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Review Article

Current advancements in the management of spinal cord injury: A comprehensive review of literature

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ABSTRACT

Background: Spinal cord injury (SCI) carries debilitating lifelong consequences and, therefore, requires careful review of different treatment strategies.

Methods: An extensive review of the English literature (PubMed 1990 and 2019) was performed regarding recent advances in the treatment of SCI; this included 46 articles written over 28 years.

Results: Results of this search were divided into five major modalities; neuroprotective and neuroregenerative pharmaceuticals, neuromodulation, stem cell-based therapies, and various external prosthetic devices. Lately, therapeutic strategies were mainly focused on two major areas: neuroregeneration and neuroprotection.

Conclusion: Despite recent advancements, more clinical trials on a larger scale and further research are needed to provide better treatment modalities of this devastating neurological disease.

Keywords: Exoskeleton, Neuromodulation, Spinal cord injury, Spine, Stem cells, Trauma

INTRODUCTION

Spinal cord injury (SCI) is a devastating illness resulting in neurological deficits and poor quality of life. It has an annual incidence of 15–40 cases per million and a prevalence of more than 1 million cases in North America.[12] The incidence and prevalence of traumatic SCI is expected to increase as the population ages, particularly secondary to traumatic falls in the elderly.[45] The annual cost of SCI exceeds 7 billion dollars.[12]

This literature review focuses on the advances in pharmacology, stem cell technologies, neuromodulation, and external prosthetics. Several pharmacological therapies have already been tested in the past and are currently being investigated. Further, both neuroprotective and neuroregenerative drugs are being implemented in clinical trials.[45] Stem cell therapy trials are also ongoing, but more data are needed from Phase II clinical trials to document efficacy.

MATERIALS AND METHODS

Peer-reviewed articles were searched through PubMed using search terms "acute SCI," "SCI treatment," "neuromodulation," "stem cell therapy for SCI," "SCI pharmaceuticals," and "SCI

exoskeleton from 1990 to 2019 (English journals). Using appropriate inclusion and exclusion criteria, 46 peer-reviewed articles were used. All studies focused on current advancements in the management of SCI, including stem cell therapies, neuromodulation, and external prosthetics.

RESULTS AND DISCUSSION

Neuroprotective and neuroregenerative pharmaceuticals [Tables 1and 2]

Methylprednisolone

Several neuroprotective and neuroregenerative pharmaceutical drugs have been investigated for SCI management. A well-known neuroprotective agent, methylprednisolone, has been associated with improved neurological outcomes. It decreases the peroxidation of membrane lipids and posttraumatic inflammation.[45] Despite its effects in preclinical settings, it does still remain controversial in the clinical setting. A Cochrane review found no significant effect for a high-dose 24 h infusion of methylprednisolone in terms of motor recovery at 6 months.[7,45] However, when started within 8 h after injury, an additional 4-point improvement in National Acute SCI Study (NASCIS) motor score was seen.[7,45] Its association with increased rates of gastrointestinal hemorrhage and wound infections also adds to its controversy.[7,45] A randomized controlled trial evaluating high-dose 48 h infusion showed no difference in NASCIS motor score recovery versus 24 h infusion.[6,45] The guidelines now suggest that methylprednisolone infusion within 8 h of injury should be performed only in certain situations, taking into consideration the associated complications.[27,45]

Naloxone, tirilazad, and nimodipine

Three drugs, naloxone, tirilazad, and nimodipine, were studied for their neuroprotective abilities. They all have Phase III randomized controlled trials which have not shown any difference in NASCIS motor score recovery or the American Spinal Injury Association (ASIA) motor score between treatment and placebo groups.[5,6,27,37,45] Tirilazad is a nonglucocorticoid 21-aminosteroid that attenuates peroxidation of neuronal lipid membranes. Tirilazad had no difference in NASCIS motor score between tirilazad and 24 h infusion of methylprednisolone.[6,45] The neuroprotective value of naloxone is believed to be due to blockage of the neurotoxic effects of the endogenous opioid dynorphin A. Nimodipine is a calcium channel blocker that inhibits calcium-dependent activation of lytic cellular enzymes as well as presynaptic glutamate release.[5,37,45]

Riluzole

Riluzole, a sodium channel blocker approved for the treatment of amyotrophic lateral sclerosis, has been studied in preclinical models of SCI. It diminishes secondary injury by blocking activation of sodium channels and reducing release of neuronal glutamate.[41,45] Phase I/II trials evaluating the

Table 1: Neuroprotective pharmaceuticals.

Drug	Mechanism	Evidence on efficacy
IV Methylprednisolone[6,7,45]	Neuroprotection through reduction of membrane lipids peroxidation and posttraumatic inflammation	Limited evidence on neuroprotective properties, most recent studies failed to prove real benefit as treatment in acute SCI
Naloxone[5,37,45]	Inhibition of neurotoxic effect of endogenous opioid dynorphin A	No evidence of improvement in NASCIS or ASIA motor scores
Tirilazad[5,37,45]	Decreases peroxidation of lipid neuronal membranes	No evidence of improvement in NASCIS or ASIA motor scores No difference in NASCIS motor score when compared to 24 h infusion of methylprednisolone
Nimodipine[5,37,45]	Calcium channel blocker that prevents calcium-dependent activation of apoptotic enzymes and blocks release of presynaptic glutamate	No evidence of improvement in NASCIS or ASIA motor scores
Riluzole[14,22,45]	Sodium channel blocker, reduces sodium-dependent glutamate release diminishing neuronal injury	Phase I trials have shown a gain of 15.5 in motor score. Phase IIB and III trials are ongoing
Minocycline[8,15,28,45]	Modified form of tetracycline (antibiotic), reduces inflammation, neuronal apoptosis, and microglial activation	Phase II trials have shown improvement in motor score (14 points). Phase III trials are ongoing
Basic fibroblast growth factors[45,44]	Neuroprotection by reducing glutamate-mediated excitotoxicity	Pending results from Phase I/II clinical trials

ASIA: American Spinal Injury Association, NASCIS: National Acute Spinal Cord Injury Study

Table 2: Neuroregenerative pharmaceuticals.

Drug	Mechanism	Evidence on efficacy
G-CSF[31,43]	Inhibition of TNF-alpha and IL-1 beta, promoting cell survival	Phase I/IIa clinical trials have shown improvement in ASIA motor score (P<0.01)
GM-1 ganglioside (Sygen)[16]	Component of neuronal membranes enhances axonal regeneration in laboratory studies	Randomized placebo-controlled trial did not show benefits
Cethrin[13,45]	Bacterial-derived toxin, BA-210, and a biohemostatic adhesive inhibit the Rho pathway of inhibitory proteins and promotes axonal growth	Benefits shown in Phase I/IIa trials. Improvement in AISA motor score
Anti-Nogo[45]	Monoclonal antibody binds and inhibits Nogo (protein that blocks axonal growth in the CNS through activation of Rho pathway), promoting neuronal regeneration	Currently in early phase clinical trials

CNS: Central nervous system, G-CSF: Granulocyte colony-stimulating factor, ASIA: American Spinal Injury Association, TNF: Tumor necrosis factor, IL: Interleukin

safety and pharmacokinetics of riluzole began in humans in 2010 and were completed in 2012.[14,22,45] In the Phase I trial, a gain of 15.5 points in motor score for patients with cervical injuries was found for the riluzole group of 24 patients over the comparison registry group of 26 patients.[22] At 180 days, there was a gain of 31.2 points for patients with cervical injuries for 24 riluzole patients and of 15.7 points for 26 registry patients.[22] There was a gain of 9 points in pinprick scores in riluzole patients with complete or incomplete cervical injuries versus registry patients.[22] A Phase IIB/III double-blinded randomized controlled trial was started in 2014 looking at the safety and neuroprotective efficacy of riluzole in patients with acute cervical SCI. These results will provide Class I evidence regarding the use of riluzole.

Minocycline

Minocycline, a modified form of tetracycline, is another neuroprotective agent that has shown some promise in animal models.[15,45] In animal models of SCI, it has been shown that minocycline decreases neuronal and oligodendrocytes apoptosis, microglial activation in addition to anti-inflammatory effects.[15] In randomized controlled Phase II clinical trials, minocycline was associated with 14-point gain in motor score over placebo in patients with cervical SCI.[8,22,45] Pinprick scores in these motor-incomplete patients were 14 points higher than placebo.[22,28,45] Phase III clinical trials will be able to provide further evidence regarding its use.

Fibroblast growth factor

Basic fibroblast growth factor has shown to provide neuroprotection by improving functional and respiratory parameters in animal models by reducing glutamate-mediated excitotoxicity.[44,45] There are current Phase I/II trials that are further investigating this therapy. Furthermore, cytokine granulocyte colony-stimulating factor which inhibits tumor necrosis factor-alpha and interleukin-1 beta, promoting cell survival has shown benefits in two nonrandomized studies.[31,43]

GM-1 ganglioside (Sygen)

A neuroregenerative agent, GM-1 ganglioside (Sygen) has been shown to enhance axonal regeneration in laboratory studies.[45] Gangliosides are important glycolipid molecules that are components of neuronal membranes. Randomized placebo-controlled trial using this agent did not show any difference in neurological recovery in patients at 6 months.[16,45]

Cethrin

Cethrin is a permeable paste that can be applied to spinal cord dura postinjury that is a combination of a bacterial-derived toxin, BA-210, and a biohemostatic adhesive. It inhibits the Rho pathway of inhibitory proteins and promotes axonal growth *in vitro*.[45] Phase I/IIa trials were done where it was applied to dura in patients with complete injuries, and no complications were seen at 1-year follow-up.[13,45] In fact, in patients with cervical injuries receiving cethrin, there was an improvement in ASIA motor score.[45]

Anti-Nogo

Another neuroregenerative drug, anti-Nogo, is a monoclonal antibody made to bind to Nogo-A, and has been shown to promote neural regeneration.[45] Nogo-A is a protein that blocks axonal growth in the central nervous system.[45] This anti-Nogo agent is still under investigation. Many of these neuroprotective and neuroregenerative agents have shown promising results and future studies will be helpful in establishing their efficacy.

Neuromodulation [Table 3]

It is well known that neuromodulation, the use of electrical stimulation to alter neuronal circuitry, has

Table 3: Other modalities; neuromodulation, stem-cell transplant, and prosthetic devices.

Modality	Mechanism	Evidence on efficacy
Neuromodulation Spinal cord stimulation (epidural and transcutaneous)[3,20,23,29] Brain stimulation (transcranial direct current stimulation and transcranial magnetic stimulation)[1,4,11,17,25,36,38]	Improves neuronal connections and circuits within the spinal cord in the remaining intact tracts	Some benefits and improved functional outcomes shown in several studies
Stem cell-based therapies[10,30,33,39,40,42,46]	Precursors for neuronal regeneration. Oligodendrocyte-induced remyelination, axonal elongation, and tract regeneration	Phase I clinical trials showed promising results, however, phase II/III trials, and ethical and legal concerns are still need to be addressed
Prosthetic devices[9,19,21,35]	Providing physical assistance, restoration of a certain level of physical activity, and improvement in cardiovascular health and gait parameters	Several studies showed improvement in functional outcomes and restoration of certain level of physical activity

been tried in various neurological disorders including SCI. Neuroplasticity-mediated functional recruitment of axons (particularly spared axons) to potentiate sprouting, regeneration, and formation of new interconnections between neurons forms the basis of modern neuromodulation techniques. This is complemented with the presence of some intact ascending and descending circuits in patients with SCI, making neuromodulation a feasible option.[29] Spinal cord stimulation, one of the forms of neuromodulation, is a rapidly growing method for SCI. For spinal cord stimulation, epidural or transcutaneous method may be used, and clinical studies have already demonstrated some improvement in motor function with these methods.[3,20,23] Besides, spinal cord stimulation techniques, brain stimulation, and peripheral nerve stimulation are other approaches to neuromodulation in SCI.[29] Several studies have demonstrated functional improvement in volitional movements of lower limbs and hand dexterity in patients with SCI.[3,17] However, whether neuromodulation is affordable and accessible to all patients remains a major challenge.[29]

Activity-dependent plasticity

Moreover, the concept of activity-dependent plasticity has been recently employed to achieve substantial improvements in motor function, based on the recent finding that neurorehabilitation is the only treatment option which can be offered to SCI patients for long-term improvement in motor function.[26] In this model, high-intensity training combined with electrical neuromodulation has shown to improve neuronal connections and circuits within the spinal cord by working synergistically at least in a subpopulation of patients.[26] This holds great promise for recovery of motor function after SCI.

Spinal cord stimulation

With respect to spinal cord stimulation, epidural spinal stimulation has well been tested in patients with chronic pain and most recently in patients with SCI. This method involves surgical placement of electrodes onto the dorsal surface of the spinal cord.[29] Several studies utilizing neuromodulation in patients with SCI ASIA A and B demonstrated an improved ability to make lower extremity voluntary movements following epidural stimulation of their spinal cord.[3,20,23] Moreover, with respect to the effects on upper body, one case study demonstrated improvements in handgrip strength and motor strength of the upper extremities in patients following epidural spinal stimulation once a day.[34] Unlike the epidural method, transcutaneous stimulation is another method and is a noninvasive approach to spinal cord stimulation. It involves placement of electrodes onto the skin surface of a patient. Aside from experimental studies on animals, more clinical trials and studies are needed to fully ascertain the advantages as well as long-term side effects of spinal cord stimulation for SCI.[29]

Brain stimulation for SCI

Brain stimulation for SCI is also currently being employed. Transcranial direct current stimulation and transcranial magnetic stimulation are two main approaches that are being used to augment the neuronal plasticity between the spinal cord and the brain in individuals with SCI.[29] Several studies have already demonstrated to improve functional outcomes from using transcranial direct current stimulation in patients with motor complete SCI.[17,36,38] Transcranial direct current stimulation is a noninvasive method to deliver direct current with the use of scalp electrodes.[17] Transcranial magnetic stimulation is another noninvasive approach that delivers

magnetic waves to the brain and has shown improvements in hand function in studies on patients with tetraplegia. Fine motor tasks and handgrip strength improved with the use of transcranial magnetic stimulation.[2,18] Transcranial magnetic stimulation can also have a positive impact on patient's walking speed as evidenced by one of the trials.[32] Larger scale trials are needed to assess these promising results. In addition, although deep brain stimulation has already been tested in experimental studies on animals, its potential in treating patients with SCI still needs to be elucidated with clinical trials and further research.[24]

Brain–machine interfaces

Brain–machine interfaces are another modern tool for patients with SCI. These devices, which can be used to control various prosthetic devices such as the exoskeleton as well as directly stimulate paralyzed muscles, have already demonstrated improved outcomes in patients with SCI through several recent studies.[1,4,11,25] Clinical trials for the use of brain–machine interfaces and their computer algorithms are ever increasing as further research into advances in technology, feasibility and accessibility of these devices are still needed. In conclusion, due to increasing promising results, neuromodulation for SCI will remain a rapidly growing field in the upcoming years.

Stem cell-based therapies [Table 3]

Stem cell-based therapies and cellular scaffolds have yielded promising progress with respect to neuronal repair.[10] Phase I clinical trials have demonstrated that transplantation of olfactory ensheathing cells can be a safe, promising option to aid in neuronal repair in patients with SCI, but more Phase II clinical trials are still needed.[33,42] Several trials have also demonstrated the safe use of transplanted neuroprotective Schwann cells for nerve repair in patients with SCI, but clinical trials assessing the actual efficacy of this method are still ongoing.[39,40,46] In addition, several clinical trials have also demonstrated safety in using stem cells from various sources for SCI, but there are many more that are in the process of recruiting patients for transplantation of various stem cells.[10] Ethical and tumorigenesis concerns with stem cell-based therapies, however, will certainly need to be addressed as their research evolves.[10]

In vitro manipulation of the embryonic stem cells (ESCs)

Recently, *in vitro* manipulation of the ESCs differentiation to neuronal and glial lineages under controlled conditions has shown promising results after transplantation in animal models of acute SCI.[30] These included oligodendrocyte-induced remyelination, axonal elongation, and tract regeneration. However, legal and ethical drawbacks have limited the employment of ESC in the treatment of SCI patients. This might be largely attributed to the destruction of the blastocyst on isolation of the cells.[30] Moreover, development of teratomas after ESCs transplantation in numerous animal models has raised significant concerns about the functionality of these cells as a potential therapeutic avenue in SCI management.[30]

Various cell-based therapies

Despite extensive research exploring various cell-based therapies such as transplantation of oligodendrocyte precursors, induced pluripotent stem cells, bone marrow-derived (BM-MSCs), adipose-derived (AD-MSCs), and umbilical cord (U-MSCs),[30] there have been a lack of large Phase III clinical trials investigating the therapeutic efficacy of stem cell therapy.

Prosthetic devices [Table 3]

Robotic exoskeletons or powered exoskeletons have emerged as an advantageous rehabilitation tool for certain disabled individuals with SCI. The studies provided preliminary evidence on efficacy of exoskeletons on cardiovascular health, energy expenditure, body composition, gait parameters, level of physical activity, neuropathic pain level, and quality of life. They can be used to restore a certain level of physical activity years after injury.[9,19,35] Body weight supported treadmill training and locomotion training with driven gait orthosis are now considered essential component in the rehabilitation of SCI patients. According to the meta-analysis of powered exoskeletons, <5% of SCI patients have the ability to ambulate without any physical assistance.[35] However, following an exoskeleton training program, 67% of patients were able to walk with exoskeleton-assisted ambulation without physical assistance.[35] This meta-analysis included exoskeletons such as ReWalk™, Ekso™, and Indego™. In addition, even in complex training situations, there were no adverse events, falls, or fractures.[35] Furthermore, the neurologically controlled exoskeleton HAL™ has recently been Food and Drug Administration approved for use in the United States. This system has been proven to be beneficial in the rehabilitation of patients with chronic spinal cord injuries.[21] This technology is constantly being evolved, and it is important to strive for an interdisciplinary team approach to provide greater accessibility to this technology. This might help patients to preserve the physical capacity before restoration becomes necessary. The future of prosthetic devices is bright for SCI patients and will continue to be investigated.

CONCLUSION

We investigated the advancements in neuroprotective pharmacology, stem cell technologies, neuromodulation, and various external prosthetics for the treatment of SCI.

However, more clinical trials and research will continue to establish their efficacy.

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Conflicts of interest

There are no conflicts of interest.

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