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Introductory Chapter: Clinical Approaches for Treating Paraplegia

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1. Introduction to spinal cord injury: epidemiology and biopsychosocial impact

Spinal cord injury (SCI), either traumatic or non-traumatic in origin, is a devastating condition that produces long-term effects that persist throughout life and are associated with severe disability and handicap. Reported traumatic SCI annual incidence rates range from 12.1 to 57.8 cases per million. Motor vehicle collisions, falls, violence, and sports represent the leading causes. In comparison to traumatic SCI, there is little literature on non-traumatic SCI epidemiology. The etiologies of this type of SCI include vertebral spondylosis (spinal stenosis), tumorous compression, vascular ischemia, congenital diseases and inflammatory conditions [1, 2].

Depending on the level of SCI, patients experience paraplegia or tetraplegia. Paraplegia is defined as the impairment of sensory and/or motor function in lower extremities. Patients with incomplete paraplegia generally have a good prognosis in regaining locomotor ability (around 76% of patients) within a year. Complete paraplegic patients experience limited recovery of lower limb function if their neurological level of injury (NLI) is above T9. An NLI below T9 is associated with 38% chance of regaining some lower extremity function and only 4% chance of recovery to an incomplete status. On the other hand, tetraplegia is defined as partial or total loss of sensory and/or motor function in all four limbs and has a worse prognosis than paraplegia [3].

Spinal cord injury is a leading cause of disability, particularly in young adults. The highest incidences of SCI occur in persons between 20 and 40 years of age [4], being more common in males (82.8%) than females [5]. However, recent reports indicate an increase in SCI prevalence among older people and females. On the other hand, when classifying the types of disabilities caused by SCI, tetraplegia represents around 60%, while paraplegia represents approximately 40% [6]. Among all secondary complications following SCI, pressure ulcers, neurogenic bladder, urinary tract infections, pain, autonomic dysreflexia, osteoporosis, and muscle atrophy represent the majority. Currently, SCI complications management is challenging, and the outcomes are unsatisfactory [5, 7–10]. Moreover, having SCI may increase the risk of developing a health condition that is an indirect consequence of the impairment itself, such as increasing sedentary behaviors that contribute to the development of obesity and diabetes. Psychological factors (depression, anxiety, drug and substance dependency, post-traumatic stress disorders, etc.) may also complicate these chronic health conditions [11]. In addition, SCI leads to an abrupt change in the professional life and future plans of the patients [12] due to the irreversible restriction of functional movement, affecting not only quality of life

but also the ability to live independently. Furthermore, not only economic, educational and social conditions can affect SCI patients. Sexual relationships as well as marriage may be affected in patients who develop a severe disability following SCI [13–15]. These issues have been the most important motivation for the implementation of studies over the last decades that look for novel strategies for SCI. Despite all the progress in both preclinical and clinical studies, new therapies are still needed in order to improve both functional recovery and quality of life following SCI.

Lastly, it is important to mention that disparities between the developing and developed countries capacity to deliver emergency and acute care are evident immediately after a SCI. In many low-resource regions, these disparities can lead to further neurological compromise and poorer first year survival [16]. On the other hand, developed countries have significantly improved survival compared with developing countries. For example, tetraplegics have lower survival rates than paraplegics; however, in developed countries, this gap has narrowed considerably over the last 40 years. Developing countries still have the highest 1-year mortality rates [17].

2. The current understanding of the SCI pathophysiology and management

The immediate event arising from the primary injury consists in a mechanical disruption of tissue. Vascular changes, edema, hemorrhage, inflammation, neuronal, and myelin changes represent the acute phase (hours to 1–2 days). The edema may be vasogenic, defined as a breakdown of the blood–brain barrier (BBB) leading to the leakage of plasma fluid into the extracellular space. This may result in pressure-induced ischemia caused by reduced blood flow to the site of injury. Cytotoxic edema (intracellular swelling) also occur, particularly in astrocytes. Such edema is caused by pro-inflammatory factors, excitotoxicity, oxidative stress, lipid peroxidation, electrolyte imbalances, among others. In regard to neurons, the mode of death appears to be necrosis; however, neuronal apoptosis has been reported as well but only in experimental animals. Myelin breakdown occurs early following SCI and is characterized initially by swelling and ultimately by its fragmentation. During the intermediate phase (days to weeks), there will be several glial responses, necrotic debris will be eliminated, edema will resolve, and there will be revascularization of the tissue associated with a restoration of the BBB. Finally, the late phase of the SCI (weeks to months/years) is characterized by Wallerian degeneration, astroglial scar formation, development of cysts and syrinx, and schwannosis (aberrant intra- and extramedullary proliferation of Schwann cells with associated axons). The Wallerian degeneration is a process that consists in the anterograde disintegration of axons and their myelin sheaths that have been transected following injury. Eventually, an astroglial scar replaces the destroyed myelinated axons; however, this astroglial scar represents an impediment to regeneration [18].

SCI can be categorized also into primary and secondary phases. The primary SCI phase involves the initial mechanical injury (compression, shearing, laceration/transection, and acute stretch) in which the physical force is directly imparted to the spinal cord, disrupting axons, blood vessels, and neural-cell membranes. After the primary injury, a cascade of secondary injury events is initiated which expands the zone of neural tissue damage and exacerbate neurological deficits and outcomes. Secondary injury is a progressive condition characterized by pro-inflammatory cytokines, reactive oxygen species, DNA/protein/lipid oxidative damage, excitatory aminoacids such as glutamate, loss of ionic homeostasis, mitochondrial dysfunction and cell death [19–21]. As

mentioned before, mechanical compression of the spinal cord following injury can impair blood flow causing ischemia and an expanded zone of neural tissue injury. Therefore, early surgical decompression is used after SCI to improve vascular supply to the injured area as well as neurobehavioral deficits [22]. Methylprednisolone (MP), a potent synthetic glucocorticoid which upregulates anti-inflammatory cytokine release, has been widely used for SCI management. However, infections are a devastating side effect that may lead to severe pneumonia and sepsis, outweighing the potential neurological benefits [23]. Lastly, blood pressure augmentation is a current strategy in the SCI field. This strategy has emerged to neuroprotect damaged tissue by enhancing perfusion. In addition to these strategies, several neuroprotective therapies targeting key components of the secondary injury phase have emerged in the SCI field. Furthermore, due to the widely recognized difficult regeneration of the adult mammalian central nervous system (CNS), including the spinal cord, the primary and secondary phases of the SCI lead to a progressive loss of neurological function overtime. However, recent progress in the field of SCI research has demonstrated that the CNS has an inherent regenerative capacity. Consequently, while neuroprotective interventions might have a great benefit in the acute phase of injury, the vast majority of SCI patients are in the chronic stage. Neuroregenerative strategies have emerged to facilitate neuronal regrowth in the chronic stage of injury [24].

3. Neuroprotective strategies

Neuroprotective agents aim to reduce secondary insults to the injured spinal cord. Multiple approaches have been studied, and many others are currently under investigation [25]. In fact, the ability of pharmacological agents to limit secondary biochemical damage and cell death has been well established not only in SCI models but also in stroke and head injury [26].

3.1 Pharmacological therapies

3.1.1 Methylprednisolone

MP is one of the most commonly used pharmacological agents due to its anti-inflammatory effects [27]. However, the beneficial effects of MP administration in the setting of acute SCI are outweighed by the risk of significant complications associated to steroids [28].

3.1.2 Riluzole

Riluzole is a benzothiazole sodium channel blocker that protects against excitotoxic cell death by restricting the presynaptic release of glutamate [29]. It is currently approved by the US Food and Drug Administration (FDA) for the treatment of amyotrophic lateral sclerosis [30]. Clinical trials are currently ongoing for investigating riluzole in the setting of acute SCI [31].

3.1.3 Minocycline

Minocycline is a tetracycline-class antibiotic that has demonstrated neuroprotective properties in preclinical models of SCI [32]. A phase II clinical trial demonstrated that early minocycline administration may improve motor recovery in patients with acute SCI [33].

3.1.4 GM-1 ganglioside

GM-1 is a glycosphingolipid found in cell membranes with the ability to enhance neurite growth and nerve regeneration [34]. However, clinical trials in SCI patients found no statistically significant improvement with GM-1 [35].

3.1.5 Fibroblast growth factor-analogue

Fibroblast growth factor (FGF) is a protein found to be neuroprotective against excitotoxicity [36]. A FGF analogue called SUN 13837 was evaluated in a phase I/II clinical trial with results pending publication [25].

3.1.6 Granulocyte colony-stimulating factor

Granulocyte colony-stimulating factor (G-CSF) is found to promote cell survival and inhibit inflammatory cytokine expression [37]. Two recent nonrandomized phase I/IIa clinical trials showed great results in SCI outcomes [38, 39]; however, randomized clinical trials are required to establish the efficacy of G-CSF for SCI.

3.1.7 Hepatocyte growth factor

Hepatocyte growth factor (HGF) increases neuronal survival in SCI models [40]. A phase I/II randomized clinical trial is now underway with results pending publication [41].

3.2 Non-pharmacological therapies

3.2.1 Therapeutic hypothermia

Therapeutic hypothermia (TH; 32°-34° C) reduces the basal metabolic rate and energy demands of the CNS [42]. TH is effective in reducing the extent of CNS injury in neonatal hypoxic ischemic encephalopathy as well as after cardiac arrest [43, 44]. Small studies in SCI patients exposed to TH showed a trend towards neurological recovery [45, 46]. Therefore, these promising results led to a phase II/III clinical trial named “The Acute Rapid Cooling Therapy for Injuries of the Spinal Cord”, which has been planned to assess efficacy [25].

3.2.2 Cerebrospinal fluid drainage

Cerebrospinal fluid drainage objective is to prevent spinal cord hypoperfusion in the postinjury period by lowering the intrathecal pressure [47]. A phase IIb clinical trial evaluating mean arterial pressure elevation with cerebrospinal drainage in SCI has been completed with results pending publication.

4. Neuroregenerative strategies

Neuroregenerative strategies aim to restore neurological function [48]. Chronic SCI sets an excellent example because there are currently no interventions to restore body functions after injury. However, due to the inherent and limited ability of the CNS to regenerate, chronic SCI involves a great challenge for regenerative medicine [49].

4.1 Pharmacological therapies

4.1.1 Rho-ROCK inhibitor

Cethrin/VX-210 is a direct Rho inhibitor applied intraoperatively using a fibrin carrier to the epidural space [50]. A phase I/IIa clinical trial of patients with cervical or thoracic acute SCI found a significant improvement in long-term motor recovery for cervical patients [51].

4.1.2 Anti-NOGO antibody

Anti-NOGO is a recombinant human antibody against NOGO-A, one of the best-known inhibitors of neurite growth and plasticity in adult CNS. Intrathecal application is well tolerated in humans; however, efficacy trials are still needed to consider anti-NOGO antibodies for SCI patients [52].

4.2 Non-pharmacological therapies

4.2.1 Spinal cord stimulation

Spinal cord stimulation (SCS) involves the application of electrical stimulus to generate muscle contractions that allows for functional limb use. SCS has been successfully applied to improve ambulatory ability in patients with incomplete SCI [31]. Moreover, a small human study has shown that SCS combined with rehabilitation provides functional recovery of voluntary lower extremity movement in the chronic phase of SCI [53].

4.3 Cell therapies

Stem cell-based regenerative therapy has many roles in SCI recovery, including modulating the inflammatory response, providing trophic support, and regenerating axons into lost neural circuits [54]. Early research in this field used embryonic stem cells (ESCs), however, ethical concerns led to the introduction of other types of stem cell populations. In fact, adult tissue-derived stem cells, specifically bone marrow-derived cells, have emerged as a leading transplantable cell type for many CNS disorders [55]. Mesenchymal stem cells, olfactory ensheathing cells, Schwann cells, neural stem cells, and oligodendrocyte progenitor cells have been evaluated in phase I/II clinical trials of SCI and have shown promising results [31].

4.4 Biomaterials

The cascade of secondary events following acute injury to the spinal cord results in demyelination, axonal degeneration, and cavitation formation. Therefore, regeneration is hindered by the lack of substrate to support cell migration and axonal growth [56, 57]. The development of tissue engineering technology has opened up new avenues for treating SCI. The main strategy of tissue engineering is to inoculate living cells on extracellular matrix substitutes (biomaterial scaffolds) that can provide a physical structure for cell growth and differentiation, as well as to guide the growth of transplanted cells and promote axonal regeneration of residual neurons [58].

The Neuro-Spinal Scaffold (InVivo Therapeutics Corp, Cambridge, Massachusetts) is a proprietary bioresorbable polymer scaffold that promotes appositional healing, spares white matter, decreases post-traumatic cyst

formation, and improves functional recovery in animal models of SCI. A pilot study evaluating the safety of Neuro-Spinal Scaffold implantation has completed recruitment and is currently in the follow-up phase. Moreover, a case report of the first patient to undergo implantation of the Neuro-Spinal Scaffold as part of this trial has been published previously. The patient was a 25-year-old man with a T11–12 fracture-dislocation following a motocross accident. At 3 months after implantation, neurological function had improved, and no complications were seen during the follow-up [31, 59].

5. Exoskeleton

In the past decade, research in SCI rehabilitation has expanded to include robotic devices that initiate or augment movement. These robotic devices are used with two goals: to enhance recovery through functional movement and to act as a mobility aid beyond orthoses and wheelchairs [60]. In fact, exoskeleton training has been developed as a rehabilitation tool and is approved for the rehabilitation of individuals with SCI. Several studies have shown that robotic exoskeleton gait training has positive effects in terms of spasticity and pain reduction, as well as improved gait function without physical assistance [61–66].

Robotic devices may offer the greatest advantages for patients with incomplete SCI, turning measurable but functionally insignificant motor function into true mobility and independence. However, the global effects of restoring motion to the skeleton and joints in terms of cardiovascular benefits, prevention of contractures, osteoclastic activity, and psychological health have not yet been measured [67].

6. Conclusion

Significant advances over the past decades have decrease the morbidity and mortality following SCI. Unfortunately, these advances have not impacted on the majority of patients affected by SCI, decreasing long-term health and quality of life. Current treatment options for SCI are restricted to systemic delivery of MP, early surgical decompression, and rehabilitation, all of which result in minimal functional recovery. Neuroprotection as well as neuroregeneration are our current targets for both pharmacological and non-pharmacological therapies; however, further research is still needed to find the best option for SCI patients.

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