REVIEW

Therapeutic approaches for spinal cord injury

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This study reviews the literature concerning possible therapeutic approaches for spinal cord injury. Spinal cord injury is a disabling and irreversible condition that has high economic and social costs. There are both primary and secondary mechanisms of damage to the spinal cord. The primary lesion is the mechanical injury itself. The secondary lesion results from one or more biochemical and cellular processes that are triggered by the primary lesion. The frustration of health professionals in treating a severe spinal cord injury was described in 1700 BC in an Egyptian surgical papyrus that was translated by Edwin Smith; the papyrus reported spinal fractures as a ''disease that should not be treated.'' Over the last two decades, several studies have been performed to obtain more effective treatments for spinal cord injury. Most of these studies approach a patient with acute spinal cord injury in one of four manners: corrective surgery or a physical, biological or pharmacological treatment method. Science is unraveling the mechanisms of cell protection and neuroregeneration, but clinically, we only provide supportive care for patients with spinal cord injuries. By combining these treatments, researchers attempt to enhance the functional recovery of patients with spinal cord injuries. Advances in the last decade have allowed us to encourage the development of experimental studies in the field of spinal cord regeneration. The combination of several therapeutic strategies should, at minimum, allow for partial functional recoveries for these patients, which could improve their quality of life.

KEYWORDS: Spinal Cord Injuries; Rehabilitation; Central Nervous System/Injuries.

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INTRODUCTION

Spinal cord injury (SCI) is a disabling and irreversible condition with high economic and social costs. The most common cause is trauma, but this injury can also be caused by tumors, infection, and vascular lesions or by iatrogenic procedures. SCI increases the risk of depression, sleep disorders, spasticity, bladder and gastrointestinal changes, bedsores, sexual dysfunction, involuntary movements, obesity, and vascular and respiratory diseases. The development of therapeutic procedures depends on a better understanding of the pathophysiology of SCI. Recent literature reviews show that there is still no treatment for SCI that results in complete neurological or functional recovery (1,2).

There are both primary and secondary mechanisms of damage to the spinal cord. The primary lesion is the mechanical injury itself, and the secondary lesion results from one or more biochemical and cellular processes that are triggered by the primary lesion (3). Allen first postulated the concept of a secondary injury in 1911 (4); he proposed that the existence of noxious biochemical agents in necrotic and hemorrhagic material caused additional spinal cord damage.

A primary lesion that is caused by an impact to the spinal cord consists of acute structural and physiological disruption of axons, nerve cell damage and blood vessel ruptures. Hemorrhage and necrosis in the central gray matter occur within the first hours after the injury (acute phase), followed by edema and hemorrhage in the seven hours following the trauma. The injury is the result of ischemia that is caused by reduced blood flow to the affected spinal segment. This reduction may be caused by a change in the spinal canal, by significant edema and hemorrhage or by reduced systemic blood pressure. Ischemia creates a chain of biochemical reactions that result in cell death. Inflammatory cells then simultaneously migrate to the injured site with glial cell proliferation. The chronic phase lasts one to four weeks; during this time, the proliferation and hypertrophy of astrocytes form a glial scar or a cyst (5).

The most recent studies of the pathophysiological processes that occur after central nervous system injury provide rational support for treatment strategies and demonstrate some improvements in neurological function in SCI patients. An improved understanding of the primary and secondary pathophysiological processes opens a research field with experimental SCI models produced in laboratories. Standardization of SCI experimental protocols allows for reproducibility of the results and analyses (6,7).

No potential conflict of interest was reported.

SCI treatment measures include the prevention of primary, secondary and tertiary lesions. Primary measures include advertising campaigns to prevent spinal fractures resulting from diving accidents, reduce the incidence of traffic accidents, and enhance vehicle safety; campaigns to promote disarmament; and projects to improve home security, particularly to reduce the incidence of falls in the elderly. Secondary prevention measures are being developed for application at the time of the accident and are based on the foundations of adequate rescue and transportation to specialized treatment centers. Tertiary prevention is the most complex rehabilitation phase. This phase involves not only the patient's family but also society as a whole. Patients should be socially reintegrated to the greatest extent possible after they leave hospitals.

THERAPEUTIC POSSIBILITIES

The frustration caused by a severe SCI was described in 1700 BC in an Egyptian surgical papyrus that was translated by Edwin Smith; it reported that spinal fractures were a ''disease that should not be treated'' (8). Over the last two decades, several studies have been performed to identify more effective SCI treatments. Most of these studies approach the treatment of acute SCI patients in one of four manners: corrective surgery (2,9) or physical (10,11), biological (12-15) and pharmacological treatment methods (16-18).

Surgical techniques

Surgical techniques for SCI repair have been used for 40 years (2,19); however, the results have been controversial, and the available data have been widely questioned (19). The most commonly used approach is surgical decompression with or without arthrodesis. However, only 1% to 1.8% of patients with cervical and thoracic SCI can walk after an attempted surgical decompression (19). The role of surgery in acute SCI is limited to spinal alignment, nerve decompression and stabilization of the spine, which prevents additional neurologic injury. The use of improved implant materials allows the stabilization of unstable fractures in reconstructive surgeries. Preventing further damage and rehabilitating patients earlier are two known surgical benefits (20).

Experimental study results have indicated that the chances of neurological recovery improve with earlier decompression (21). However, these studies did not coincide with the findings of the best clinical studies (22). A 2012 study corroborated the findings of these experimental studies. It indicated that when decompression is performed within 24 hours after trauma, the chance of functional recovery improves (23). These results emphasize the need for promptly reducing dislocations and decompressing fractures, either by cranial traction or through open surgery (20,24,25).

Complications are another commonly reported challenge in surgical treatment; however, they are decreasing as more treatment centers specialize in spine surgery. The incidence of complications related to the surgical approach is low (26). Implant positioning errors are rare (27), ranging between 1 and 3% for the most modern techniques of fixation with screws. This technique is even feasible in children (28).

Some surgical approaches are still considered experimental, such as those seeking to build bridges to cross the damaged area of the spinal cord. Central and peripheral nerve cell grafts, coated Schwann cell tubes, olfactory glial cells and genetically engineered fibroblasts are used for this purpose (14). These techniques, combined with exogenous neurotrophic factors (14), contribute new perspectives to the study of functional axonal regeneration in SCI.

Biological therapy

Factors that promote neuronal regeneration, such as tissue growth factors and autologous or homologous totipotent cells, are biological therapies for SCI. Stem cell and precursor cell transplantation for treatment of SCI has been studied for approximately 10 years. Undifferentiated cells are multipotent cells that have the capacity to proliferate and propagate cells of any lineage or tissue type. It has been previously shown in animal models that stem cells transplanted into a normal or injured spinal cord can differentiate into neurons or glia. Neuronal precursor cells can be isolated and propagated in cultures in the presence of mitogens and, when transplanted, may yield neurons and oligodendrocytes. Stem cells can also differentiate into astrocytes, indicating that environmental signals are crucial for the specification of the lineage (29-31). Transplanted stem and fetal cells could function not only as a bridge between damaged spinal areas but might also potentially release factors that stimulate axonal regeneration and replace damaged cells (14,15). However, because of the short-term monitoring and evaluation used in these therapeutic studies, there is no clear consensus regarding their results. Despite this controversy, stem cells remain a future possibility for finding a cure for SCI (12).

More recently, studies involving central nervous system cell transplantation have been directed to restore or reduce the loss of function resulting from injury. It has been reported that a transplant may decrease functional deficits or increase functional recovery, particularly in degenerative diseases. After central nervous system damage, transplants may positively influence functional recovery through a wide range of mechanisms, which include the non-specific consequences of transplantation, trophic actions, the release of hormones and transmitters and even mechanisms involving the specific reinnervation of host cells and establishment of reciprocal connections between the host and transplanted tissues (13,32). Fetal central nervous system cell transplantation bridges the gap between the spinal cord and the supraspinal levels through the lesion site. In addition, these cells can provide a population of cells at the site of injury, which can serve as a substrate for re-establishing communication between the levels above and below the lesion (13).

The requirements for anatomical and functional SCI repair are more complex than the requirements for the recovery of other types of neurological damage, which often only require that neurotransmitters be restored for functional recovery (14). Transplantation using cells from the central nervous system can improve motor function after SCI and provides a more complex microenvironment than that provided by the transplantation of peripheral nerves, cell suspensions or genetically modified cells (14,33).

One recently discovered concept is that adult cells might be reprogrammed to express genes that are typical of differentiated cells in any of the three lineages (mesoderm, ectoderm and endoderm). This discovery suggests that a cell's status is reversible and is subject to continuous

regulation by the surrounding medium. For example, one study reported that bone marrow-derived cells administered intravenously after sublethal irradiation resulted in cells expressing neuron-specific genes (34,35). The manipulation of these stem cells allows the prospect of future cures for diseases currently considered incurable (14,36).

Physical means

Physical approaches are also employed to minimize secondary spinal cord damage. The most studied approaches are hypothermia, hyperbaric oxygen and exercise, particularly on a treadmill. Several studies have also shown the beneficial effects of local cooling by perfusion or irrigation with hypothermic saline (37,38). This approach is based on the assumption that low temperatures protect central nervous system tissues from the effects of hypoxia and ischemia. However, it is difficult to apply this technique, and it carries a high mortality rate. In addition, cooling therapy does not prevent potassium loss, such as occurs in steroid therapy (39).

Hyperbaric oxygen therapy is a treatment modality that is based on achieving a high partial pressure of oxygen in the tissue by having the patient breathe pure oxygen inside a hyperbaric chamber at a pressure greater than the atmospheric pressure (40). The rationale for this therapeutic approach is that a decrease in perfusion can be compensated for by increasing the partial pressure of oxygen (11). Positive results have been reported with the use of hyperbaric oxygen treatment in SCI (37,41).

Several recent studies have reported the benefits of exercise in animals subjected to SCI or in human victims of accidents involving such injuries (42,43). Treadmill training results in improvement in recovery, coordination and neurological performance with various types of exercise. There is extensive literature demonstrating the beneficial effect of exercise on a treadmill on neuronal plasticity in mice. This activity resembles exercises that can be practiced by humans and are mandatory items in clinical rehabilitation programs in SCI (44). Several studies have suggested that one effect of training is to enable intrinsic neuronal circuits (10). In these studies, the improvement in gait ability and in movement dynamics and mechanics is remarkable and encourages further investigation. Most of the work in the international literature has demonstrated the different methods of evaluating the benefits of physical training alone. Few studies have evaluated the benefits of exercise in combination with other therapeutic modalities (45).

Pharmacological therapy

Pharmacology plays an important role in treating SCI. Experimental and clinical trials show that medication can effectively contribute to the treatment of secondary SCI (46). Corticosteroids and gangliosides are already approved for human use (47).

The most frequently studied corticosteroids are dexamethasone and methylprednisolone. Three multicenter randomized, double-blind clinical trials have been conducted to study the action of methylprednisolone and report on its effectiveness in patients with SCI. Together, these studies were called the National Acute Spinal Cord Injury Study (NASCIS). The first (NASCIS1) was published in 1985 (48), the second (NASCIS 2) in 1992 and the third (NASCIS3) in 1997 (16,49).

Steroid treatment of SCI is used mainly because the anti-inflammatory action of steroids and their effectiveness in treating cerebral edema. However, methylprednisolone also increases blood flow and stabilizes the cell membranes, inhibiting lipid peroxidation with a consequent reduction in the production of free radicals (16,50).

Methylprednisolone has been experimentally tested as a prophylactic method in surgeries with elevated risk of spinal cord manipulation or lesion. However, no functional improvement was observed in this clinical approach (51). In addition, studies reviewing the methodologies used in NASCIS and other research projects reported the deleterious side effects of massive doses of corticosteroids. These side effects have led many centers to avoid routinely using corticoids, particularly methylprednisolone (53), for SCI lesions (52).

Gangliosides are glycolipid molecules that are derived from sialic acid. *In vitro*, they increase the formation and growth of neurites, protoplasmic expansions of axons that originate new functional connections, induce neuronal regeneration and promote neuroplasticity (54). The GM1 ganglioside has been studied in SCI. There was a demonstrated improvement in motor and sensory indices, even in the sphincter function, in the SCI patients who received GM1 compared to placebos (51). A recent systematic review of drugs used in SCI showed that GM1 administration in combination with physical therapy improved motor scores and walking velocity and distance over a placebo or physical therapy alone in individuals with incomplete SCI (55).

In patients with traumatic SCI associated with neurologic damage, the recommended ganglioside loading dose is 300 mg followed by 100 mg once daily for 30 days, via intravenous or intramuscular injection. This drug should not be administered simultaneously with methylprednisolone (51).

Because oxidative stress is considered a hallmark of SCI (56), the reduction of oxidative stress has been studied as a therapeutic intervention for SCI. The goal was to prevent free-radical-induced, iron-catalyzed lipid peroxidation and oxidative or nitrative damage to the neuronal proteins in the spine (50). Lipid peroxidation induced by oxygen is a key biochemical step in secondary damage to spinal cord cells (53). Experimental studies show that antioxidants and free radical blockers, alone or in combination, can accelerate the functional recovery of rats with SCI (17).

Membrane disruption is thought to play an important role in the pathology of SCI. Intracellular calcium is essential to membrane releasing, and elevated intracellular calcium has been linked to axonal deterioration (57). Myelin damage creates aberrant potassium channels that inhibit conduction (58). Some studies have shown that calcium channel blockers increase medullary microcirculation (58). One blocker that was clinically tested is nimodipine, but the evidence did not recommend its clinical use in patients with traumatic SCI (54). A selective inhibitor of KCa3.1 channels, TRAM-34 (triarylmethane-34), improved locomotor function, reduced tissue loss and increased neuron and axon sparing (59).

Aminopyridine is a potassium channel blocker that improves nerve conduction in demyelinated axons (54,57), with both motor and sensory functional improvement (60,55). However, more studies are necessary to prove that aminopyridine produces better results than a placebo (55).

High doses of methylprednisolone are required to achieve neuroprotective effects and concern about the possible side effects of this drug, which include gastrointestinal bleeding and infection, have led researchers to develop drugs with the protective effects of methylprednisolone but without its side effects. Tirilazad (the non-glucocorticoid 21-aminosteroid tirilazad) has been noted as a promising medication in clinical trials (56). It was tested in NASCIS 3, but is not used clinically (49,61). Naloxone is an opioid antagonist that was tested in animal models (62) and cases of SCI in the last decade. Naloxone administration resulted in an increase in spasticity (63). It was also studied during the NASCIS 2, but exhibited no benefit over a placebo (64). This substance is still experimentally studied, but is not yet used in clinical practice.

The loss of regulatory descending serotonergic mechanisms after SCI contributes to motor deficits. However, the use of selective serotonin reuptake inhibitors (antidepressants) has been reported to have a positive effect on limb movement in SCI and increases the number of serotonin receptors in the segments below the SCI. This increased number of receptors may be indicative of a potential treatment method because the increased administration of serotonin receptor agonists has been previously reported to ameliorate motor deficits (65,45). In addition, the administration of serotonin precursors has also been reported to have positive effects on motor recovery (66).

FINAL CONSIDERATIONS

Until recently, the mammalian central nervous system was believed to be unable to repair or regenerate itself after devastating injury. However, the spinal cord does not necessarily need to be rebuilt for SCI patients to recover quality of life (67). Disproportionate benefits can be obtained from minimal anatomical repairs. Further advances, which may contribute to new SCI treatments, are expected in the fields of cellular engineering and gene therapy (68).

Science is continually unraveling the mechanisms of cell protection and neuroregeneration, but clinically, we are only providing supportive care for SCI patients. Therapeutic advances made in the last decade have allowed the development of experimental work in the field of spinal cord regeneration. The combination of several strategies should make, at minimum, partial functional recovery possible for SCI patients, which might consequently lead to an improvement in their quality of life. Through combined treatment strategies, the enhanced functional recovery of SCI patients will likely be achieved.

AUTHOR CONTRIBUTIONS

All the authors participated in the writing and review of the manuscript.

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