Restorative Treatments for Spinal Cord Injury

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KEYWORDS

• Spinal cord injury • Neuroprotection • Cell-based therapies • Electrical stimulation

KEY POINTS

- Therapeutic hypothermia after spinal cord injury may prevent secondary damage after spinal cord injury.
- Cell transplantation with glial cells, stem cells, or a combination may enhance spinal cord regeneration and functional recovery after spinal cord injury.
- Electrical stimulation may assist in recruiting new motor circuits to improve function after spinal cord injury.

INTRODUCTION

Spinal cord injury (SCI) occurs in approximately 10,000 to 12,000 individuals per year in North America, and 250,000 individuals are living with an SCI.[1] Current treatment is focused on limiting secondary complications and maximizing residual function. However, with the life expectancy of individuals with SCI increasing, therapeutic strategies focused on restoring functional independence is becoming increasingly important. In this article, the authors discuss the range of strategies that are currently being used and researched in order to restore function after SCI.

NEUROPROTECTION

After the initial trauma of SCI, cell death and tissue loss continue over several weeks.[2,3] During this initial window the main strategies used to restrict secondary damage are surgical decompression, therapeutic hypothermia, and drugs targeting inflammation or excitotoxicity.

Therapeutic Hypothermia

Therapeutic hypothermia slows biological reactions and processes resulting in improved electrophysiologic, histologic, and motor outcomes in experimental models of SCI. The mechanism of protection includes reducing excitotoxicity,[4] vasogenic edema,[5] neuroinflammation,[6] ischemia,[7] oxidative stress,[8] and apoptosis.[9] This increasing body of evidence of efficacy has been derived primarily from animal studies and case series.[10–16]

Several case series in the 1970s described potential benefits with the use of local spinal cord cooling after SCI.[17–23] In these experimental models, cooling was performed by application of an extradural heat exchanger or perfusion of subarachnoid space with cold solution. However, the results were mixed and the procedure invasive; thus, the technique was gradually abandoned. However, in a recent case series, 20 patients with complete cervical or thoracic SCI underwent triple therapy including dexamethasone, surgical decompression, and deep cord cooling with

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extradural saddles (dural temperature of 6°C). At 1 year after injury, 16 patients (80%) regained some sensory or motor function.[24] Although this study is exciting, the evidence is preliminary and merits further investigation.

Systemic cooling with intravascular heat exchange cooling catheter techniques is of great modern interest as it has been shown to be safe[25–27] and potentially beneficial in a case control study (Fig. 1). In this study of 31 patients with complete cervical SCI (who showed no improvement within 24 hours of injury), 11 (35%) of patients regained some sensory or motor function with systemic intravascular cooling (Fig. 2).[28] The finding is promising as the rate of spontaneous recovery is reported to be approximately 15% to 20% in complete cervical SCI.[29,30] The surmounting body of evidence of efficacy will be further elucidated by the results of an ongoing clinical trial (NCT01739010) to test modest systemic hypothermia.

Pharmacologic Therapies

Pharmacologic therapies are also being studied to target secondary damage from inflammation and excitotoxicity. The most heavily studied pharmacotherapy agent for SCI has been methylprednisolone, which is thought to limit the inflammatory response after SCI. However after 4 prospective blinded randomized controlled trials, there is no class I medical evidence of any benefit.[31–34] Furthermore, methylprednisolone may have harmful effects, including increased rates of wound infections, gastrointestinal hemorrhage, and hyperglycemia. Thus, the most recent guidelines from the Congress of Neurological Surgeons/American Association of Neurological Surgeons recommends against the use of methylprednisolone for the treatment of acute SCI.[32,35]

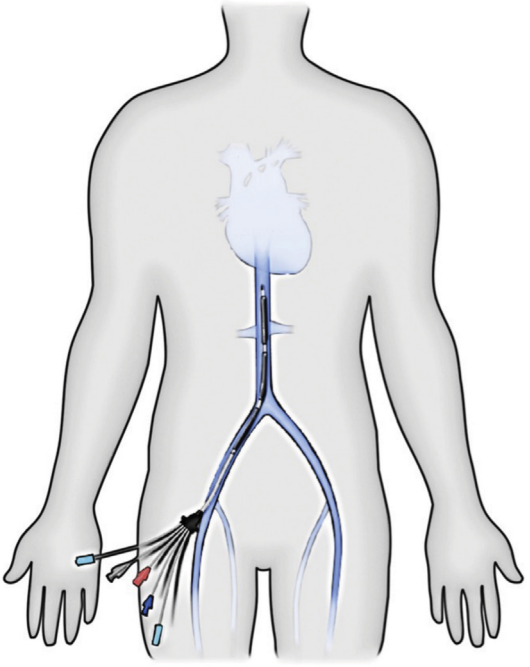

Fig. 1. An intravascular heat exchange, cooling catheter that functions by circulating ice-cold saline in balloons within the inferior vena cava in a closed circuit without adding any intravascular volume. In the University of Miami hypothermia protocol, this device is used to cool patients to a target temperature 33°C.

Other agents currently being studied include minocycline and riluzole. Minocycline is a semisynthetic tetracycline antibiotic, which is currently in a phase 3 clinical trial for neuroprotective benefits after acute SCI. It has been shown to reduce inflammatory cytokines, free radicals, and matrix metalloproteinases.[36–40] Riluzole is a glutamate antagonist and sodium channel blocker that is currently being tested in a phase 1 trial for acute SCI, with initial data suggesting that riluzole is well tolerated and may have neuroprotective efficacy.[41] Further discussion of the pharmacologic agents for SCI (see Michael Karsy and Gregory Hawryluk's article, "Pharmacologic Management of Acute Spinal Cord Injury," in this issue).

CELL TRANSPLANTATION AND REGROWTH

Traumatic SCI results in a disruption of axonal myelination, resulting in a loss of function. *Glial cell transplantation* has emerged as a potential target for axonal regeneration after SCI. Schwann cells are the most common glial cell in the peripheral nervous system. Their therapeutic potential is thought to be due to their ability to secrete high levels of neurotrophic growth factors and extracellular matrix molecules that promote axon growth.[42] Schwann cell grafts have been extensively studied in animal models and have been shown to increase cell survival, decrease the size of the cystic lesion after SCI, and improve locomotion scores.[43,44] However, only 3 studies have reported the use of Schwann cells in humans with SCI (Fig. 3).[45–47] The largest of these studies involved 33 patients with chronic American Spinal Injury Association (ASIA) grade A or B SCI in which there was a marked improvement in sensory scores but no improvement in motor function.[45] From this preclinical data, a phase 2 clinical trial of autologous Schwann cells in chronically spinal cord injured subjects is presently underway in the Miami Project to Cure Paralysis.[47]

Another cell type that is being studied for axonal regeneration after SCI is the *olfactory ensheathing cell* (OEC). OECs are a distinct population of cells that wrap the axons of olfactory receptor axons in