Korean J Neurotrauma. 2022 Apr;18(1):22-30
https://doi.org/10.13004/kjnt.2022.18.e21
pISSN 2234-8999·eISSN 2288-2243

KJNT

Review Article

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Review: Steroid Use in Patients With Acute Spinal Cord Injury and Guideline Update

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OPEN ACCESS

Received: Feb 28, 2022
Accepted: Apr 5, 2022
Published online: Apr 19, 2022

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Conflict of Interest
Je Hoon Jeong serves as an Editor-in-Chief of the Korean Journal of Neurotrauma, but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported.

ABSTRACT

Acute spinal cord injury (SCI) is a devastating condition that causes enormous damage to a patient's physical, mental, and economic situation and requires a multidisciplinary approach to treatment. Research on SCI has been performed for a long time, and the management of SCI has developed dramatically in recent decades as a mechanism of injury and the pathophysiology of SCI have been revealed from the primitive stage in the past. In the treatment of patients with acute SCI, there is a lot of debate regarding surgical treatment strategies and pharmacological management, such as steroid use. In particular, the efficacy of steroid use, such as methylprednisolone sodium succinate, has been increasing and decreasing and is still intensely debated. The practice guidelines reported so far for this are also at the "suggest" stage with weak recommendations. Therefore, this review aims to summarize the effects of steroid use on SCI. This review provides an overview of current practical guidelines and clinical studies on steroid use in patients with SCI.

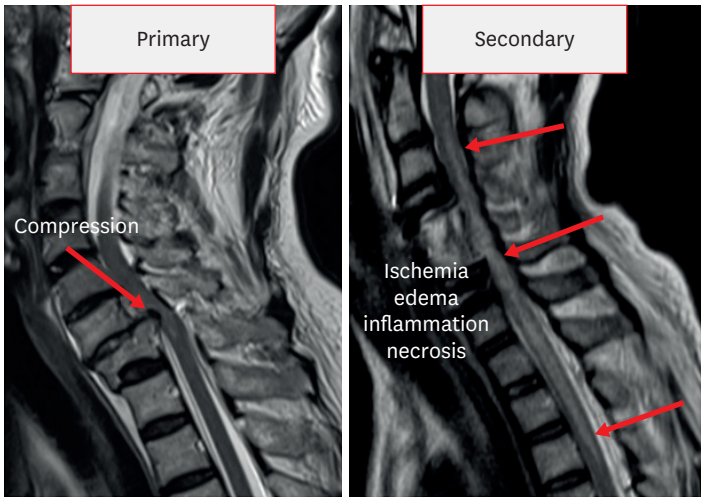
Keywords: Spinal cord injuries; Pathophysiology; Steroid; Guideline

INTRODUCTION

Spinal cord injury (SCI) is a catastrophic problem that can cause severe dysfunction in neurologic condition and decrease in quality of life for affected individuals.[11] In addition, the ongoing cost of treatment and rehabilitation for SCI has a huge impact on the socio-economic status of individuals and families, further placing a significant financial burden on the national health care system.[1,3] The prevalence and incidence of SCI vary according to geopolitical and economic conditions, and about 1,000 new cord injury patients occur every year in South Korea.[14] Also, until now, the pathophysiology of SCI has been studied very deeply in terms of cellular and molecular aspects, and accordingly, there have been many studies and discussions on the management of SCI, but there are still controversies especially regarding the use of steroid. Therefore, we aim to provide updated reviews and guidelines for the use of steroids in acute SCI. And later, it is considered necessary to updated review the contents surgical and cellular treatment strategies for SCI and future perspective.

PATHOPHYSIOLOGY OF SCI

SCI can be classified into primary and secondary injuries.[1] The primary injury is an initial mechanical injury that causes damage to the axon, blood vessel, and cell membrane by direct force applied to the spinal cord through persistent or transient compression, vertebral fracture, and cord laceration or transection.[1,3,43] Primary injuries are the direct result of mechanical forces at the time of injury and lead to cell death and bleeding. However, anatomically, it is rare for the spinal cord to be fully transected or disrupted.[44] So, the remaining extra axons are very important because they act as neural substrates for new treatment strategies. Previous studies have reported that only 5% of the original axons in animal experiments can maintain nerve function.[20] After the primary injuries, a secondary injury begins immediately, resulting in the extension of the nerve injury site and exacerbating the neurologic deficit.[52] The therapeutic focus of SCI is to avoid and inhibit secondary injuries. Secondary injury can be divided into acute (within 48 hours), subacute (2–14 days), intermediate (14 days–6 months), and chronic (more than 6 months) phases (**FIGURE 1**). During the acute phase, edema, hemorrhage, and ischemia occur at the injury



Secondary injury: subdivision

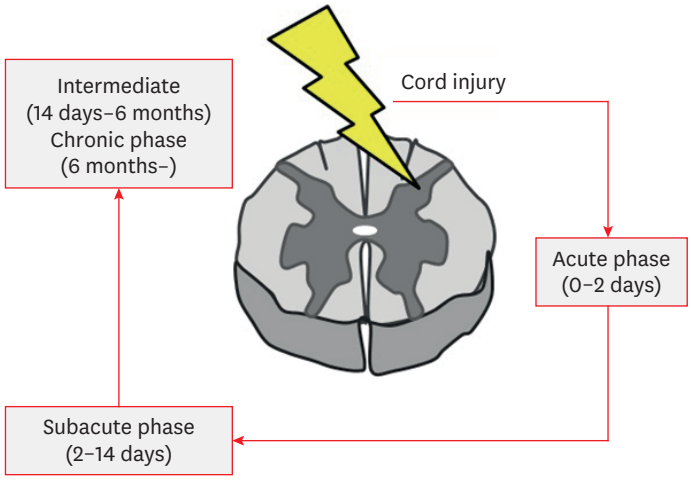


FIGURE 1. Phases and subdivisions of spinal cord injury.

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site. Inflammatory cells (macrophages, microglia, T-cells, and neutrophils) also infiltrate the injury site and these cells trigger the secretion of inflammatory cytokines (tumor necrosis factor-α, interleukin [IL]-1α, IL-1β, and IL-6) and causes disruption of the blood-spinal cord barrier. The level of release of these cytokines peaks at 6 to 12 hours after injury and is maintained until 4 days after injury.[42,48] In addition, loss of ionic homeostasis of nerve cells by injury increases intracellular calcium ion, which activates calcium-dependent proteases, causing mitochondrial dysfunction, which ultimately leads to apoptotic cell death (Ca2+-dependent glutamate-associated cell death).[24,45] During process of apoptotic cell death, ATP, potassium ions, and DNA are released, which induce the microglia to release additional proinflammatory cytokines and attract more inflammatory cells to the injury site. In addition, debris from process of apoptotic cell death is cleared by phagocytes. In this process, phagocytes release reactive oxygen species (oxygen and nitrogen free radicals), which causes delayed necrosis and apoptosis through DNA oxidative damage, protein oxidation, and lipid peroxidation.[4,15,24] Oligodendrocytes are particularly sensitive to apoptosis. Therefore, the sensitive response of oligodendrocytes to apoptosis extends far from the epicenter of SCI, eventually leading to demyelination of preserved axons.[16] Also, a prominent feature in the acute phase is excitotoxicity caused by excitatory neurotransmitters such as glutamate and aspartate. Excitatory neurotransmitters are overproduced by damaged nerve cells, and the excessive activation of excitatory neurotransmitter receptors causes excitotoxicity. This process also eventually leads to apoptosis of glial cells and neurons.[30,31,41,50] During the subacute phase, edema progresses, leading to vascular compromise and further exacerbation of ischemia. Persistent inflammatory cell infiltration is maintained. Ongoing ischemia and persistent inflammatory cell infiltration induce a more cytotoxic microenvironment, resulting in further apoptotic cell death and formation of cystic microcavities.[29-31,50] In the intermediate and chronic phases, vascular remodeling, alterations in the extracellular matrix composition, and reorganization of neural circuits around the injury site occur. The continuous loss of neurons causes coalesce of the cystic microcavities, which acts as an important barrier for axon regrowth, regeneration, and cell migration (**FIGURE 2**).[3,37,40] Astrocytes within the perilesional area proliferate and strongly interweave their extended processes together. This prevents further expansion of the lesion by isolating the lesion core. However, these tightly interwoven astrocytes form a physical barrier called a glial scar to inhibit axonal regeneration (**FIGURE 3**). Astrocytes also form a chemical barrier by secreting a lot of chondroitin sulfate proteoglycan (CSPGs) that inhibits axon regeneration. CSPGs bind to leukocyte common antigen-related receptors such as protein tyrosine phosphatase and activate the GTPase RhoA and Rho-associated protein kinase to cause regeneration failure.[3,12,13,22,34] The infiltrated fibroblast also acts as a chemical barrier for axonal regeneration by depositing inhibitory extracellular matrix molecules.[1,10] Prolonged apoptosis of oligodendrocytes progresses to chronic demyelination, eventually leading to fiber with disrupted myelin sheath called Wallerian degeneration.[24,49]

UPDATE OF STEROID MANAGEMENT FOR ACUTE SCI

Many studies have been conducted to prevent or reduce the effects of secondary injury, and among them, research on steroids with neuroprotective effects have been discussed for a long time. Steroids are the only drugs that have been evaluated in Phase III trials. The use of corticosteroids in patients with acute SCI began in the 1960s with the idea that corticosteroids with anti-inflammatory properties would also reduce the spinal cord edema based on the experience of using steroids for brain swelling.[18] Although animal studies

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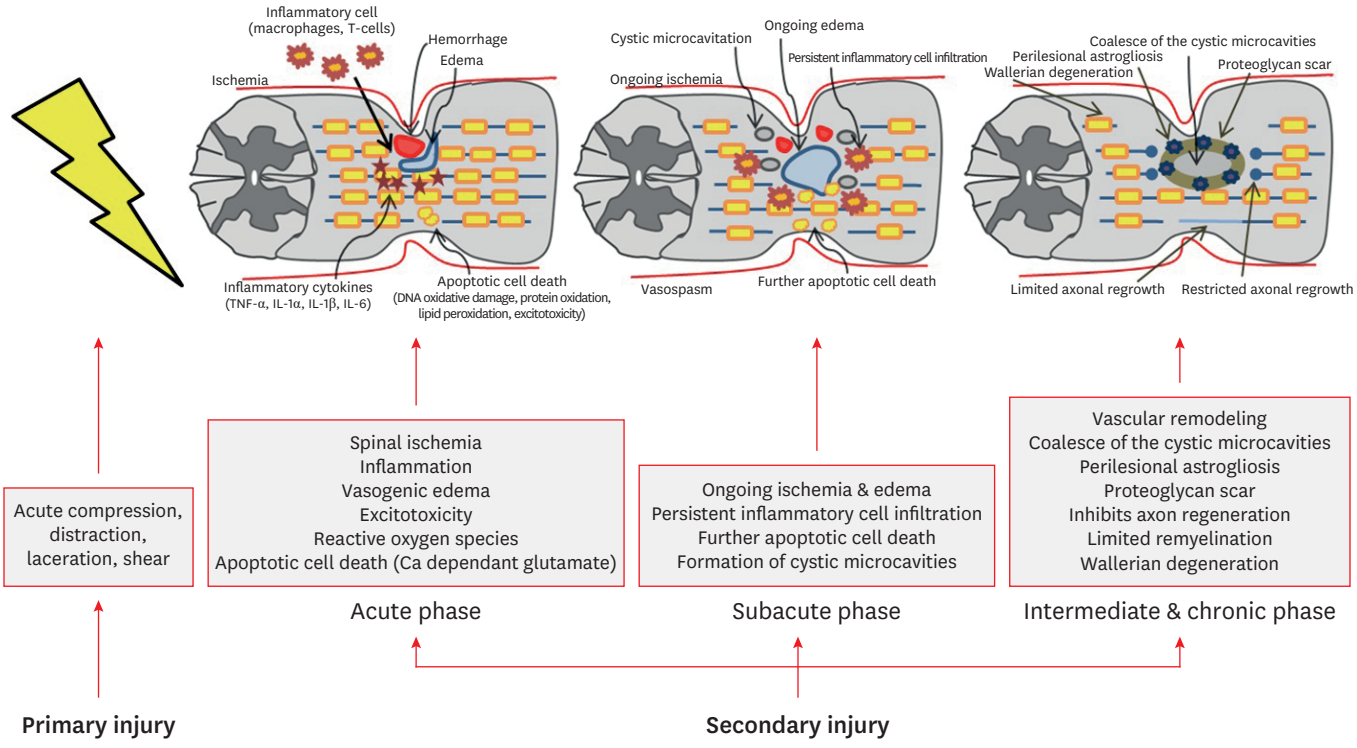

FIGURE 2. Pathophysiology of spinal cord injury.

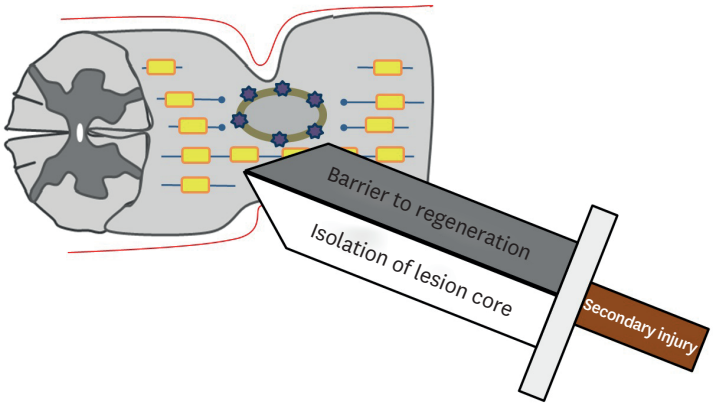

FIGURE 3. A double-edged sword for secondary injury.

cannot absolutely explain the beneficial effects of steroid use, the results of many animal studies support the positive effects of steroid use in acute SCI.[18,19] Corticosteroids are known to have neuroprotective effects, including improvement of vascular perfusion, prevention of calcium influx and accumulation, modulation of the inflammatory cells, prevention of the loss of spinal cord neurofilament proteins facilitate neuronal excitability and impulse conduction, and inhibition of lipid peroxidation and inflammatory cytokines. Among them, inhibition of lipid peroxidation has the strongest neuroprotective feature. Among these glucocorticoids, methylprednisolone sodium succinate (MPSS) is particularly effective for neuroprotection than other glucocorticoids, so MPSS is currently mainly used.[9] The best-known large prospective randomized multicenter clinical trials for evaluating the effects of corticosteroids in SCI are the National Acute Spinal Cord Injury Studies (NASCIS). This was

https://doi.org/10.13004/kjnt.2022.18.e21

implemented up to NASCIS I, II, and II. A summary of the NASCIS trial is as follows. NASCIS I, published in 1984, compared the effects of low-dose (100-mg bolus and 100 mg/daily) and high-dose (1,000-mg bolus and 1,000 mg/daily) MPSS in 330 patients within 48 hours after SCI, and there was no difference in neurological improvement. Rather, complications such as wound infection and sepsis occurred more in patients using high-dose MPSS.[5] However, since not using corticosteroids for SCI patients in actual clinical practice could be ethically problematic, a placebo that can compare the MPSS and natural history of spinal cord recovery was not used in this study. In animal experiments, the 1,000-mg dose was a low dose to achieve effective neuroprotection, and it was suggested that an initial dose of 30 to 40 mg/kg followed by intravenous maintenance was more appropriate.[8,23] Therefore, in NASCIS II, MPSS (initial bolus of 30 mg/kg followed by a 23-hour infusion of 5.4 mg/kg per hour), naloxone (opioid receptor antagonist), or placebo were randomly used to 487 patients within 12 hours after SCI and compared with each other. There was no difference in neurological effect between groups, but motor and sensory recovery were significantly improved in both complete and incomplete patients treated with MPSS within 8 hours after SCI. In the group using MPSS, the risk of wound infection and pulmonary embolism increased, so there were concerns about the risk of complications after using steroid.[6] NASCIS II was the first clinical study to show the effects of pharmacological agents after SCI, and it was a study that became the basis for the use of steroids after SCI worldwide, and contributed to promoting the activation of research on other neuroprotective agents after SCI. In NASCIS III, the using duration of MPSS in 499 patients within 8 hours after SCI was compared, and the effect of tirilazad mesylate was additionally evaluated. Tirilazad mesylate, a member of the 21-aminosteroid family of antioxidant molecules, inhibits lipid peroxidation without activation of glucocorticoid receptors, and was expected to have a positive effect on SCI without complications of steroid.[2,27] Patients in the study received 30-mg/kg bolus of methylprednisolone (MP) during the first hour and randomly maintained either 5.4 mg/kg/hour of 23 hour MPSS or 5.4 mg/kg/hour of 47 hour MPSS infusion or maintained for 48 hours at 2.5-mg/kg every 6 hours of Tirilazad mesylate from initial time. Motor and sensory recovery showed similar effects in all 3 group arms when treatment was started within 3 hours after SCI. However, patients who started MPSS within 3 hours after SCI and received 24-hour infusion showed improvement in neurologic function after 1 year and who received MPSS within 3–8 hour followed by a 48-hour infusion also improved.[7] In actual clinical practice, the method of maintaining the MPSS for 24 hours after the initial bolus was mainly used because of the low complications of steroid. Many criticisms have been raised about measurement of primary outcome, poor randomization, failure to demonstrate functional improvement, manipulation of data, and interpretation and conclusion of data in the NASCIS series. Although the increase in the incidence of complications after steroid use in this series was not statistically significant, it was found that the wound infection rate, pulmonary embolism, sepsis, and even secondary death due to respiratory complications after MPSS use were higher. A question arose as to whether there was an overall benefit to using steroid for SCI. Nevertheless, NASCIS II and III have established the administration of MPSS as the standard clinical practice for acute SCI worldwide. In the early 2000s, papers on the occurrence of complications of high-dose steroids after SCI were continuously reported.[26,28,33,38] As the evidence for serious side effects has been accumulating, a gradual change in the practice of steroid for SCI in actual clinical practice has become inevitable. In a survey conducted by spine surgeons in Canada, British, Switzerland, and Germany, it was reported that the rate of using of steroid for SCI decreased from 70%–80% to 20%–30%.[17,25,51] Also, in a survey conducted on Cervical Spine Research Society members in 2014, the usage rate of MP for SCI decreased significantly compared to the past, reaching about 50%.[46]

https://doi.org/10.13004/kjnt.2022.18.e21

Therefore, the need for recommendation of professional organization for the use of MP in SCI for clinical practice has emerged. In 2013, the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guideline on the use of MP for SCI was published as a level 1 recommendation, and unlike the guidelines recommended by the same joint committee in 2002, the use of MP for SCI was not recommended. Afterwards, the European spine society, which includes the British National Institute for Health and Care Excellence guidelines and the guidelines of The Polish Society of Spinal Surgery, also did not recommend the use of steroids for SCI.[35,36,39] Despite the recommendations of professional organizations that do not use steroid for SCI, in 2017, AOSpine practice guideline suggested that 24-hour infusion of high-dose MPSS should be provided in patients with SCI within 8 hours as a treatment option without presenting any new evidence.[21] However, a meta-analysis including 3 randomized controlled trials and 13 observation studies did not show the effectiveness of high-dose MPSS in patients with SCI within 8 hours of injury.[32] Also, the latest meta-analysis published in 2020 showed the same results.[47] Globally, the prescription rate of MPSS has decreased from 76% to 24% in Canada, from 68% to 19% in the UK, and from 73% to 27% in Poland.[25,36,51] In South Korea, the prescription rate of MPSS in SCI patients for the past 11 years was 59%, and it was the highest at 76% in 2012, and then gradually decreased to 41% in 2017.[14] Most prevalent rationale for using steroids in SCI patients is because of the belief that it will work and medical litigation.[36] Compared to the North America or Europe, South Korea still has a high proportion of steroid prescriptions for SCI. Therefore, it is necessary to educate and inform the spine surgeon that steroid use is not effective in SCI patients, and that there is no objective rationale for steroid use even for patients within 8 hours after injury.

CONCLUSION

In 2017, AOSpine practice guideline suggested that 24-hour infusion of high-dose MPSS should be provided in patients with SCI within 8 hours as a treatment option without presenting any new evidence. However, subsequent meta-analysis studies consistently show that high dose MPSS use in SCI patients has no effect on neurological improvement. However, South Korea still has high prescription rate of MPSS for SCI compare to other countries. Therefore, it is necessary to fully understand the effects and side effects of steroid use and to apply them appropriately in clinical practice.

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