The progress and controversies regarding steroid use in acute spinal cord injury

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Abstract. – Acute spinal cord injury (SCI) is a devastating disease that causes immense physical and mental harm to the patient and the family, and society and requires a multidisciplinary approach to treatment. The study of acute SCI has a long history but is still emerging. As the mechanism and pathophysiology of acute SCI are continuously being studied and explored, the treatment of SCI has developed significantly. Steroids are thought to provide neuroprotection in patients with acute SCI by improving perfusion, reducing edema, modulating inflammatory cells, and inhibiting lipid peroxidation, leading to their widespread application in clinical medicine. The use of steroids for SCI is controversial because of limited clinical evidence. With the accumulation of evidence on the effectiveness of steroid treatment in improving neurological function and the evidence of severe side effects, a gradual change in the treatment of SCI with steroids has become inevitable. Most scholars have focused on the routine use of steroids because of the indefinite improvement in neurological function and the occurrence of severe adverse events. Therefore, this review aims to provide an overview of the mechanism, progress, and related controversies to comprehensively understand the value and future direction of steroid application in acute SCI.

Key Words: Spinal cord injury, Steroid, Methylprednisolone, Treatment.

Introduction

Acute spinal cord injury (SCI) is a temporary or permanent impairment of neurological function due to an acute traumatic injury to the nerve structures in the spinal canal (spinal cord and cauda equina). As a traumatic disease with a high disability rate, acute SCI is also a common traumatic disease in hospitals and is caused mainly by severe trauma such as falls from heights and traffic accidents. Despite recent progress in the pathogenesis and treatment of acute SCI, it remains catastrophic. Once the spinal cord is injured, mild damage can lead to changes in the sensory, motor, and autonomic functions below the plane of injury. However, severe damage can lead to paraplegia or quadriplegia and even death.

The prevalence and incidence of acute SCI vary according to geopolitical and economic conditions. The estimated global annual incidence of traumatic SCI is (10.4-83.0)/100,000, while the incidence of SCI in the United States and Australia are (27-83)/100,000 and (21-32.3)/100,000, respectively. An earlier study showed that the incidence of traumatic SCI in China rose rapidly, from 45.1 cases per million in 2009 to 66.5 cases per million in 2018. This indicates that the incidence of acute SCI remains high worldwide. In addition, several studies have shown that acute SCI causes severe physical and psychological harm to patients and imposes a substantial economic burden on their families and society. The medical costs are estimated to range from $30,770 to $62,653 per year. The pathophysiology of acute SCI has been explored in great depth in terms of cellular and molecular aspects. Although many studies and discussions have been conducted on the management of acute SCI, controversies regarding therapeutic strategies remain, especial-
ly regarding the use of steroids. Therefore, this review aims to provide an overview of the mechanisms, progress, and related controversies to achieve a relatively comprehensive understanding of the value and future direction of steroid application for acute SCI.

**Pathophysiology of Acute SCI**

There are two main types of acute SCI: direct and indirect. Direct SCI primarily refers to SCI caused by a direct external force (such as a stab injury or bullet penetration injury). In contrast, indirect SCI is primarily caused by spinal fracture or dislocation due to injuries such as traffic accidents, heavy force injuries, and falls from height. Therefore, regardless of its type, SCI is an injury to the central nervous system caused by severe trauma.

The pathological reaction after SCI involves a series of cascading reactions, including primary and secondary injury phases\(^{13}\). The former is caused by the direct compression or contusion of the spinal cord by fracture fragments or intervertebral disc material, resulting in vascular injury, spinal cord edema, ischemia, nerve cell damage, and axonal disruption. These pathological reactions cause damaging lesions in the surrounding spinal cord tissue, further deepening the extent of the injury and enlarging its scope\(^{14,15}\). However, it is rare for the spinal cord to be completely transected or destroyed because of anatomical features\(^{16}\). The remaining undamaged axons are essential because they serve as neural substrates for new therapeutic strategies\(^{17}\). It is believed that SCI is only partially caused by physical forces and that secondary injuries often cause more injuries. Secondary injury begins immediately after the primary injury, extending the nerve injury area and exacerbating the neurological deficit, with secondary mechanisms of injury lasting longer after trauma\(^{18,19}\). Therefore, secondary pathological reactions after SCI play an essential role in the treatment and prognosis of SCI. However, most primary SCI cases are not preventable; therefore, treatment of acute SCI focuses on avoiding and suppressing secondary injuries\(^{20,21}\).

Secondary SCI can be subdivided into acute, subacute, intermediate, and chronic phases, each of which has its own characteristic pathology (Figure 1)\(^{22-27}\). Hemorrhage, apoptotic cell death, inflammatory cell infiltration, and edema are often present around lesions during the acute phase of injury. Subsequently, ongoing ischemia and edema, persistent inflammatory cell infiltration, and destruction of the vascular system are apparent in the subacute phase. In the intermediate and chronic phases, glial scar formation interferes with the regeneration of neuronal axons and recovery of function. These studies\(^{22-27}\) have revealed the pathological features of specific molecules at different stages, involving the exploration of molecular mechanisms, including inflammatory responses, tissue edema, neuronal axonal damage, neuronal apoptosis, abnormal astrocyte proliferation, and glial scar formation.

Treatment of acute SCI focuses on avoiding and suppressing secondary injury. As one of the vital pathological reactions after SCI, neuroinflammation has a significant role in the pathological response process of SCI and directly affects the microenvironment of neuronal and axonal regeneration\(^{27,28}\).

**Mechanism of Steroids in Acute SCI**

The use of steroids in patients with acute SCI began in the 1960s based on the observation that steroids reduced brain edema, and steroids with anti-inflammatory features also reduced spinal edema\(^{29}\). Several animal studies\(^{29-32}\) suggest that glucocorticoids may protect the injured spinal cord through the following mechanisms: improving blood perfusion, stabilizing lysosomal membranes, reducing edema, preventing calcium influx and accumulation, regulating inflammatory cells, preventing the loss of spinal neurofilament proteins, promoting neuronal excitability and impulse transmission, and inhibiting lipid peroxidation and inflammatory cytokines (Figure 1). In addition, glucocorticoids promote the release of neurotrophic, neuroregenerative, and protective factors that facilitate recovery from SCI\(^{33}\). Recent studies\(^{34}\) have shown that in the acute phase of traumatic SCI, the use of steroids increases early miR-21 expression, which increases astrocyte proliferation and regulates inflammatory factors, facilitating the recovery of the injured spinal cord. Inhibition of lipid peroxidation and reduction of cellular Ca\(^{2+}\) inward flow through the stabilization of lysosomal and biological membrane ion channels resulting in antioxidant effects are probably the most important mechanisms of action of steroids\(^{32}\). Among these steroids, methylprednisolone is currently used primarily for treating SCI because of its particularly effective neuroprotective effect compared to other steroids\(^{35}\).
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Figure 1. Pathogenesis of different stages and periods of SCI. *Mechanism of steroids.
Many studies have been performed to prevent or reduce the effects of secondary injuries, and steroids have been shown to improve the neurological prognosis of patients with acute SCI. However, evidence supporting the use of cortisol is limited and controversial. The role of neuroprotective effects has long been discussed, and several animal studies have demonstrated that steroids improve neurological prognosis. In contrast, most human trials have focused on investigating the potential benefits of methylprednisolone. The most widely recognized studies include the National Acute Spinal Cord Injury Study (NASCIS) I, II, and III, published between 1985 and 1998.

NASCIS I compared the effects of low-dose (100 mg bolus and 100 mg/day for 10 consecutive days) and high-dose (1,000 mg bolus and 1,000 mg/day for 10 consecutive days) methylprednisolone in 256 patients within 48 hours of acute SCI. There was no difference in the improvement of neurological function (motor and sensory) after 12 months of follow-up. Conversely, patients receiving high doses of methylprednisolone are more likely to develop complications such as infection and death.

In NASCIS II, 487 patients were randomized to receive methylprednisolone (initial bolus of 30 mg/kg followed by a 23-hour infusion of 5.4 mg/kg/h), naloxone (opioid receptor antagonist), or placebo within 12 hours of acute SCI and were then compared with each other. Motor and sensory recovery significantly improved within 8 hours in patients with complete or incomplete SCI treated with methylprednisolone. In the post hoc analysis (Level III evidence), motor scores improved by a mean of 5 points, and sensory scores improved by 4 points at 6 months. However, there was a 1.5-fold higher incidence of gastrointestinal bleeding and a 2-fold higher incidence of wound infections in the group using methylprednisolone. Therefore, there is concern regarding the risk of complications after using methylprednisolone. NASCIS II was the first clinical study to demonstrate the effects of a drug after acute SCI. This study provides the basis for the global use of methylprednisolone after SCI and helped facilitate research on the use of other neuroprotective agents after acute SCI.

In NASCIS III, 499 patients were compared for different durations of methylprednisolone within 8 hours after acute SCI. Patients in the study received a high dose of 30 mg/kg methylprednisolone within the first hour and were randomized to maintain a 23-hour infusion of methylprednisolone at 5.4 mg/kg/h or a 47-hour infusion at 5.4 mg/kg/h or 2.5 mg/kg every 6 hours for 48 hours from the initial time. Among patients who started treatment 3-8 hours after the injury, the 48-hour methylprednisolone group showed significant improvements in movement and sensation at 6 weeks and 6 months. Patients who received the 48-hour regimen and started treatment at 3-8 hours had greater improvements in neurological classification and functional independence scale scores at 6 months than those in the 24-hour methylprednisolone and tirazate groups. Although there were no statistically significant differences in the increase in complication rates and mortality after methylprednisolone use in this study, higher rates of wound infection, severe pneumonia, sepsis, and even secondary death due to respiratory complications were observed. Therefore, the overall benefit of methylprednisolone for acute SCI remains questionable. Nevertheless, NASCIS II and III have established the administration of methylprednisolone as standard clinical practice for acute SCI globally.

Previous studies have shown an increased risk of infection with a 48-hour high-dose methylprednisolone regimen. However, a lower complication rate was observed with a shorter 24-hour high-dose methylprednisolone regimen (initial bolus of 30 mg/kg followed by a 23-hour infusion of 5.4 mg/kg/h), while still providing long-term neurological benefit. The 2002 American Association of Neurological Surgeons/Conference of Neurological Surgeons Guidelines for the Management of Acute SCI recommends a 24- or 48-hour treatment regimen of methylprednisolone for patients with SCI. However, physicians need to also be aware of the signs of side effects when using methylprednisolone, and not just its benefits. Similarly, a 2012 Cochrane review summarized six large studies on acute SCI and found an overall increase in American Spinal Cord Injury Association (ASIA) motor scores when methylprednisolone was used, if the initial dose was administered within 8 hours of injury. Subsequently, the AOSpine guidelines (available at: https://journals.sagepub.com/toc/gsja/7/3_suppl) showed a slight improvement in motor scores with methylprednisolone infusion within 8 hours of injury. Practice guidelines recommend that a 24-hour high-dose methylprednisolone infusion should
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be offered as a treatment option for patients with acute SCI within 8 hours, whereas treatment with methylprednisolone is not recommended beyond 8 hours. The guidelines also recommend against the administration of a 48-hour continuous infusion of high-dose methylprednisolone. The 2019 Orthopaedic Evidence-Based Clinical Guidelines of the Chinese Association of Orthopaedic Surgeons recommend that high-dose methylprednisolone should not be used as a routine treatment option (recommended strength: level 3). It also recommends high-dose methylprednisolone as a treatment option (recommended strength: level 3). Meanwhile, studies on complications following high-dose steroid treatment for acute SCI have been reported from 1990 to 2022 (Table 1). The side effects of steroids in treating traumatic SCI have prompted clinicians to consider the rationality of their application. In addition to the benefits of steroid treatment, the side effects of high-dose steroid treatment, such as hyperglycemia, gastrointestinal bleeding, urinary tract infections, pneumonia, wound infections, and other complications, are getting increasing attention. As evidence of serious side effects continues to accumulate, a gradual change in the practice of steroid treatment for SCI has become inevitable in actual clinical practice. Therefore, it is necessary for professional organizations to recommend steroid treatment for SCI. In 2013, the American Association of Neurological Surgeons/Congress of Neurological Surgeons joint guidelines on using steroids for acute SCI were published as Level 1 recommendations. Unlike the 2002 guidelines, steroids are not recommended for treating acute SCI. Their guidelines highlight that the Food and Drug Administration has not approved steroids for acute SCI and that there is no Level 1 and 2 medical evidence to support clinical efficacy, but there is Level 1, 2, and 3 evidence of harmful side effects, including infection and death. Subsequently, the European Spine Society, including the UK National Institute for Health and Management Excellence guidelines and the Polish Society of Spine Surgery guidelines, also do not recommend using steroids for acute SCI. A meta-analysis of 3 randomized controlled trials and 13 observational studies did not show the effectiveness of high-dose steroids administered within 8 hours of SCI in patients with acute SCI. In addition, a meta-analysis published in 2020 showed that steroid treatment within the first 8 hours after acute SCI failed to provide short- or long-term improvements in the overall motor or neurological scores, but there was an increased risk of pneumonia and hyperglycemia. These previous meta-analyses included groups with different SCI types, ages, and numbers, rendering their conclusions difficult to apply, and limiting their overall utility in clinical practice. The 2020 French Society of Anaesthesia and Intensive Care Medicine (SFAR) guidelines mention that the early use of steroids to improve neurological prognosis after traumatic SCI is not recommended (Grade 1, strong recommendation). The most recent meta-analysis published in 2022 analyzed eight guidelines (related to the treatment of acute SCI) developed between 2008 and 2020 for the use of methylprednisolone: three guidelines recommended its use (3/8=37.5%) (one evidence-based, two consensus-based), three guidelines recommended no use (3/8=37.5%) (all evidence-based), and two guidelines recommended neutral use (2/8=25%). Thus, there is an inconsistency between the recommendations for using steroids, with evidence-based recommendations leaning against and consensus-based recommendations leaning in favor. In summary, scholars opposed to the routine use of steroids for acute SCI are overwhelmingly concerned about the results of the NASCIS trials, including the overreliance on subgroup analyses (particularly based on the time point and duration of methylprednisolone initiation), unclear neurological improvements in the study results, and the risk of causing harmful severe adverse events. In addition, many studies have demonstrated that using steroids increases the expression of water channel aquaporin 4 (AQP 4), thus worsening edema after SCI. In the face of different expert recommendations and research findings, high-dose steroids in the acute phase of SCI need to be further validated.

Current Utilization of Steroids in the Treatment of Acute SCI

Evidence-based medicine combines the characteristics and clinician expertise with the best available external evidence. Clinicians, researchers, and other evidence users should consider relevant evidence before applying the results to patient management to facilitate clinical decision-making. The use of steroids in clinical practice has decreased in recent years. Surveys conducted by spine surgeons in Canada, the United Kingdom, Switzerland, and Germany showed a decrease in steroid use for acute SCI from 70-80%
Table I. Studies on complications of MP treatment after acute SCI.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>MP  (n)</th>
<th>P/C (n)</th>
<th>Follow-up (M)</th>
<th>Pneumonia</th>
<th>UTI</th>
<th>Gastrointestinal bleeding</th>
<th>Sepsis</th>
<th>Wound infections</th>
<th>Pulmonary embolism</th>
</tr>
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<tbody>
<tr>
<td>Sunshine et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>2017</td>
<td>160</td>
<td>151</td>
<td>2</td>
<td>27 (16.9)</td>
<td>4</td>
<td>2.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Khan et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td>2014</td>
<td>216</td>
<td>134</td>
<td>NR</td>
<td>NR</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ito et al&lt;sup&gt;43&lt;/sup&gt;</td>
<td>2009</td>
<td>38</td>
<td>41</td>
<td>3</td>
<td>19 (50)</td>
<td>13</td>
<td>(34.2)</td>
<td>6 (15.8)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Suberviola et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>2008</td>
<td>59</td>
<td>23</td>
<td>&lt;1</td>
<td>16 (27.1)</td>
<td>7</td>
<td>(11.9)</td>
<td>NR</td>
<td>8 (13.6)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Tsutsumi et al&lt;sup&gt;45&lt;/sup&gt;</td>
<td>2006</td>
<td>37</td>
<td>33</td>
<td>6</td>
<td>1 (2.7)</td>
<td>4</td>
<td>(10.8)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Matsumoto et al&lt;sup&gt;46&lt;/sup&gt;</td>
<td>2001</td>
<td>23</td>
<td>23</td>
<td>2</td>
<td>1 (30.4)</td>
<td>1</td>
<td>(4.3)</td>
<td>NR</td>
<td>1 (4.3)</td>
<td>NR</td>
</tr>
<tr>
<td>Levy et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>1996</td>
<td>55</td>
<td>181</td>
<td>6</td>
<td>25 (45.3)</td>
<td>45</td>
<td>(82.0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bracken et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>1990</td>
<td>162</td>
<td>171</td>
<td>1.5</td>
<td>46 (28.2)</td>
<td>74</td>
<td>(45.5)</td>
<td>7 (4.5)</td>
<td>9 (5.8)</td>
<td>11 (7.1)</td>
</tr>
</tbody>
</table>

Source: the online databases of PubMed and Cochrane Library for all the available randomized controlled trials as well as observational studies published up to November 2022. MP=methylprednisolone; P/C=placebo/control; NR=not reported; UTI=urinary tract infections.
to 20-30%. In a 2014 survey of the members of the Cervical Spine Research Society, the use of steroids for acute SCI decreased significantly to 50% compared to the past. Globally, the percentage of specialists reporting routine steroid use declined from 76% in 2001 to 24% in 2006 in Canada, from 68% in 2004 to 19% in 2012 in the UK, and from 73% to 27% in Poland. In Korea, the prescription rate of steroids for patients with acute SCI was 59% in the past 11 years, peaking at 76% in 2012, which then gradually decreased to 41% in 2017. A higher percentage of steroids is still prescribed for acute SCI in Korea compared to North America or Europe. In a 2018 global survey of steroid use for acute SCI, among the 2,659 surgeons from Europe, Asia-Pacific, North America, and the Middle East who responded, 1,198 (52.9%) surgeons used steroids, of whom 595 (50%) used steroids primarily based on NASSCIS III. The most common reasons for using steroids in patients with acute SCI are the belief that it will improve prognosis and that not using methylprednisolone may lead to medical disputes. Therefore, steroid use in patients with acute SCI warrants further investigation. Clinicians should be more careful when using steroids to treat patients with acute SCI.

**Prospect**

Steroids remain the most significant research direction and a controversial topic in the field of acute SCI. Further research is required to determine whether steroids can be used in patients with acute SCI. Therefore, clinicians should be cautious when using steroids to treat acute SCI. Given the completion of several large, high-quality randomized controlled trials (RCTs) on using steroids for acute SCI and that there is little need for additional similar studies, particularly when resources are limited, and the aforementioned treatment has not been proven in large-scale clinical trials. Clinical researchers can look for drugs with fewer side effects and effective treatments to reduce or replace the dose of steroids in the treatment of acute SCI; this will help protect neural tissue and promote neurological recovery while reducing the side effects caused by high doses of steroids. In the field of translational medicine, novel neuroprotective agents have been used in preclinical and early-phase clinical studies. However, there is currently insufficient evidence of their effectiveness. In China, several experimental animal studies on Chinese herbal medicines for acute SCI have proven their neuroprotective effects, but they are rarely translated into clinical application. Future research should focus on assessing the efficacy of these drugs alone or in combination with steroids. These require multicenter collaborative clinical trials for comparative analyses with larger homogeneous groups to accelerate the translation of clinical trials into clinical applications.

**Conclusions**

Acute SCI can have a devastating impact on the physical and mental health of patients. Timely and specialized treatment is crucial for emergencies in which patients present with severe neurological deficits. There is limited evidence that steroid treatment improves neurological outcomes in patients with acute SCI, and most current guidelines do not support its use. With a complete understanding of its potential risks and uncertain efficacy, the use of high-dose steroid treatment in the acute phase of acute SCI remains to be further validated; however, high-dose steroid treatment should not be used as a routine treatment option.

**Conflict of Interest**

The Authors declare that they have no conflict of interests.

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**Ethics Approval**

Not applicable.

**Informed Consent**

Not applicable.


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