroid treatment within 8 hr of sustaining injury.</p>	<ol style="list-style-type: none"> <li>1. Patients who received MP did not significantly improve in neurological recovery based on the Frankel scale compared to patients who did not receive MP (p&gt;0.05).</li> <li>2. Patients who received MP did not significantly improve in autonomy after injury or the ability to ambulate compared to patients who did not receive MP (p&gt;0.05).</li> <li>3. There were no significant differences in adverse event outcomes during hospitalization between patients who received MP and patients who did not (p&gt;0.05).</li> </ol>
<p><a href="#">Gerhart et al.</a> (1995)                      USA                      Case Control                      N<sub>1990-1991</sub>=151,                      N<sub>1993</sub>=127</p>	<p><b>Population:</b> Mean age: not specified; Gender: not specified; Level of injury: cervical-sacral; Severity of injury: Frankel A-D.</p> <p><b>Treatment:</b> Patients either received methylprednisolone (MP) according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines or did not receive MP. Two observation periods were analyzed: 1990-1991 and 1993.</p>	<p><b>Analyses During 1990-1991:</b></p> <ol style="list-style-type: none"> <li>1. Patients who received MP improved by at least one Frankel grade more than patients who did not receive MP, but this trend was not significant (p=0.118).</li> <li>2. There were no significant differences in neurological recovery by two or more Frankel grades between patients receiving MP and not receiving M (p=0.486).</li> </ol>



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	<p><b>Outcome Measures:</b> The following at hospital discharge: neurological function based on the Frankel Scale.</p> <p><b>Chronicity:</b> Not specified.</p>	<p><b>Analyses During 1993:</b></p> <ol style="list-style-type: none"> <li>3. Patients who received MP improved by at least one Frankel grade significantly more than patients who did not receive MP (<math>p=0.044</math>).</li> <li>4. There were no significant differences in neurological recovery by two or more Frankel grades between patients receiving MP and not receiving MP (<math>p=0.942</math>).</li> </ol>
<p><a href="#">George et al.</a> (1995) USA Case Control <math>N_{initial}=145</math>, <math>N_{final}=130</math></p>	<p><b>Population:</b> Mean age=34 yr; Gender: male=77%, female=23%; Level of injury: cervical, dorsal spine region, lumbar; Severity of injury: complete=64%, incomplete=36%.</p> <p><b>Treatment:</b> Patients were analyzed from a 1989-1992 registry. Those from the first half of this time span were given no methylprednisolone (MP) and patients from the second half of this time span were given MP according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines.</p> <p><b>Outcome Measures:</b> The following at hospital discharge: mortality, patient mobility, adverse event outcomes.</p> <p>The following at rehabilitation discharge (when available): Functional Independence Measure (FIM).</p> <p><b>Chronicity:</b> Mean time from injury to treatment administration was 152 minutes.</p>	<ol style="list-style-type: none"> <li>1. There were no significant differences in mortality between the two groups (<math>p&gt;0.05</math>).</li> <li>2. There was significantly poorer mobility at the time of discharge in patients treated with MP compared patients receiving no treatment (<math>p&lt;0.05</math>).</li> <li>3. There were no significant differences in FIM scores upon discharge between MP and no MP group (<math>p&gt;0.05</math>).</li> <li>4. There was a higher occurrence of complications in patients who received MP, but this trend was not significant (<math>p&gt;0.05</math>).</li> </ol>
<p><a href="#">Prendergast et al.</a> (1994) USA Case Control N=54</p>	<p><b>Population:</b> Mean age=35.8 yr; Gender: male=80%, female=20%; Level of injury: not specified; Severity of injury: complete=46%, incomplete=54%.</p> <p><b>Treatment:</b> Patients were given no methylprednisolone (MP; before 1990) or were given MP according to National Acute Spinal Cord</p>	<ol style="list-style-type: none"> <li>1. There were no significant differences in motor function between the MP treated group and the control group after 1 week, 2 weeks, 1 month, and 2 months (<math>p&gt;0.05</math>).</li> <li>2. There were no significant differences in sensory function between the MP treated group and the control group after 1 week, 2 weeks, 1 month, and 2 months (<math>p&gt;0.05</math>).</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	Injury Study (NASCIS) II guidelines (after 1990). <b>Outcome Measures:</b> The following after 4 days, 1 week, 2 weeks, 1 month, and two months: motor function, sensory function (pinprick and light touch). <b>Chronicity:</b> Not specified.	3. Of patients with penetrating SCI, those treated with MP had significantly lower motor functioning at 4 days and at one week post SCI than those treated with no MP ( $p < 0.05$ ).
<a href="#">Kiwinski</a> (1993) Poland Case Control N=620	<b>Population:</b> Mean age: not specified; Gender: not specified; Level of injury: cervical; Severity of injury: complete=60%, incomplete=40%. <b>Treatment:</b> Patients received one of three treatments during 1976-1991: low doses dexamethasone (<24 mg), high doses dexamethasone (>24 mg), or no dexamethasone. The dosages and duration of delivery varied from patient to patient. <b>Outcome Measures:</b> The following during hospital stay: neurological recovery (outcome measure not specified). Recovery is considered 'marked' if patient advanced 2 degrees on the scale or if paresis disappeared. <b>Chronicity:</b> Individuals were admitted to hospital within 24 hr post injury.	1. Patients with a complete injury receiving dexamethasone achieved a 'marked' recovery significantly more than those receiving no dexamethasone. 2. Among patients with incomplete injuries, there was no overall difference in neurological recovery between patients who received dexamethasone and those who did not. However, significantly more patients who received dexamethasone achieved a 'marked' recovery compared to those who did not receive dexamethasone. 3. Among patients with complete injuries, neurological recovery did not differ significantly between those who received a high dose of dexamethasone and those who received a low dose; however, patients with incomplete injuries who received higher doses of dexamethasone experienced more neurological recovery than those who received low doses of dexamethasone. 4. The authors note that the effect of dexamethasone was most effective if given within the first 8 hr after injury. No statistical analyses were reported.
<a href="#">Galandiuk et al.</a> (1993) USA Case Control N=32	<b>Population:</b> Mean age: not specified; Gender: not specified; Level of injury: cervical-thoracic; Severity of injury: complete=69%, incomplete=31.	1. The length of hospital stay was longer in patients receiving MP compared to patients not receiving MP, however this trend was not significant ( $p = 0.65$ ).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p><b>Treatment:</b> Patients received either methylprednisolone (MP; from 1990-1993) 30 mg/kg followed by 5.4 mg/kg/h for 23 hr, according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines, or no MP (from 1987-1993).</p> <p><b>Outcome Measures:</b> The following during hospital stay: length of hospital stay, adverse event outcomes and length of hospital stay, the immunosuppressive effects of steroids. The following after 6 months: motor function, sensory function.</p> <p><b>Chronicity:</b> Not specified.</p>	<ol style="list-style-type: none"> <li>2. There were no significant differences in the episodes of pneumonia or infections between the MP group and the no MP group (p=0.20).</li> <li>3. Inhibition of chemotaxis of macrophages and neutrophils, inhibition of interleukin-2 and interleukin gamma, inhibition of antigens, and decrease of immunoglobulin G levels were observed in the MP group compared to the no MP group. No statistical tests were performed on these measures.</li> <li>4. Patients treated with MP experienced significant improvements in motor score after 6 months compared to patients who did not receive MP (p=0.015).</li> <li>5. Patients treated with MP experienced greater sensory function gains after 6 months compared to patients who did not receive MP, but this trend was not significant (p=0.20).</li> </ol>

## Discussion

MP has been the main pharmacological treatment of acute SCI since the 1980s (Michael B Bracken et al., 1984), but its effectiveness still remains unclear. The first large-scale RCT to report significant neurological recovery due to do this pharmaceutical agent (NASCIS II, (M. B. Bracken et al., 1990), and its follow up study (NASCIS III, (M. B. Bracken et al., 1997) initiated the mandatory protocol that MP be the standard of care for all acute SCI patients. These studies have since received several criticisms for their statistical analyses, randomization methods and interpretations (Coleman et al., 2000; Hurlbert, 2000; Nesathurai, 1998; Short, El Masry, & Jones, 2000). For example, the initial overall findings reported no improvement between the group receiving MP and the groups that did not. Significant results were only obtained from subsequent post hoc analyses of a subset of individuals, and these results showed only minor improvements.

Following these concerns, several studies were launched to specifically address the efficacy of MP. As a result of the initial broad acceptance of MP as a required therapy, a randomized placebo comparison study was not feasible in North America due to ethical considerations. Researchers instead conducted retrospective studies comparing individuals injured before and after MP administration was mandated. Many of these studies found no effect of MP on neurological

recovery (e.g., (Ito et al., 2009; Pointillart et al., 2000; Pollard & Apple, 2003; Poynton et al., 1997; Suberviola et al., 2008), with a few exceptions (Rasool T, 2004; Tsutsumi et al., 2006). Overall improvements in motor and sensory function (due to MP or other methods) tend to be more likely in younger patients (Burns et al., 1997; Pollard & Apple, 2003) and in patients with incomplete injuries more so than complete injuries (Tsutsumi et al., 2006; Zhuang C, 2008).

One of the main concerns with administering MP unnecessarily is that it is known to have many side effects. The final NASCIS study reported MP to be significantly associated with urinary tract infections (M. B. Bracken et al., 1997). Studies have since confirmed that patients receiving MP experience significantly more total infections (Suberviola et al., 2008), pneumonia (Gerndt et al., 1997; Ito et al., 2009), pancreatitis (Heary et al. 1997) and gastrointestinal complications (Chikuda et al., 2014; Matsumoto et al., 2001) compared to patients who do not receive the drug. Higher rates of hyperglycemia (Pointillart et al., 2000), myopathy (Qian et al., 2005) and wound infection (Michael B Bracken et al., 1984; Ito et al., 2009) have also been attributed to MP. Because of rising concerns that this drug may only incur moderate benefits at the cost of high risk side effects, MP is now only a therapeutic option, and no longer the mandate, for treating acute SCI.

There have been no RCTs published investigating the effects of dexamethasone. One retrospective study examining the effect of this steroid also found no effect on neurological improvement, and this drug was associated with significantly more gastrointestinal complications than the control group (Heary et al., 1997).

One study prospectively assessed the effectiveness of progesterone and vitamin D in improvign neurological recovery post acute SCI in a randomized clinical trial; Aminmansour et al. (Aminmansour et al., 2016) reported a neurological benefit (motor and sensory scores) for the experimental, but not placebo, group at 6 months. However, there were no improvements in ASIA scores.

## Conclusion

There is level 1a evidence (from four RCTs, one pre-post test, one prospective controlled trial, and nine case control studies; (M. B. Bracken et al., 1990; M. B. Bracken et al., 1997; M. B. Bracken et al., 1998; George et al., 1995; Gerhart et al., 1995; Heary et al., 1997; Ito et al., 2009; Levy et al., 1996; Pointillart et al., 2000; Pollard & Apple, 2003; Poynton et al., 1997; Prendergast et al., 1994; Rasool T, 2004; Suberviola et al., 2008; Zhuang C, 2008) that methylprednisolone is not effective in promoting neurological recovery in acute SCI individuals.

There is level 1a evidence (from two RCTs and three case control studies; (M. B. Bracken et al., 1997; Heary et al., 1997; Ito et al., 2009; Pointillart et al., 2000; Suberviola et al., 2008) that methylprednisolone is associated with the development of medical complications when used in acute SCI individuals; However, there is level 3 evidence (from three case control studies; (Galandiuk et al., 1993; Levy et al., 1996; Tsutsumi et al., 2006) that methylprednisolone is not associated with the development of medical complications in acute SCI individuals.

There is level 3 evidence (from two case control studies; (Heary et al., 1997; Kiwerski, 1993) that dexamethasone is not effective in promoting neurological recovery in acute SCI individuals.

There is level 3 evidence (from two case control studies; (Heary et al., 1997; Merry et al., 1996) that dexamethasone may be associated with the development of medical complications when used to treat acute SCI individuals.

There is level 1b evidence (from one RCT;(Aminmansour et al., 2016)) that progesterone and vitamin D is not effective in promoting neurological recovery in acute SCI individuals.

### Key Points

Methylprednisolone is not effective for neurological recovery during the acute phase post SCI, and there is conflicting evidence whether its use is associated with the development of medical complications.

Dexamethasone is not effective for neurological recovery during the acute phase post SCI and may be associated with the development of medical complications.

Progesterone and vitamin D is not effective for neurological recovery during the acute phase post SCI.

## 4.2 Naloxone

Naloxone is an opiate-receptor blocker that is thought to improve spinal blood flow in SCI patients (Flamm et al., 1985). Animal models of acute SCI have shown that naloxone effectively reduces ischemia and promotes neurological recovery (Faden, Jacobs, & Holaday, 1981a, 1981b; Young, Flamm, Demopoulos, Tomasula, & DeCrescito, 1981). One early phase-one clinical trial deemed naloxone to be safe when administered to patients with acute SCI (Flamm et al., 1985).

Table 3. Naloxone for Neuroprotection in Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<a href="#">Bracken et al.</a> (1990) USA RCT PEDro=10 N=487	<b>Population:</b> Age range=13-34 yr; Gender: not specified; Level of injury: not specified; Severity of injury: complete= 60%, incomplete=40%. <b>Treatment:</b> Patients were randomized to receive either naloxone (25 mg/mL), methylprednisolone (MP; 62.5 mg/mL) or placebo. Both drugs were administered as a 15 minute loading dose followed by a 23 hr maintenance dose. <b>Outcome Measures:</b> The following after 6 weeks and 6 months: motor function,	<b>Overall Analysis:</b> 1. There were no significant improvements in motor function or sensory function in patients who received either naloxone or MP compared those who received placebo 6 weeks and 6 months after injury (p>0.05). 2. There were no significant differences in adverse event outcomes during

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	sensory function (pinprick and light touch), adverse event outcomes. <b>Chronicity:</b> Individuals were randomized to study groups within 12 hr of sustaining injury.	hospitalization between those who received naloxone, those who received MP, and those who received placebo (p>0.05).

## Discussion

The only study since 1990 that has investigated the neuroprotective effectiveness of naloxone in acute SCI was conducted by Bracken et al. (1990). Overall, the authors found no significant differences between individuals who received naloxone and those in the placebo group in terms of motor recovery, sensory recovery and medical complications.

## Conclusion

There is level 1b evidence (from one RCT; (M. B. Bracken et al., 1990) that naloxone is not effective for the promotion of neurological recovery in acute SCI individuals.

### Key Points

Naloxone is not effective for neurological recovery during the acute phase post SCI.

## 4.3 Tirilazad Mesylate

The discovery that a main neuroprotective function of MP is due to its lipid peroxidase action instead of its glucocorticoid receptor action initiated the development of steroid analogues that were mechanistically similar but did not cause associated side-effects. One such drug, tirilazad mesylate, was especially effective for recovering neural function in spinal cord injured animal models (e.g., (Anderson et al., 1988; E. D. Hall, 1988; Holtz & Gerdin, 1991, 1992). Like MP, tirilazad mesylate inhibits lipid peroxidation and stabilizes neuronal membranes by scavenging oxygen free radicals. Tirilazad mesylate incorporates into the membrane lipid bilayer, where it restricts the movement of free oxygen radicals and prevents them from spreading to neighbouring nerves (Kavanagh & Kam, 2001). In a large RCT of tirilazad mesylate used in head injured individuals, this pharmaceutical agent was shown to have no effect on recovery after six months compared to placebo (Marshall et al., 1998). Only one clinical trial has examined the effectiveness of tirilazad mesylate in acute SCI (Bracken et al. (1997), where its neuroprotective benefits were compared to those of MP.

Table 4. Tirilazad Mesylate for Neuroprotection in Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<p><a href="#">Bracken et al.</a> (1997) USA RCT PEDro=7 N=499</p>	<p><b>Population:</b> Mean age: not specified; Gender: male=85%, female=15%; Level of injury: not specified; Severity of injury: complete=50%, incomplete=50%.</p> <p><b>Treatment:</b> Patients were randomly assigned to receive either tirilazad mesylate for 48 hr (2.5 mg/kg), methylprednisolone (MP) for 24 hr (5.4 mg/kg), or MP for 48 hr (5.4 mg/kg). All treatment groups initially received a bolus of MP (30 mg/kg). The 24 hr MP group served as the reference; there was no placebo group.</p> <p><b>Outcome Measures:</b> The following after 6 weeks and 6 months: motor function, sensory function (pinprick, light touch, deep pain), adverse event outcomes.</p> <p>The following after 6 months: Functional Independence Measure (FIM).</p> <p><b>Chronicity:</b> Individuals received the study treatment within 8 hr of sustaining injury.</p>	<ol style="list-style-type: none"> <li>1. Patients who received tirilazad mesylate recovered motor function at rates similar to or slightly higher than patients who received 24 hr MP (<math>p&gt;0.05</math>).</li> <li>2. Patients who received tirilazad mesylate did not achieve significantly higher FIM scores compared to patients who received 24 hr MP 6 weeks (<math>p=0.27</math>) and 6 months (<math>p=0.15</math>) after injury.</li> <li>3. There were no significant differences in sensory function (pinprick, light touch, deep pain) among patients who received any of the treatments at 6 weeks or 6 months post injury (<math>p&gt;0.05</math> in all cases).</li> <li>4. Patients who received tirilazad mesylate or 24 hr MP experienced significantly less severe pneumonia after 6 weeks than patients who received 48 hr MP (<math>p=0.02</math>).</li> </ol>
<p><a href="#">Bracken et al.</a> (1998) (One year follow up to Bracken et al. 1997)</p>	<p><b>Outcome Measures:</b> The following after 1 year: motor function, sensory function (pinprick and light touch), Functional Independence Measure (FIM).</p>	<p><b>Initial Analysis:</b></p> <ol style="list-style-type: none"> <li>5. Patients who received tirilazad mesylate recovered motor function at rates similar to patients who received 24 hr MP (<math>p&gt;0.05</math>).</li> <li>6. There were no significant differences in FIM scores across any of the treatment groups (<math>p&gt;0.05</math>).</li> <li>7. Patients who received tirilazad mesylate and 48 hr MP experienced more deaths from pneumonia, respiratory distress syndrome, and respiratory failure compared to patients who received 24 hr MP, however this difference was not significant (<math>p=0.056</math>).</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
		8. Urinary tract infections were significantly more common in patients who received 48 hr tirilazad mesylate compared to patients who received MP ( $p=0.01$ ). <b>Analyses of patients treated within 3 hr compared to patients treated between 3-8 hr:</b> 9. Patients who received any treatment within 3 hr did not differ significantly in motor function ( $p>0.05$ ). <b>Analyses of Severity of the Injury (complete vs. incomplete):</b> 10. The authors note that patients with incomplete injuries experienced more motor function recovery than patients with complete injuries (data not shown).

### Discussion

At present, there have been no studies comparing acute SCI individuals who received tirilazad mesylate to those who received a placebo. The only study involving this drug to date was conducted by Bracken et al. (1997) that compared a long-term and short-term dose of MP to a long term dose of tirilazad mesylate. In this study, tirilazad mesylate exhibited the same effectiveness as a short-term dose of MP and was also associated with significantly higher rates of complications (M. B. Bracken et al., 1998).

### Conclusion

There is level 1b evidence (from one RCT; (M. B. Bracken et al., 1997) that tirilazad mesylate is no more effective than methylprednisolone in promoting neurological recovery in acute SCI individuals.

### Key Points

Tirilazad mesylate is no more effective than methylprednisolone for neurological recovery during the acute phase post SCI



## 4.4 Nimodipine

Nimodipine is a calcium channel blocker initially developed to treat high BP. Its mechanism of action in treating acute SCI is thought to include lowering of BP and slowing the flow of calcium into blood vessels to reduce injury related ischemia (Fehlings & Baptiste, 2005). Nimodipine has only been investigated in one clinical trial for acute SCI in humans to date.

Table 5. Nimodipine for Neuroprotection in Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<p><a href="#">Pointillart et al. (2000)</a> (English translation of Petitjean et al. (1998)) France RCT PEDro=6 N=106</p>	<p><b>Population:</b> Age range=20-47 yr; Gender: male=90%, female=10%; Level of injury: not specified; Severity of injury: complete=45%, incomplete=55%.</p> <p><b>Treatment:</b> Patients were randomly assigned to one of four groups: methylprednisolone (MP), nimodipine, MP + nimodipine, or no treatment. The dosages of nimodipine were 0.15 mg/kg/h over 2 hr followed by 0.03 mg/kg/h for 7 days. The dosages of MP followed National Acute Spinal Cord Injury Study (NASCIS) II guidelines and were 30 mg/kg over 1 hr followed by 5.4 mg/kg/h for 23 hr.</p> <p><b>Outcome Measures:</b> The following after 1 year: neurological function based on American Spinal Injury Association (ASIA) score (motor and sensory), adverse event outcomes.</p> <p><b>Chronicity:</b> Individuals were hospitalized within 8 hr of sustaining injury.</p>	<ol style="list-style-type: none"> <li>1. After 1 year, there were no significant differences in neurological recovery based on ASIA scores among the four groups (<math>p&gt;0.05</math>).</li> <li>2. Patients who received nimodipine and those who received no medication had significantly lower rates of hyperglycemia than patients who received MP (<math>p&lt;0.05</math>).</li> <li>3. The authors noted that patients with incomplete injuries experienced significantly more neurological recovery than patients with complete injuries (<math>p&lt;0.0001</math>).</li> </ol>

## Discussion

Pointillart et al. (2000) did not find any significant differences in terms of neurological recovery among individuals receiving MP, nimodipine, MP plus nimodipine, or no treatment. Animal studies have shown that nimodipine on its own may not be beneficial for treating SCI (Faden, Jacobs, & Smith, 1984; Ford & Malm, 1985), but when used in combination with other agents, such as adrenaline, there were significant effects on enhancing spinal cord blood flow (Ross & Tator, 1991). Larger, randomized clinical trials are necessary to determine the effectiveness of nimodipine on neurological recovery in acute SCI.

## Conclusion

There is level 1b evidence (from one RCT; (Pointillart et al., 2000) that nimodipine is not effective in promoting neurological recovery in acute SCI individuals.

### Key Points

Nimodipine is not effective for neurological recovery during the acute phase post SCI.

## 4.5 Erythropoietin

Erythropoietin (EPO) is a glycoprotein hormone that primarily controls red blood cell production. Interest in utilizing this pharmaceutical agent to treat acute SCI stems from one of its most commonly studied secondary functions, the prevention of neuronal apoptosis in the presence of ischemia (Siren et al., 2001). Potential mechanisms by which EPO may reduce neuronal apoptosis include its ability to elicit anti-inflammatory properties, minimize lipid peroxidation, scavenge free radicals, regenerate axons, and reduce calcium ions and influx of glutamate in *in vitro* and *in vivo* animal studies (Matis & Birbilis, 2009). Experimental studies in animal models of SCI have shown that EPO elicits a neuroprotective benefit that contributes to neurological recovery after SCI (Hong, Hong, Chen, Wang, & Hong, 2011; Okutan, Solaroglu, Beskonakli, & Taskin, 2007). To date, there are four studies that have evaluated EPO for possible neuroprotection after SCI in humans.

Table 6. Erythropoietin for Neuroprotection in Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<a href="#">Alibai et al.</a> 2015 Iran RCT PEDro= 8 N <sub>initial</sub> = 27, N <sub>final</sub> = 20	<p><b>Population:</b> Mean age= 40.1±9.5yr; Gender: male= 90%, female= 10%; Level of injury: cervical; Severity of injury: complete= 60%, incomplete= 40%</p> <p><b>Treatment:</b> Patients were first administered methylprednisolone per standard protocol. Patients were then randomly assigned to receive erythropoietin or placebo. The EPO dosage was 500 IU/mL immediately and 24 hours later.</p> <p><b>Outcome Measures:</b> Assessed baseline, 1, 6, and 12 months post-injury: ASIA sensory and motor scores.</p>	<ol style="list-style-type: none"> <li>1. No significant differences between EPO and placebo groups on ASIA motor scores at any time point (<math>p&gt;0.05</math>).</li> <li>2. No significant differences between EPO and placebo groups on ASIA sensory scores at any time point (<math>p&gt;0.05</math>).</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p><b>Chronicity:</b> Individuals were studied within 8 hr of sustaining injury.</p>	
<p><a href="#">Costa et al.</a> 2015                      Italy                      RCT                      PEDro= 7                      N<sub>initial</sub>= 19, N<sub>final</sub>= 19</p>	<p><b>Population:</b> Mean age= 27.67y Gender: male= 94.7%, female= 5.3%; Level of injury: cervical, thoracic; Severity of injury: AIS A or B</p> <p><b>Treatment:</b> Participants were randomized to receive either methylprednisolone or erythropoietin treatment groups for 48 hours.</p> <p><b>Outcome Measures:</b> ASIA motor and sensory, MAS, Penn Score, VAS, SCIM. Evaluated at baseline, day 3, 7, 14, 30, 60, and 90.</p> <p><b>Chronicity:</b> Screened and enrolled within 8 hours of sustaining injury.</p>	<p>1. No between-groups difference on ASIA motor and sensory, MAS, Penn score, VAS or SCIM (p&gt;0.05) at day 90.</p>
<p><a href="#">Alibai et al.</a> 2014                      Iran                      RCT                      PEDro=6                      N=30</p>	<p><b>Population:</b> Age range=18-65 yr; Gender: male=77%, female=23%; Level of injury: cervical-thoracic; Severity of injury: complete=47%, incomplete=53%.</p> <p><b>Treatment:</b> Patients were randomly assigned to receive either recombinant human erythropoietin (rhEPO) + methylprednisolone sodium succinate (MPSS; 500 unit/kg of rhEPO) or placebo + MPSS. MPSS was administered according to National Acute Spinal Cord Injury Study (NASCIS) III guidelines.</p> <p><b>Outcome Measures:</b> The following after 1 week, 1 month, and 6 months: neurological recovery using the AIS. The following after 6 months: sexual dysfunction.</p> <p><b>Chronicity:</b> Individuals studied were admitted to hospital within less than 6 hr after trauma.</p>	<p>1. Patients who received rhEPO + MPSS recovered significantly more neurological function according to the AIS compared to patients who received placebo + MPSS after 1 week (p=0.046), 1 month (p=0.021) and after 6 months (p=0.018).</p> <p>2. There were no significant differences in sexual dysfunction between patients who received rhEPO + MPSS and patients who received placebo + MPSS (p&gt;0.05).</p>
<p><a href="#">Xiong et al.</a> 2011                      China                      Prospective Control Trial                      N=63</p>	<p><b>Population:</b> Mean age=53 yr; Gender: male=62%, female=38%; Level of injury: cervical-thoracic; Severity of injury: complete=14%, incomplete=86%.</p> <p><b>Treatment:</b> Patients who developed ischemia-reperfusion injuries during spinal decompression surgery received either erythropoietin (EPO) + methylprednisolone (MP) or MP alone. MP</p>	<p>1. Patients who received EPO + MP experienced significantly higher neurological recovery based on the ASIA scale compared to those receiving MP alone after 1 week, 1 year, and 2 years (p&lt;0.05).</p> <p>2. Patients who received EPO + MP achieved significantly</p>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>was delivered intravenously according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines. EPO was injected intramuscularly three times a week (3000U/vial) for 8 weeks.</p> <p><b>Outcome Measures:</b> The following after 1 week, 1 year, and 2 years: neurological recovery using ASIA score (motor function and sensory function), activities of daily living (ADLs), and adverse event outcomes.</p> <p><b>Chronicity:</b> Individuals were studied at 1 week, 1 year and 2 years post spinal surgery.</p>	<p>higher ADL scores than patients who received MP alone 1 week and 1 year after treatment (<math>p &lt; 0.05</math>).</p> <p>3. Three patients who received EPO + MP and two patients who received MP alone experienced adverse event outcomes that resolved after treatment. No statistical tests were performed to determine significant differences between the two groups.</p>

## Discussion

Although two early unblinded studies showed promising results for EPO in treating acute SCI (E. Alibai, Zand, Rahimi, & Rezaianzadeh, 2014; Xiong et al., 2011), two subsequent, blinded studies failed to demonstrate benefit to EPO for neurologic outcomes post-SCI. It is important to note that all studies had very small sample sizes ( $n < 70$ ) and that in the positive trials, participants were neither blinded nor randomized. Both studies using randomized double-blind (E. A. Alibai, Baghban, Farrokhi, Mohebali, & Ashraf, 2015) or single-blind (Costa et al., 2015) methodology did not detect a statistically significant difference between EPO and control, although sample sizes were small ( $n < 30$ ) and may have been underpowered to detect a difference. Large-scale blinded RCTs are warranted to determine the effectiveness of EPO in treating acute SCI. At present, there are no guidelines that recommend the use of EPO for neuroprotection in the acute phase of SCI.

## Conclusion

There is level 1a evidence (from one double-blind RCT; (E. A. Alibai et al., 2015) and one single-blind RCT; (Costa et al., 2015) that acute administration of erythropoietin does not improve neurological outcomes post-SCI; however, there is level 1b evidence (from one RCT; (E. Alibai et al., 2014) and one prospective controlled trial; (Xiong et al., 2011)) that erythropoietin is effective in promoting neurological recovery in acute SCI individuals.

## Key Points

There is conflicting evidence regarding the effectiveness of erythropoietin for neurological recovery during the acute phase post SCI.

## 4.6 GM-1 Ganglioside

Gangliosides are naturally occurring molecules in nerve cell membranes. They are thought to have a role in neural development, as well as cellular recognition and neuronal communication (Yu, Tsai, & Ariga, 2012). Synthetic versions of these molecules, such as monosialotetrahexosylganglioside GM1 sodium salt (commonly referred to as GM-1 ganglioside), have been used in the treatment of other neurological conditions such as stroke (Candelise & Ciccone, 2002) and Parkinson’s disease (J. S. Schneider, 1998). Although their exact mechanism of action is unknown, it is currently thought that gangliosides prevent cellular apoptosis, elicit anti-excitotoxic activity, and help initiate neurogenesis in the central nervous system (Mocchetti, 2005).

Table 7. GM-1 Ganglioside for Neuroprotection in Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<p><a href="#">Geisler et al.</a> (2001)  <a href="#">Geisler et al.</a> (2001)  <a href="#">Geisler et al.</a> (2001)                      USA                      RCT                      PEDro=8                      N=760</p>	<p><b>Population:</b> Age range=17-69 yr; Gender: male=80%, female=20%; Level of injury: cervical-thoracic; Severity of injury: complete=63.4%, incomplete=36.6%.</p> <p><b>Treatment:</b> Patients were randomly assigned to receive either low dose monosialotetrahexosylganglioside (GM-1) ganglioside (Sygen®; 300 mg loading dose, followed by 100 mg/day for 56 days), high dose Sygen® (600 mg loading dose followed by 200 mg/day for 56 days), or placebo within 72 hr of injury. Treatments were administered through a gastric nasal tube. All patients initially received methylprednisolone sodium succinate (MPSS) according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines for the first 24 hr before receiving Sygen® treatment.</p> <p><b>Outcome Measures:</b> The following at 6 months: neurological recovery using the AIS and the modified Benzel Classification scale, ASIA motor function, ASIA sensory function (pinprick and light touch),</p>	<ol style="list-style-type: none"> <li>1. Overall, there were no significant differences in neurological recovery (both motor and sensory) between Sygen® groups or the placebo (p&gt;0.05).</li> <li>2. Neurological recovery according to the Modified Benzel Classification scale occurred faster in patients receiving Sygen® (p&lt;0.0128), but patients who received placebo reached the same level of improvement by 26 weeks. Also, patients who received Sygen® experienced a faster recovery of ASIA motor and sensory functions, but patients who received placebo reached the same degree of function.</li> <li>3. There were trends for patients receiving Sygen® to show improved bowel and bladder function, sacral sensation, and anal contraction compared to patients who received the placebo, but these were not significant (p&lt;0.05).</li> <li>4. There were no significant differences in mortality between patients who received low dose Sygen®, high dose Sygen®, or placebo (p&gt;0.05). Patients with complete injuries had a</li> </ol>

	<p>bowel and bladder function, sacral sensation, anal contraction, mortality, adverse event outcomes.</p> <p><b>Chronicity:</b> Mean time from injury to study treatment was 55.6 hr, 54 hr and 54.4 hr for Sygen® 100 mg, Sygen® 200 mg and placebo groups, respectively.</p>	<p>significantly higher mortality rate than patients with incomplete injuries (p=0.017).</p> <p>5. There were no significant differences in adverse event outcomes between patients who received Sygen® and patients who received placebo (p&gt;0.05).</p>
<p><a href="#">Geisler et al. 1990</a>  <a href="#">Geisler et al. 1991</a>                  USA                  RCT                  PEDro=9                  N<sub>initial</sub>=37, N<sub>final</sub>=34</p>	<p><b>Population:</b> Age range=18-71 yr; Gender: not specified; Level of injury: cervical-thoracic; Severity of injury: complete=29%, incomplete=71%.</p> <p><b>Treatment:</b> Patients were randomly assigned to receive either monosialotetrahexosylganglioside (GM-1) ganglioside (GM-1 group; 100 mg/day) or placebo within 72 hr of injury. Amount of doses varied per patient. All patients received 250 mg methylprednisolone (MP) on admission followed by 125 mg MP every 6 hr for 72 hr.</p> <p><b>Outcome Measures:</b> The following after one year: neurological recovery based on Frankel grades, ASIA motor function, adverse event outcomes, death.</p> <p><b>Chronicity:</b> Mean time from injury to study entry was 48.2 hr and 51 hr for the GM-1 group and placebo group, respectively.</p>	<p>1. Patients who received GM-1 ganglioside improved in the form of at least 1 Frankel grade significantly more (p=0.034) than patients who received placebo. Significantly more patients who received GM-1 ganglioside were able to improve 2 or more grades compared to patients who received placebo (p=0.033).</p> <p>2. Patients who received GM-1 ganglioside experienced significantly more neurological recovery in the form of ASIA grade improvements compared to patients who received placebo (p=0.043).</p> <p>3. Significantly more patients who received GM-1 ganglioside were able to recover from 'paralyzed' to 'useful power' muscle grades on the ASIA motor scale compared to patients who received placebo (p=0.039). The authors noted that the improvement was due to the patients regaining useful function in paralyzed muscles rather than to paretic muscles improving in strength.</p> <p>4. No patients in the trial died and there were no significant differences in adverse event outcomes between the two groups (p&gt;0.05).</p>

## Discussion

After two clinical trials using GM-1 ganglioside as a treatment option for acute SCI, it is still unclear whether this drug truly elicits significant benefits. The first small scale trial (Geisler, Dorsey, & Coleman, 1990, 1991) reported significant motor improvement compared to a placebo group; however, when the same authors later conducted a large scale multicenter trial, no effects were seen after the study period had ended, although the administration of GM-1 ganglioside appeared to expedite the recovery process (Geisler, Coleman, Grieco, & Poonian, 2001a, 2001b; Geisler FH, 2001). One potential reason could be the delay in treatment between the two studies; patients from the second trial did not begin to receive the drug until 24 hours after the

injury to accommodate the initial mandatory dose of MP (Geisler FH, 2001). It is possible that the results varied between these two studies because GM-1 ganglioside was administered following the optimal therapeutic window in the latter clinical trial.

Currently, there are no major adverse effects that result from using GM-1 ganglioside, although sporadic cases of Guillain-Barre syndrome have been reported (Chinnock & Roberts, 2005). At this time, it is impossible to reach a conclusion regarding its effectiveness on improving feeling, movement, or quality of life for those who have acquired a SCI.

### Conclusion

There is level 1b evidence (from one RCT; (Geisler et al., 2001a, 2001b; Geisler FH, 2001) that GM-1 ganglioside is not effective in promoting neurological recovery in acute SCI individuals; However, there is level 1b evidence (from one RCT; (Geisler et al., 1990, 1991) that GM-1 ganglioside may be effective in promoting neurological recovery in acute SCI individuals.

### Key Points

There is conflicting evidence regarding the effectiveness of GM-1 ganglioside for neurological recovery during the acute phase post SCI.

## 4.7 Granulocyte-Colony Stimulating Factor

Granulocyte-colony stimulating factor (G-CSF), a pharmaceutical agent that is normally used to treat neutropenia, has recently been investigated for its potential role in the treatment of acute SCI. The main function of G-CSF is apoptosis inhibition and stimulation of neuron differentiation from new bone marrow-derived cells (A. Schneider, Kuhn, & Schabitz, 2005). It also suppresses the expression of inflammation-causing cytokines and protects the myelin sheath surrounding the axons of neurons (Takahashi et al., 2012). Recent studies in animal models have found G-CSF to enhance neurological recovery (Koda et al., 2007; Nishio et al., 2007) and its potential use in other neurological disorders, such as stroke, is under investigation (A. Schneider et al., 2005).

Table 8. Granulocyte-Colony Stimulating Factor for Neuroprotection in Acute SCI

Author Year Country Research Design Sample Size	Methods	Outcomes
<a href="#">Kamiya et al.</a> 2014 Japan Cohort N=28	<b>Population:</b> Age range=18-35 yr; Gender: male=75%, female=25%; <b>Level of injury:</b> C3-C7; <b>Severity of injury:</b> complete=7%, incomplete=93%, AIS A-D.	1. ASIA motor score: Overall, patients who received G-CSF recovered significantly more motor function than patients in the historical control group (p<0.01). This significant difference remained

Author Year Country Research Design Sample Size	Methods	Outcomes
	<p><b>Treatment:</b> In this phase I/IIa clinical trial, all patients received 10 µg/kg/day granulocyte colony-stimulating factor (G-CSF) intravenously for 5 days beginning within 48 hr of injury. Historical records of patients administered methylprednisolone sodium succinate (MPSS) according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines served as a control.</p> <p><b>Outcome Measures:</b> The following after 3 months: ASIA motor function, neurological recovery based on AIS, adverse event outcomes.</p> <p><b>Chronicity:</b> Treatment was initiated within 48 hr after injury.</p>	<p>even after removing patients with complete injuries.</p> <ol style="list-style-type: none"> <li>2. AIS: Overall, there was no difference in neurological recovery of one step of the AIS between patients who received G-CSF and the historical control group (<math>p&gt;0.05</math>); however, significantly more patients who received G-CSF experienced an improvement of 2 steps than those in the historical control group (<math>p&lt;0.05</math>). This significant difference remained even after removing patients with complete injuries.</li> <li>3. Patients in the historical control group experienced significantly more incidences of pneumonia than patients who received G-CSF (<math>p&lt;0.05</math>).</li> </ol>
<p><a href="#">Takahashi et al.</a> 2012 Japan Prospective Controlled Trial N=16</p>	<p><b>Population:</b> Age range=18-75 yr; Gender: male=81%, female=19%; Level of injury: cervical-thoracic; Severity of injury: complete=6%, incomplete=94%.</p> <p><b>Treatment:</b> In this open label phase I/IIa clinical trial, patients received either low dose granulocyte-colony stimulating factor (G-CSF) (5 µg/kg/day) or moderate dose G-CSF (10 µg/kg/day). Treatment was administered intravenously for five days beginning within 48 hr of injury. Historical records of patients administered methylprednisolone sodium succinate (MPSS) according to National Acute Spinal Cord Injury Study (NASCIS) II guidelines served as a control.</p> <p><b>Outcome Measures:</b> The following daily during the first week, 1 month after injury, and 3 months after injury: body temperature, blood data, ASIA motor function, ASIA sensory</p>	<ol style="list-style-type: none"> <li>1. There were no significant differences in body temperature in either patients who received low dose G-CSF or those who received high dose G-CSF during the first week of hospital stay, 1 month after injury, or 3 months after injury compared to baseline (<math>p&gt;0.05</math>).</li> <li>2. During the first 5 days after administration, there was a significant elevation of white blood cells in both low dose and moderate dose patients compared to their baseline levels (<math>p&lt;0.01</math>) that returned to normal after the G-CSF administration ended. There was a significant elevation of C-reactive protein after 1 day in patients who received high dose G-CSF (<math>p&lt;0.05</math>) but these levels returned to normal the day after.</li> <li>3. Patients who received moderate dose G-CSF experienced significantly higher motor function score after 1 day (<math>p&lt;0.01</math>), pinprick score after 2 days (<math>p&lt;0.05</math>), and light touch score after 2 days (<math>p&lt;0.05</math>) that remained significant at every follow up time point.</li> <li>4. Patients who received low dose G-CSF and patients in the historical control</li> </ol>



Author Year Country Research Design Sample Size	Methods	Outcomes
	function (pinprick and light touch). The following after 3 months: Neurological recovery based on the ASIA scale. <b>Chronicity:</b> Individuals were treated within 6.4-48 hr of sustaining injury.	group did not experience significant improvements in motor or sensory function ( $p>0.05$ ). 5. There were no significant differences in neurological recovery of 1 grade based on the AIS among the 3 groups after 3 months ( $p>0.05$ ). 6. Patients who received either low or moderate dose G-CSF did not experience significant adverse event outcomes compared to patients in the historical control ( $p>0.05$ ). There were significantly higher rates of pneumonia in the MPSS historical control group compared to the G-CSF groups ( $p>0.05$ ).

### Discussion

Two clinical trials (Kamiya et al., 2014; Takahashi et al., 2012) have been recently conducted to examine whether G-CSF improves neurological recovery in acute SCI. It is promising to see initial improvements in neurological function compared to baseline measurements, especially in those experiencing incomplete injuries (Kamiya et al., 2014). However, despite positive findings, it is important to note that the sample sizes were small and the protocols lacked blinding and randomization. While the authors noted significantly fewer episodes of pneumonia using G-CSF instead of MP, there is still a concern with other side effects such as elevated levels of white blood cells. It is known that white blood cell counts in the levels of 50 000 cells/mm<sup>3</sup> can cause splenic rupture, and significantly higher white blood cell counts were observed in both groups receiving treatment, with one patient experiencing counts in this dangerous level (Kamiya et al., 2014). Additional RCTs examining the role of G-CSF in acute SCI are recommended.

### Conclusion

There is level 2 evidence (from one prospective controlled trial; (Takahashi et al., 2012) and one cohort study; (Kamiya et al., 2014)) that a moderate dose (10 µg/kg/day) of granulocyte-colony stimulating factor may be effective in promoting motor and sensory recovery in acute SCI individuals.

### Key Points

Granulocyte-colony stimulating factor may be effective for neurological recovery during the acute phase post SCI.

## 4.8 Thyrotropin-Releasing Hormone

Thyrotropin-releasing hormone (TRH) is naturally produced by the hypothalamus. Under normal conditions, it is involved in regulating the release of thyroid stimulating hormone and prolactin. Among individuals with SCI, TRH can take on several functions to remediate secondary injuries such as increasing blood flow, acting as an antioxidant and stabilizing membranes (Fehlings & Baptiste, 2005). The exact mechanism of action of this pharmaceutical agent is still unknown. Animal studies examining TRH for acute SCI have found it to contribute to significant long-term motor recovery (Faden et al., 1981b; Faden et al., 1984), even when the first treatment administration was delayed up to one week (Hashimoto & Fukuda, 1991). Animal studies have found that when compared to naloxone and dexamethasone, TRH is significantly more effective than either drug (Faden, Jacobs, Smith, & Holaday, 1983). In humans, preliminary TRH clinical studies have also been conducted to examine its effect on amyotrophic lateral sclerosis (Brooks, Sufit, Montgomery, Beaulieu, & Erickson, 1987).

Table 9. Thyrotropin-Releasing Hormone for Neuroprotection in Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<p><a href="#">Pitts et al.</a> 1995 USA RCT PEDro=5 N<sub>initial</sub>=20, N<sub>final</sub>=17</p>	<p><b>Population:</b> Mean age: not specified; Gender: not specified; Level of injury: cervical-lumbar; Severity of injury: complete=35%, incomplete=65%. <b>Treatment:</b> Patients were randomly assigned to receive either thyrotropin-releasing hormone (TRH; 0.2 mg/kg bolus plus 0.2 mg/kg/h infusion over 6 hr) or placebo within 12 hr of injury. <b>Outcome Measures:</b> The following after 4 months: motor function, sensory function (pinprick and light touch), severity of neurological recovery using Sunnybrook cord injury scale. <b>Chronicity:</b> Individuals were entered into the study within 12 hr of sustaining injury.</p>	<p><b>Analyses of patients with incomplete injuries:</b></p> <ol style="list-style-type: none"> <li>1. Patients who received TRH had significantly higher motor functioning compared to patients who received placebo (p=0.043).</li> <li>2. Patients who received TRH experienced significantly higher sensory function compared to those who received placebo (p=0.031).</li> <li>3. Patients who received TRH had significantly higher Sunnybrook cord injury scores than patients receiving placebo (p=0.044).</li> </ol> <p><b>Analyses of patients with complete injuries:</b></p> <ol style="list-style-type: none"> <li>4. There were no significant differences with regards to motor function or sensory function between the two groups (p&gt;0.05).</li> <li>5. There were no significant differences with regards to Sunnybrook cord injury between the two groups (p&gt;0.05).</li> </ol>

## Discussion

In one, small RCT conducted by Pitts et al. (Pitts et al., 1995), TRH was effective in promoting neurological recovery in patients with incomplete SCI, however not for those with complete SCI. Despite this promising observation, larger clinical trials are required to validate these results.

## Conclusion

There is level 1b evidence (from one RCT;(Pitts et al., 1995)) that thyrotropin-releasing hormone may be effective in promoting neurological recovery in individuals with incomplete acute SCI.

### Key Points

Thyrotropin-releasing hormone may be effective for neurological recovery during the acute phase post SCI in individuals with incomplete injuries.

## 4.9 Gacyclidine

Gacyclidine is a non-competitive antagonist for the NMDA receptor, such that its binding deactivates the receptor and blocks the negative effects of significant downstream influx of calcium into the cells. It was developed to inhibit excitotoxicity by reducing excessive glutamate concentrations surrounding neurons. Investigations of animal SCI models treated with gacyclidine have reported the animals to recover significantly more motor skills and have less damage around the spinal cord compared to animals that received a placebo (Gaviria et al., 2000). Gacyclidine has also been suggested as being more effective for neurological recovery compared to other NMDA antagonists (Feldblum, Arnaud, Simon, Rabin, & D'Arbigny, 2000). To date, one RCT has examined the neuroprotective effectiveness of gacyclidine in humans (Tadie M, 2003).

Table 10. Gacyclidine for Neuroprotection in Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Tadie et al. (2003) France RCT PEDro=4 N <sub>initial</sub> =280, N <sub>final</sub> =228	<b>Population:</b> Age range=18-65 yr; Gender: male=87%, female=13%; Level of injury: cervical-thoracic; Severity of injury: complete=72%, incomplete=28%. <b>Treatment:</b> Patients were randomly assigned to receive either 0.005 mg/kg gacyclidine, 0.01 mg/kg gacyclidine, 0.2 mg/kg gacyclidine,	1. There was an overall trend toward increased motor function in all groups, especially among those with incomplete injuries, but there were no significant differences among the four groups after 1 month (p=0.09) and after 1 year (no statistical analyses provided).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	<p>or placebo, administered intravenously within 2 hr of injury and followed by a second dose given within the next 4 hr.</p> <p><b>Outcome Measures:</b> The following after 1 month and after 1 year: ASIA motor function, ASIA sensory function (pinprick and light touch), Functional Independence Measure (FIM), adverse event outcomes.</p> <p><b>Chronicity:</b> Individuals were studied beginning within 2 hr of sustaining injury.</p>	<ol style="list-style-type: none"> <li>2. There were no significant differences among groups with regards to pinprick score or light touch score after 1 month (<math>p=0.68</math> and <math>p=0.85</math>, respectively) and 1 year (no statistical analyses provided).</li> <li>3. There were no significant differences in FIM scores among the four groups after 1 month (<math>p=0.07</math>) and 1 year (<math>p=0.87</math>).</li> <li>4. There were no significant differences in adverse event outcomes among the groups (<math>p&gt;0.05</math>).</li> </ol>

## Discussion

The only RCT to investigate the neuroprotective effectiveness of gacyclidine in acute SCI found no significant improvement in neurological recovery among individuals with acute SCI (Tadie M, 2003). Even though patients showed a trend toward neurological improvement over time, this was seen across all groups including the control group. It is currently not recommended that patients receive gacyclidine as treatment for acute SCI. Further trials examining gacyclidine for SCI in humans have been terminated (Fehlings & Baptiste, 2005).

## Conclusion

There is level 2 evidence (from one RCT; (Tadie M, 2003) that gacyclidine is not effective in promoting neurological recovery in acute SCI individuals.

## Key Points

Gacyclidine is not effective for neurological recovery during the acute phase post SCI.

## 5 Additional Phase I and Phase II Clinical Trials for Neuroprotective Pharmaceutical Agents During Acute SCI

### Cethrin®

The release of pro-inflammatory cytokines and growth inhibitory proteins after a SCI results in enhanced signaling of the protein Rho. When Rho is activated, axon regrowth is inhibited. Cethrin® specifically inactivates Rho and therefore enables axons to regrow. In addition, Cethrin® has been shown to reduce inflammation by decreasing hematogenous monocytes, reducing glial scar formation and augmenting neuron remyelination (McKerracher & Guertin, 2013). Unlike most acute spinal cord drugs reviewed so far that have been delivered intravenously, Cethrin® is applied topically to the spinal cord during the time of surgery.

### Minocycline

Another emerging neuroprotective drug is minocycline, a broad spectrum antibiotic. Minocycline is able to cross the blood-brain barrier and exhibits anti-inflammatory and anti-excitatory properties (Baptiste & Fehlings, 2006). Studies investigating SCI in animal models have suggested that this drug inhibits microglial proliferation, reduces cellular apoptosis and neutralizes free radicals (Yong et al., 2004). These properties have made it a promising candidate for neurological disorders such as Parkinson's disease, stroke, and multiple sclerosis in addition to SCI (S. Casha et al., 2012).

### Riluzole

During secondary injury, an influx of sodium enters nerve cells and instigates an osmotic response where the neurons begin to swell to dangerous levels. In response, calcium rushes into the cell and triggers an amplified sodium excretion from the cell. Subsequently, the high intracellular concentration of calcium results in glutamate release and therefore excitotoxicity (Wilson & Fehlings, 2014). Riluzole acts to block these sodium channels, thus preventing excitotoxicity. Animal studies have found spinal cord injured rats that received riluzole to have improved motor function, more brain stem neurons and a smaller lesion size after 6 weeks compared to rats that received different sodium channel blockers or a placebo (Schwartz & Fehlings, 2001). Earlier human trials with riluzole have led to its approval by the Food and Drug Administration in the US for the treatment of amyotrophic lateral sclerosis (Wilson & Fehlings, 2014).

Table 11. Pharmaceutical Agents for Neuroprotection in Acute SCI in Phase I and II Clinical Trials

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
<b>Cethrin®</b>		
<a href="#">Fehlings et al.</a> 2011 Canada Prospective Controlled Trial N <sub>initial</sub> =48, N <sub>final</sub> =35	<p><b>Population:</b> Age range=16-70 yr; Gender: male=84%, female=16%; Level of injury: cervical-thoracic; Severity of injury: complete=100%, incomplete=0%, AIS A.</p> <p><b>Treatment:</b> Patients received 1 of 5 doses of Cethrin®: 0.3 mg, 1 mg, 3 mg, 6 mg, and 9 mg at the time of spinal surgery.</p> <p><b>Outcome Measures:</b> The following during hospital stay: drug safety and tolerability, drug pharmacokinetics.</p> <p>The following after 1 year: neurological recovery using AIS, ASIA motor function.</p> <p><b>Chronicity:</b> Individuals underwent spinal surgery within 7 days of sustaining injury.</p>	<ol style="list-style-type: none"> <li>The authors conclude that Cethrin® is a safe and tolerable drug.</li> <li>The authors note there were no serious adverse effects related to the drug.</li> <li>Cethrin® exhibited little systemic exposure in patients.</li> <li>There was a large preliminary effect in ASIA motor scores with the most improvement seen in patients with cervical injuries who received 1 mg and 3 mg of Cethrin®*.</li> <li>There were very few improvements in sensory scores in patients who received varying doses of Cethrin®*.</li> <li>After one year, 31% of cervical injured patients and 6.3% of thoracic injured patients recovered at least 2 steps on the AIS,</li> </ol> <p>*There were no statistical analyses performed.</p>
<b>Minocycline</b>		
<a href="#">Casha et al.</a> 2012 Canada RCT PEDro=6 N <sub>initial</sub> =52, N <sub>final</sub> =44	<p><b>Population:</b> Mean age=37 yr; Gender: male=77%, female=23%; Level of injury: cervical-thoracic; Severity of injury: complete=69%, incomplete=31%, AIS A-D.</p> <p><b>Treatment:</b> Patients were randomly assigned to receive either minocycline or a placebo with a subclavian central venous catheter for 7 days within 12 hr of injury. The first five patients received 200 mg twice daily (low dose), whereas all patients after that received an 800 mg loading dose and 400 mg twice daily (high dose).</p> <p><b>Outcome Measures:</b> The following during hospital stay</p>	<p><b>Initial Analysis</b></p> <ol style="list-style-type: none"> <li>After three months, there were no significant differences in motor function between patients who received minocycline and those who received placebo (p=0.20). The most improvement was seen in patients with cervical injuries (p=0.05), whereas no significant improvement was seen among patients with thoracic injuries (p=0.20).</li> <li>There were no significant differences in pinprick (p=0.15) or light touch (p=0.27) scores between patients who received minocycline and those who received placebo.</li> <li>There were no significant differences in any functional recovery measure between patients who received</li> </ol>

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	and after the patient plateaued in motor function (i.e. 3-12 months post SCI): ASIA motor function, ASIA sensory function, functional recovery using Functional Independence Measure (FIM), Spinal Cord Independence Measure, the London Handicap Scale and Short Form 36 questionnaire, and adverse events.  <b>Chronicity:</b> Individuals studied were within 12 hr of sustaining injury.	minocycline and patients who received placebo ( $p>0.05$ ). 4. Adverse events did not vary significantly among the placebo, low dose, or high dose minocycline groups ( $p>0.05$ ).
<b>Riluzole</b>		
<a href="#">Grossman et al.</a> 2014 USA Cohort N <sub>initial</sub> =36, N <sub>final</sub> =35	<b>Population:</b> Age range=18-69 yr; Gender: male=83%, female=17%; Level of injury: cervical-thoracic; Severity of injury: complete=53%, incomplete=47%, AIS A-C. <b>Treatment:</b> Patients were administered riluzole (50g twice daily within 12 hr of injury for 7 days). Patients were compared to others in the North American Clinical Trials Network SCI Registry who did not receive riluzole. 39% of patients in riluzole group and 58% of patients in registry group received corticosteroids according to hospital protocol. <b>Outcome Measures:</b> The following during hospital stay and 90 days and 180 days after injury: the pharmacokinetics of the drug, adverse event outcomes, ASIA motor function, ASIA sensory function, neurological recovery based on AIS, functional recovery using Spinal Cord Independence Measure (SCIM). <b>Chronicity:</b> Individuals were screened and enrolled in the	1. The plasma concentration and systemic exposure to riluzole varied significantly among patients ( $p<0.05$ ). 2. There were no significant differences in adverse event outcomes between patients who received riluzole and the registry group, however a mild to moderate elevation of liver enzymes was observed in riluzole group compared to baseline measurements ( $p>0.05$ ). <b>Analyses comparing patients with cervical injuries only:</b> 3. After 90 days, patients who received riluzole experienced significant improvement in motor function compared to patients in registry ( $p=0.021$ ). This difference was no longer seen after 180 days ( $p>0.05$ ). 4. After 90 and 180 days, there were no significant differences in sensory function between patients who received riluzole and patients in the registry ( $p>0.05$ ). 5. A higher percentage of patients who received riluzole converted to a higher grade than patients from the registry. 6. After 180 days, there were no significant differences in functional recovery based on SCIM scores between patients who

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
	study within 12 hr of sustaining injury.	<p>received riluzole and patients in the registry (<math>p&gt;0.05</math>).</p> <p><b>Analyses comparing patients with thoracic injuries only:</b></p> <p>7. The authors note the 8 patients with thoracic injuries gained motor function, pinprick sensation, and improved by at least 1 grade on the AIS, however no statistical analyses were reported. The authors did not mention improvements in light touch sensation or functional recovery using SCIM scores.</p>

## Discussion

Despite the small sample sizes and open label protocols, Cethrin®, Minocycline and Riluzole show initial promise in terms of effectiveness for treating acute SCI and safe administration in humans; further trials are recommended.

## Conclusion

There is level 2 evidence (from one prospective controlled trial; (Fehlings et al., 2011)) that Cethrin® is a safe and tolerable drug and may promote neurological recovery in acute SCI individuals.

There is level 1b evidence (from one RCT; (S. Casha et al., 2012)) that minocycline is not effective in promoting motor or sensory recovery in acute SCI individuals.

There is level 2 evidence (from one cohort study; (Grossman et al., 2014)) that riluzole may be effective in promoting long term motor or sensory recovery in acute SCI individuals.

## Key Points

Cethrin® is a safe and tolerable drug, but its effect on neurological recovery remains unknown during the acute phase post SCI.

Minocycline is not effective for neurological recovery during the acute phase post SCI.

Riluzole may be effective for neurological recovery during the acute phase post SCI.



## 6 Summary

There is level 1a evidence (from four RCTs, one pre-post test, one prospective controlled trial, and nine case control studies; (M. B. Bracken et al., 1990; M. B. Bracken et al., 1997; M. B. Bracken et al., 1998; George et al., 1995; Gerhart et al., 1995; Heary et al., 1997; Ito et al., 2009; Levy et al., 1996; Pointillart et al., 2000; Pollard & Apple, 2003; Poynton et al., 1997; Prendergast et al., 1994; Rasool T, 2004; Suberviola et al., 2008; Zhuang C, 2008) that methylprednisolone is not effective in promoting neurological recovery in acute SCI individuals.

There is level 1a evidence (from two RCTs and three case control studies; (M. B. Bracken et al., 1997; Heary et al., 1997; Ito et al., 2009; Pointillart et al., 2000; Suberviola et al., 2008) that methylprednisolone is associated with the development of medical complications when used in acute SCI individuals; However, there is level 3 evidence (from three case control studies; (Galandiuk et al., 1993; Levy et al., 1996; Tsutsumi et al., 2006) that methylprednisolone is not associated with the development of medical complications in acute SCI individuals.

There is level 3 evidence (from two case control studies; (Heary et al., 1997; Kiwerski, 1993) that dexamethasone is not effective in promoting neurological recovery in acute SCI individuals.

There is level 3 evidence (from two case control studies; (Heary et al., 1997; Merry et al., 1996) that dexamethasone may be associated with the development of medical complications when used to treat acute SCI individuals.

There is level 1b evidence (from one RCT;(Aminmansour et al., 2016)) that progesterone and vitamin D is not effective in promoting neurological recovery in acute SCI individuals.

There is level 1b evidence (from one RCT; (M. B. Bracken et al., 1990) that naloxone is not effective for the promotion of neurological recovery in acute SCI individuals.

There is level 1b evidence (from one RCT; (M. B. Bracken et al., 1997) that tirilazad mesylate is no more effective than methylprednisolone in promoting neurological recovery in acute SCI individuals.

There is level 1b evidence (from one RCT; (Pointillart et al., 2000) that nimodipine is not effective in promoting neurological recovery in acute SCI individuals.

There is level 1a evidence (from one double-blind RCT; (E. A. Alibai et al., 2015)and one single-blind RCT; (Costa et al., 2015) that acute administration of erythropoietin does not improve neurological outcomes post-SCI; however, there is level 1b evidence (from one RCT;(E. Alibai et al., 2014) and one prospective controlled trial; (Xiong et al., 2011)) that erythropoietin is effective in promoting neurological recovery in acute SCI individuals.

There is level 1b evidence (from one RCT; (Geisler et al., 2001a, 2001b; Geisler FH, 2001) that GM-1 ganglioside is not effective in promoting neurological recovery in acute SCI individuals; However, there is level 1b evidence (from one RCT; (Geisler et al., 1990, 1991) that GM-1 ganglioside may be effective in promoting neurological recovery in acute SCI individuals.

There is level 2 evidence (from one prospective controlled trial; (Takahashi et al., 2012) and one cohort study; (Kamiya et al., 2014)) that a moderate dose (10 µg/kg/day) of granulocyte-colony

stimulating factor may be effective in promoting motor and sensory recovery in acute SCI individuals.

There is level 1b evidence (from one RCT;(Pitts et al., 1995)) that thyrotropin-releasing hormone may be effective in promoting neurological recovery in individuals with incomplete acute SCI.

There is level 2 evidence (from one RCT; (Tadie M, 2003) that gacyclidine is not effective in promoting neurological recovery in acute SCI individuals.

There is level 2 evidence (from one prospective controlled trial; (Fehlings et al., 2011)) that Cethrin® is a safe and tolerable drug and may promote neurological recovery in acute SCI individuals.

There is level 1b evidence (from one RCT; (S. Casha et al., 2012)) that minocycline is not effective in promoting motor or sensory recovery in acute SCI individuals.

There is level 2 evidence (from one cohort study; (Grossman et al., 2014)) that riluzole may be effective in promoting long term motor or sensory recovery in acute SCI individuals.

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## Abbreviations

ADL	activities of daily living
AIS	ASIA Impairment Scale
ANS	autonomic nervous system
ASIA	American Spinal Cord Injury Association
BP	blood pressure
EPO	erythropoietin
FIM	Functional Independence Measure
G-CSF	granulocyte-colony stimulating factor
GM-1 ganglioside	Monosialotetrahexosylganglioside
HR	heart rate
MP	Methylprednisolone
MPSS	Methylprednisolone Sodium Succinate
MRI	magnetic resonance imaging
NASCIS	National Acute Spinal Cord Injury Study
NMDA	N-methyl-D-aspartate
PNS	parasympathetic nervous system
RCT	randomized controlled trial
rhEPO	recombinant human erythropoietin
SCI	spinal cord injury
SNS	sympathetic nervous system
TRH	thyrotropin-releasing hormone