Research Article

Assessment and management of acute spinal cord injury: From point of injury to rehabilitation

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Context: Spinal cord injury (SCI) is a devastating condition that can lead to significant neurological impairment and reduced quality of life. Despite advancements in our understanding of the pathophysiology and secondary injury mechanisms involved in SCI, there are currently very few effective treatments for this condition. The field, however, is rapidly changing as new treatments are developed and key discoveries are made.

Methods: In this review, we outline the pathophysiology, management, and long-term rehabilitation of individuals with traumatic SCI. We also provide an in-depth overview of emerging therapies along the spectrum of the translational pipeline.

Evidence synthesis: The concept of "time is spine" refers to the concept which emphasizes the importance of early transfer to specialized centers, early decompressive surgery, and early delivery of other treatments (e.g. blood pressure augmentation, methylprednisolone) to affect long-term outcomes. Another important evolution in management has been the recognition and prevention of the chronic complications of SCI including respiratory compromise, bladder dysfunction, Charcot joints, and pressure sores through directed interventions along with early integration of physical rehabilitation and mobilization. There have also been significant advances in neuroprotective and neuroregenerative strategies for SCI, many of which are actively in clinical trial including riluzole, Cethrin, stem cell transplantation, and the use of functional electrical stimulation.

Conclusion: Pharmacologic treatments, cell-based therapies, and other technology-driven interventions will likely play a combinatorial role in the evolving management of SCI as the field continues to evolve.

Keywords: Spinal cord injury, Stem cell, Treatment, Regeneration, Neuroprotection, Rehabilitation, Surgical decompression, Pathophysiology

Introduction

Acute spinal cord injury (SCI) is a devastating condition that results in significant personal and societal loss. In the United States alone, over 1 million patients live with a SCI and more than 12 000 new cases occur every year. In the setting of military medicine, SCIs account for nearly 11% of service member deaths.[1] The fundamental tenets of SCI management are shared between civilian and military medicine, however, dangerous battlefield conditions and challenging extraction logistics can complicate the delivery of treatments. A key concept in either setting is 'Time is Spine' which highlights the importance of directed interventions within the acute injury period to improve long-term outcomes. While a cure for the neurologic sequelae of SCI has not yet been found, many novel approaches are currently under clinical investigation and have shown promise to substantially improve long-term functional recovery. This article will review the pathophysiology and clinical management of acute and chronic SCI followed by a discussion of emerging therapies along the translational pipeline. Throughout, we will highlight special considerations in the setting of military medicine.

Clinical Case

A 42-year-old man sustained a fracture-dislocation at T6–7 after a motor vehicle collision. An initial physical

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exam showed a complete T6 neurologic injury assessed as an American Spinal Injury Association scale (ASIA) grade 'A' (complete loss of motor and sensory function). He was immediately transported to a spine trauma center where he was medically stabilized and underwent surgical decompression with instrumented fusion from T3 to T10. Following hospital discharge, he remained in inpatient rehabilitation for 3 months. Urodynamic studies showed evidence of an overactive decompensated bladder for which he was started on anticholinergics along with intravesical botox and ongoing intermittent catheterization. During rehabilitation he was treated with gabapentin for ongoing neuropathic pain; however, six months post-injury he developed symptoms of bilateral ascending numbness and pain extending well above T7. An MRI revealed a large post-traumatic syrinx with extension up to the cervicomedullary junction (Fig. 1) for which a syringopleural shunt was inserted. The patient went on to require two subsequent revisions to his shunt which was ultimately replaced with a syringosubarachnoid shunt. He recovered well post-operatively and serial MRI imaging showed no increase in the size of his syrinx. This case illustrates some of the many acute and chronic complications after SCI and the interdisciplinary management techniques required at various stages in the post-injury period. These and other options will be discussed throughout this review.

Pathophysiology

Primary Injury

SCI is divided into primary and secondary injury phases (Fig. 2). The primary injury results from direct physical trauma to the spinal cord due to various mechanisms

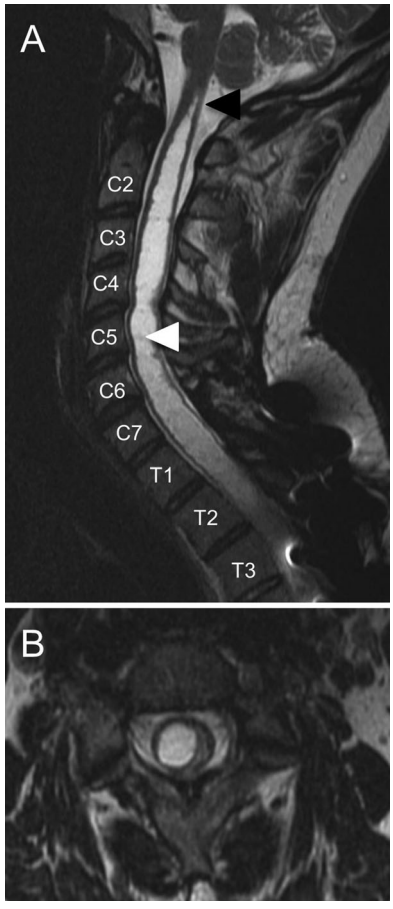

Figure 1. Post-traumatic syringomyelia following T6–7 thoracic spinal cord injury. (A) Sagittal T2-weighted magnetic resonance image demonstrating evidence of an extensive syrinx (white arrowhead) within the cervical and thoracic cord extending as high as the cervico-medullary junction (black arrowhead). (B) Corresponding axial cut at the C3 level highlighting the ventral-dorsal and medial-lateral size of the syrinx

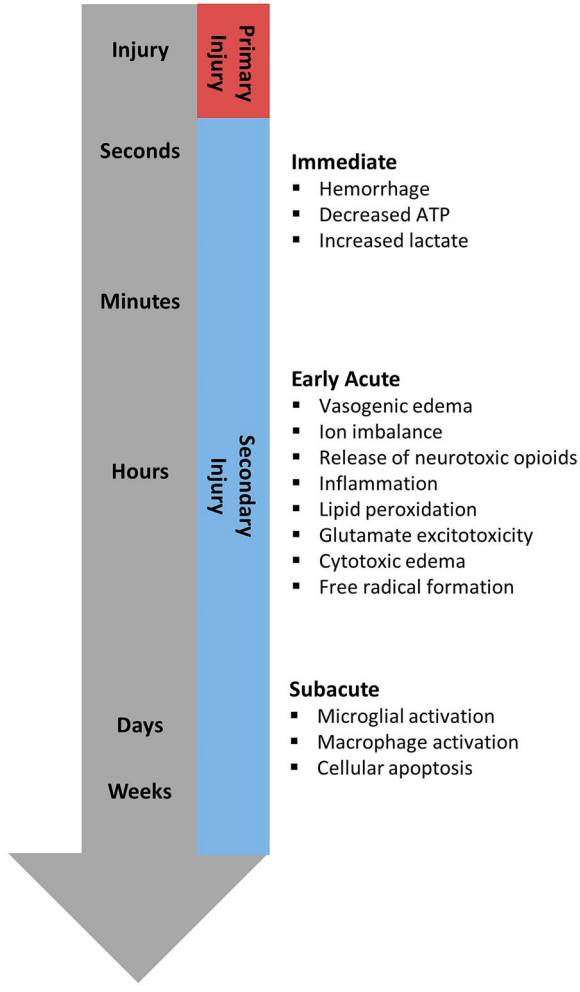

Figure 2. Primary and secondary injuries of spinal cord injury. An initial primary physical insult initiates a rapid cascade of secondary biochemical injuries extending over the immediate, early acute and subacute phases. Figure adapted from Wilson *et al.*[33].

classified as either penetrating or blunt injuries. Penetrating injuries include gunshot wounds, fragmentation injury from a blast mechanism, or low-velocity injuries (e.g. knife wounds). Blunt injuries are most often caused by falls, crush injuries, collisions, or tertiary injuries from a blast. While these mechanisms of injury can be seen in both civilian and military SCI, the latter are often associated with more complex injury patterns and concomitant organ damage. Moreover, in the military setting, SCIs sustained in battle may have a worse prognosis than non-battle SCI. A retrospective study of American service members conducted between 2003 and 2008 found that SCIs sustained in battle were more often caused by a blast mechanism, involved multiple spinal levels, and had a trend towards increased injury severity scores and longer hospital stay compared to non-battle SCI.[2] Similarly, Blair *et al.* reported increased rates of surgical intervention and a trend toward poorer neurologic recovery after SCIs sustained in battle relative to non-battle SCI, which may reflect more extensive injuries.[3] In addition, lumbosacral dissociations, low lumbar burst fractures and post-amputation scoliosis, while rare in the setting of civilian medicine, are more frequently seen in combat injuries.[4] While different injury mechanisms result in different degrees of secondary injury, early neurologic sequelae are most often the result of direct mechanical injury to the cells and the sensitive microvasculature of the cord.

Secondary Injury

A cascade of physiologic, extracellular biochemical, and intracellular insults comprises the secondary injury phase.[5] Local disruption of the vasculature results in acute hemorrhage and ongoing spinal cord ischemia. Disruption of neurons and a failure to reuptake by glial cells leads to excess extracellular glutamate concentration promoting excitotoxic cell death. Disruption of the critical blood-spinal cord barrier also results in an influx of cytokines, vasoactive peptides, and peripheral inflammatory cells which cyclically contribute to cord edema and the pro-inflammatory state.[6] Over hours to days, cells continue to undergo cell death releasing potent pro-apoptotic signals and recruiting regional microglia. Together, these events introduce numerous cytotoxic by-products (e.g. ATP, potassium ions, DNA, reactive oxygen species, etc.) into the local microenvironment which further propagates cell death.[7]

Barriers to Regeneration

During the acute-subacute period parenchymal volume is lost and microcystic cavitations begin to form. These fluid-filled spaces gradually coalesce into larger bodies in the subacute-chronic phases creating a physical barrier to cell migration and endogenous regenerative attempts. Similarly, astrocytes in the region surrounding the injury epicenter migrate, activate, and proliferate to contain damage in the acute injury period. However, large numbers of astrocytes with tightly interwoven processes continue to persist in the perilesional region for years after injury making regeneration beyond this glial scar challenging. The inhibitory effects are further compounded by the local deposition of chondroitin sulfate proteoglycans (CSPGs) which have been suggested to act via the Rho-ROCK (rho-associated protein kinase) pathway to inhibit neurite outgrowth. Together, these and other mechanisms severely restrict endogenous regeneration and anatomic plasticity after traumatic SCI.

Spinal Shock

In the immediate period following severe SCI, spinal shock has classically been defined as complete loss of motor and sensory function below the level of injury, loss of deep tendon reflexes, and absent sphincter reflex. The absence of the sphincter reflex is indicative of spinal shock making attempts at prognostication inaccurate. Return of the bulbocavernosus reflex has traditionally indicated the end of spinal shock and continued complete motor and sensory loss would indicate a complete SCI at that time. Recently, a four-phase model of spinal shock has emerged that provides further insight into the ongoing spectrum of clinical changes and physiological mechanisms underlying this condition.[8] An initial phase of absent or diminished reflexes occurs during the first 24 hours after injury where deep tendon and cutaneous reflexes below the injury level are generally both absent, however, the latter may begin to recover during this stage. This period of areflexia is a result of lost supraspinal excitation from damaged descending tracts along with increased spinal inhibition. The second phase occurs between 1 to 3 days post-injury, and is characterized by an initial return of cutaneous reflexes such as the bulbocavernosus reflex. These changes are largely attributed to denervation sensitivity along with upregulation of excitatory NMDA receptors. Following this and lasting up to one month, a period of early hyperreflexia ensues with the return of deep tendon reflexes as a result of axon-mediated synapse growth. The last phase of spinal shock lasts between 1 to 12 months after injury and is characterized by spasticity and hyperreflexia of cutaneous and deep tendon reflexes. During this phase, synapse growth continues via soma-mediated

mechanisms. It is critical to remain aware of spinal shock and assess the sphincter reflex in patients presenting with a complete injury as early interventions may still produce long-term functional benefits for patients with incomplete injuries masked by spinal shock. Moreover, enhanced understanding of the evolving phases of spinal shock may help inform future interventions targeting spinal cord plasticity after injury.

Cardiorespiratory Compromise

Acute SCI can lead to both cardiovascular and respiratory compromise. Damage to the sympathetic tracts in the intermediolateral column from high spinal (cervical and upper thoracic) injuries can result in neurogenic shock characterized by bradycardia and hypotension from decreased vascular tone due to unopposed parasympathetic vagal outflow. This further exacerbates ischemia to the sensitive injured cord by producing global hypoperfusion and is compounded in the setting of blood loss (i.e. polytrauma patients). Cervical and thoracic injuries can also result in hypoxemia and hypercarbia due to compromised innervation of the diaphragm, intercostal muscles, and/or abdominal muscles. This is particularly true in patient with decreased reserve due to age or concomitant thoracoabdominal injuries (e.g. blast fragments, gun shot wounds, fractures, contusions, etc.) Impairment in cough and secretion clearance may also predispose patients with SCI to an increased risk of pneumonia and respiratory infections in both the acute and chronic periods.

Acute Management

The concept of 'time is spine' is a key tenet in the acute management of SCI and should guide interventions. Treatment begins in the field and a streamlined approach to management in the acute phase is essential for efficient delivery of care and improved outcomes (Summarized in Fig. 3).[9]

Point of Injury and Stabilization

As with civilian medicine, management of a patient with SCI on the battlefield should aim to follow standard Advanced Traumatic Life Support (ATLS) guidelines. Evidence or suspicion of a cervical spine injury necessitates immediate immobilization at the scene with either a rigid cervical collar or supportive blocks and straps on a backboard. Similarly, thoracic and lumbosacral fractures should be immobilized on a backboard using the logroll maneuver for transfers. For patients with a penetrating injury, immobilization should be attempted as long as it does not significantly interfere with resuscitation efforts.[10] Any evidence of airway compromise requires establishment of a definitive airway and careful attention must be paid to ongoing spine immobilization during intubation. Circulatory support may also be necessary as service members in the field may concomitantly suffer from a combination of exhaustion/dehydration, blood loss, and/or neurogenic shock.[10] Even brief periods of hypotension (systolic blood pressure [SBP] <90mmHg) have been shown to have detrimental effects on long-term outcomes after SCI.[11] IV fluids are often the first means to maintain blood pressure though in cases of neurogenic shock vasopressors may also be required. For injuries in the upper thoracic and cervical spine with clinical features of neurogenic shock, infusions of norepinephrine or dopamine to reduce peripheral vasodilation may be appropriate in combination with crystalloid volume resuscitation.[12]

Transfer

Following an acute spinal cord injury, patients should be rapidly resuscitated or transferred to a local hospital for resuscitation. When this is not available due to access or

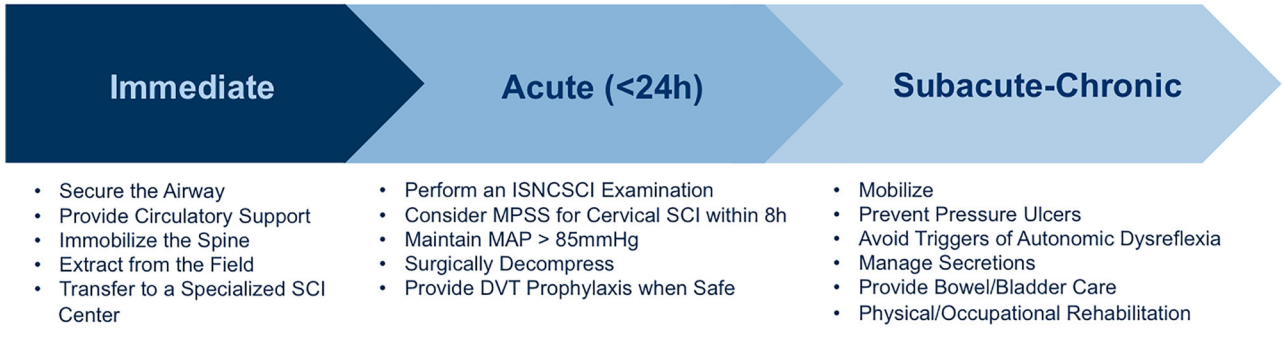

Figure 3. Overarching management goals at each stage following spinal cord injury. Each target must be considered within the broader care of an individual, coexisting polytrauma, and local resources. Time windows are a suggestion, however, the 'Time is Spine' concept should be emphasized as earlier initiation of treatments/prophylactic measures, when safe, may have beneficial effects

medical resource restrictions in the field, it may be necessary to transfer patients first to a safer location such as a Casualty Collection Point or Field Treatment Site prior to immobilization and resuscitation to avoid further casualties.[13] Once stabilized, early transfer (< 24 hours) to a specialized SCI center has been associated with improved long-term outcomes.[14] In civilian medicine, Burney *et al.* found no difference in the probability of neurologic improvement between air and ground transport and there was no associated worsening of injury during transfer provided that proper spine immobilization was maintained.[15] In military medicine, the safe extraction and transportation of patients will be dictated by local geography, regional medical resources, and the severity of co-existing injuries.

Diagnostic Assessments

Once stabilized, clinical examination using the ASIA International Standards for Neurological Classification of SCI (ISNCSCI) should be done to determine the level of injury and extent of functional impairment.[16] This careful baseline assessment is important for treatment selection, monitoring of recovery, clinical trial eligibility, and prognostication. Early imaging is important to determine the extent of structural spinal column injury, assess for missed associated injuries, and ultimately guide further treatment. CT is the modality of choice in the initial work up of acute SCI.[16] MRI may also help assess for ligamentous injuries, large disc herniations, and epidural hematomas, however, availability is most often the limiting factor. MRI is not mandatory in the initial workup of patients except in instances of unexplained neurological deficits where it is critical to rule out ongoing cord compression or missed ligamentous injuries.[17] If available, however, MRI is recommended as it has prognostic value and is integrated into several important clinical prediction scores.[18]

Early Treatment

Surgical Decompression

Early surgical decompression has been shown to improve outcomes after acute SCI. The Surgical Timing in Acute Spinal Cord Injury Study (STASCIS),[19] found that among 313 patients with cervical SCI, early decompressive surgery (performed within 24 h of injury) increased the odds of a 2-grade AIS improvement by 2.8 times compared to patients who received surgery more than 24 hours after injury. A multicenter Canadian cohort study of 84 patients further supported these findings reporting a greater proportion of patients receiving early surgery with at least a two-grade AIS improvement.[20] Early surgery has also been associated with decreased hospital length of stay (LOS) for patients with ASIA grades A and B injuries.[21] A multicenter prospective, observational European study (SCI-POEM) is currently underway.[22] While the major criticism of these studies has been their cohort design which was selected for practical and ethical reasons, this literature represents the highest-quality large-scale data available on surgical decompression for SCI and offers evidence to support a commonly practiced intervention in a field with otherwise limited treatment options for patients.[23] Stemming from these positive findings, forthcoming AOSpine 2017 guidelines from an international expert panel suggest early decompressive surgery when feasible.[24,25]

Methylprednisolone

Systemic steroid therapy upregulates anti-inflammatory cytokine release and promotes neural cell survival in animal models of injury. Multiple clinical studies have investigated the role of methylprednisolone (MPSS) in the treatment of SCI, the best available evidence for which is found in the National Acute Spinal Cord Injury Study (NASCIS) series.[26–28] While the primary analysis found no statistically significant improvement in outcomes, secondary subgroup analyses planned a priori revealed significant motor recovery in patients receiving high-dose MPSS within 8 hours of injury.[27] There was an increased infection risk (e.g. severe pneumonia and sepsis) with a 48-hour regimen of high-dose MPSS, however, substantially lower complication rates were observed with 24 hours of high-dose MPSS (30 mg/kg bolus + 5.4 mg/kg/hr x 23 hours) while still providing long-term neurological benefits.[28] A 2012 Cochrane review summarizing 6 large-scale studies on MPSS in acute SCI found an overall 4-point increase in ASIA motor score when MPSS was administered within 8 hours of injury.[29] While the 2013 AANS/CNS guidelines for the management of acute SCI did not recommend MPSS in the treatment of SCI,[30] forthcoming AOSpine 2017 guidelines from an international expert panel suggest administration of IV MPSS for 24 hours be considered within 8 hours of cervical injury in patients without significant medical contraindication.[31,32]

Blood Pressure Augmentation

Cord edema and damage to the microvasculature result in ongoing perilesional ischemia for days after injury. Systemic blood pressure augmentation looks to reduce this risk by increasing perfusion to at-risk neural tissue. The most recent AANS/CNS guidelines

recommend mean arterial pressure (MAP) be maintained for 7 days post-injury at ≥ 85–90 mmHg as this has been shown to improve long-term ASIA Impairment Scale (AIS) outcomes.[33] This often necessitates continuous blood pressure monitoring (most often by arterial line) in an ICU setting, normovolemia to slight hypervolemia, and central access to administer vasopressors.[34] To investigate whether these challenging requirements can be reduced, a non-inferiority trial comparing clinical outcomes with MAP ≥ 65mmHg vs MAP ≥ 85mmHg is current underway (Mean Arterial blood Pressure Treatment for Acute Spinal Cord Injury [MAPS]; NCT02232165) with results expected in 2017.[22]

Complications and Management of Chronic SCI

Cardiovascular Complications

Autonomic Dysreflexia

Autonomic dysreflexia (AD) most commonly occurs in patients with an injury level at or above T6 and is characterized by sudden, acute hypertension which can be life-threatening. The pathophysiology underlying a dysreflexic episode involves sympathetic discharge triggered by a stimulus below the level of injury causing peripheral vasoconstriction with a strong parasympathetic response above the level of injury leading to sweating, sinus congestion, and headaches. Common triggers include bladder or bowel distension and thus appropriate voiding and bowel regimens are a central tenet in preventing AD events. Treatment of AD involves conservative measures such as upright positioning and removing any triggers or possible noxious stimuli. If SBP remains high despite conservative measures, rapid acting antihypertensive agent such as immediate-release nifedipine, captropril or nitroglycerine should be initiated.[35]

Orthostatic Hypotension

Loss of sympathetic regulation and reflex vasoconstriction after SCI predisposes patients to orthostatic hypotension and peripheral upregulation of nitric oxide may also further exacerbate hypotensive episodes.[36] Non-pharmocological treatment of orthostatic hypotension includes regulation of fluid and salt intake, elastic stockings or abdominal binders. Pharmocological agents aimed at increasing peripheral vascular tone (e.g. midodrine) or volume expansion (e.g. Fludrocortisone, salt tablets) may also be considered.[35] Episodes tend to occur more frequently initially and gradually improve over weeks to months though some individuals are chronically affected.[37]

Respiratory Complications

Respiratory complications are a major cause of morbidity and mortality in patients with acute SCI. High cervical injuries can impair phrenic innervation of the diaphragm leading to ventilator dependence. Injuries below C5 can still produce substantial weakness of muscles of respiration (e.g. intercostals and abdominal muscles) compromising respiratory function. Aggressive management of secretions is of utmost importance in caring for a patient with SCI to prevent mucous plugs, atelectasis and pneumonia. Percussion, vibration, or assisted suctioning may be used as means to help mobilize secretions.[38] Respiratory muscle training may also improve respiratory function in patients with SCI, however, there is little evidence to support its widespread use.[39] There is a high risk of deep vein thrombosis (DVT) and subsequent pulmonary embolus in patients with SCI due to prolonged immobility, impaired venous return and coagulopathy. Thus, DVT prophylaxis in the form of unfractionated heparin, low-molecular weight heparin (LMWH), novel oral anti-coagulants (NOACs) or pneumatic compression devices should be instituted in all patients with acute and subacute SCI and severe motor deficits.[40]

Urologic Complications

Individuals with SCI often suffer from neurogenic bladder dysfunction, which can lead to a multitude of complications. As catheter dependency is common, affected people are prone to the development of recurrent urinary tract infections (UTIs). Several studies have examined the role of prophylactic antibiotics in patients with SCI and while results vary between studies, the overall consensus does not support its routine use as it does not reduce clinical UTIs and increases the chances of developing resistant bacteria. Other catheter-related complications include urethritis, prostatitis and epididymitis.[41] Appropriate bladder care must be carefully adhered to in patients with SCI. Clean intermittent catheterization is preferred over an indwelling Foley as it reduces the risk of infections. As an adjunct, anticholinergics may be used for neurogenic detrusor muscle over-activity.

Musculoskeletal Complications

Charcot Joints

Charcot joints or neuropathic arthropathy is characterized by progressive destruction of a joint which has reduced sensation due to unchecked repeated microtraumas and localized hyperemia secondary to changes in autonomic innervation. When localized to the spinal joints, charcot spinal arthropathy (CSA), although a rare entity, can progress rapidly and carry

significant morbidity. CSA commonly presents clinically with evidence of spinal deformity, sitting imbalance and back pain and is radiographically suspected by evidence of discovertebral destruction, vacuum discs and osseous joint debris.[42] Conservative treatment includes a multimodal approach with physiotherapy, bracing for stabilization and pain management. Surgical treatment may be required in severe cases to correct the deformity and provide stabilization.[43]

Pressure Sores

Pressure sores are a common complication after SCI that can lead to significant morbidity/mortality, prolonged hospitalization and even act as a trigger for autonomic dysreflexia. The most common sites are on the buttocks (31%), over the greater trochanter (26%) and on the sacrum (18%).[44] Prevention strategies must be implemented immediately after injury and careful adherence must be instituted for the long term.[45] Daily skin inspections and utilization of pressure redistribution support surfaces are essential in any pressure ulcer prevention strategy. It is recommended that individuals be repositioned every 2 hours in the acute phases of injury. Prevention of moisture accumulation and promotion of good nutrition are also important. This can be particularly challenging in remote or highly-humid regions but is very important to reduce the long-term morbidity of these lesions. Treatment of pressure ulcers after they develop follows principles similar to prevention along with careful wound cleaning, debridement and possible surgery for deep non-healing ulcers.

Physical Therapy

Traditional rehabilitation strategies following SCI include range of motion and strengthening exercises, bed mobility and transfer exercises along with locomotor training. Aggressive and early mobilization is a primary tenet of rehabilitation after SCI. Body-weight supported treadmill training (BWSTT) provides task-specific sensory input and is a promising strategy to enhance locomotor function after SCI. A systematic review by Lam *et al.* found level 3 evidence that BWSTT improves locomotion after chronic SCI.[46] Braces and orthoses may also be used for support in SCI rehabilitation strategies.

Emerging Therapies In Clinical Trial

Neuroprotection

Riluzole

Riluzole, a sodium channel antagonist, is the only agent approved for use in patients with amyotrophic lateral sclerosis and has shown promising results in the treatment of SCI in laboratory and clinical studies.[47] Treatment with riluzole after SCI in rodents decreases cell death, reduces cavitation size and enhances functional recovery.[48,49] Riluzole-mediated neuroprotection is thought to act by inhibiting pre-synaptic glutamate release and modulating neuronal voltage gated sodium channels. A phase I trial examining the safety of riluzole in patients with SCI found significant motor improvement in patients with cervical injuries treated with riluzole compared to controls. The Riluzole in Spinal Cord Injury Study (RISCIS; NCT01597518) is a phase II/III international clinical trial examining the efficacy of riluzole in patients with acute C4–8 ASIA grade A/B/C injuries currently underway with results expected by 2020.[7,50]

Minocycline

Minocycline, a tetracycline-class antibiotic, has shown neuroprotective effects in animal models of acute SCI. Specifically, treatment with minocycline has been found to modulate cytokine expression, reduce cell death, decrease lesion size and improve functional recovery following SCI in rodents.[51] These promising results led to a phase II clinical trial on 25 patients with acute, incomplete cervical SCI which demonstrated an additional 14-point ASIA motor score recovery with minocycline treatment.[52] A larger phase III study (Minocycline in Acute Spinal Cord Injury [MASC]; NCT01828203) is now investigating 7 days of intravenous minocycline compared with placebo.[22]

Systemic Hypothermia

Reducing core temperature to 32–34°C is known to reduce neuroglial cell death and inflammatory cell activation/infiltration in the central nervous system (CNS) with clinical success in cardiac arrest and hypoxic-ischemic encephalopathy.[53–55] Systemic hypothermia following SCI in rodents has shown benefit as well by reducing lesion size and enhancing motor recovery.[56] A pilot study in 14 patients with AIS-A SCI found a trend for improved neurologic recovery at 1 year post-injury in the group who underwent cooling.[57] A phase II study called "Acute Rapid Cooling Therapy for Injuries of the Spinal Cord" (ARCTIC) has been planned to definitively address the efficacy of this intervention for SCI.

Granulocyte Colony-Stimulating Factor (G-CSF)

Granulocyte colony-stimulating factor (G-CSF) has been shown to decrease lesion size,[58] attenuate cell death and promote functional recovery[59] after SCI in rodents. The mechanism of action is thought to be due to inhibition of neuronal apoptosis,[59] promotion of

angiogenesis,[60] promotion of neurotrophic factor expression and down regulation of pro-inflammatory factors.[61] Multiple phase I/II clinical trials showed improvements in AISA motor scores with delivery of G-CSF after SCI, however, well-designed randomized trials will need to be conducted to confirm efficacy.[62,63]

AC105

Magnesium is an NMDA antagonist and known anti-inflammatory molecule. It has shown important neuroprotective effects in various models of neuronal cell injury and there is robust pre-clinical evidence demonstrating the neuroprotective effects of magnesium in experimental models of SCI.[64,65] Clinically, delivery of magnesium in combination with polyethylene glycol (PEG) in a formulation called AC-105 has allowed high cerebrospinal fluid levels to be achieved while avoiding systemic toxicity. A phase II study of AC-105 in patients with acute traumatic SCI was initiated in 2012 by Acorda Therapeutics Inc. (Chelsea, MA, USA), however, the trial was discontinued.[22]

Neuroregeneration

Stem Cells

Stem cell therapies have shown significant potential for regeneration after SCI, particularly with recent advances in developmental biology and cell culture techniques.[66] Various types of multipotent and differentiation cells (e.g. neural precursor cells, Schwann cells, neurons, etc.) have been examined in preclinical and clinical trials of SCI and are thought to act through multiple mechanisms including cell replacement, neurotrophic factor release and immunomodulation.[67]

Two main sources of parent cell exist in current cell therapies. Embryonic stem cells are a pluripotent cell type found in the inner cell mass of blastocytes that can be induced to differentiate into any other cell type *in vitro* prior to transplantation. Induced pluripotent stem cells (IPSCs) are adult cells that have been reprogrammed to an ESC (embryonic stem cell)-like pluripotent state providing them with the same capacity to differentiation into any somatic cell type. IPSCs avoid the ethical concerns surrounding the use of aborted fetal tissue to harvest ESCs and provide a unique opportunity to potentially be autologously-derived.

Transplantation of neural stem cells (NSCs), derived from both ESCs and iPSCs, into rodents with SCI has been shown to provide histological and functional improvements across multiple preclinical studies.[68,69] A well-known pair of Phase II trials by Stem Cells Inc. examining the use of human CNS stem cells for patients with cervical or thoracic injuries was terminated early in 2016. While publication of the results is pending, interim data suggested no significant increase in adverse events with cell treatment and the conduct of the study confirmed the feasibility of cell transplant as a treatment strategy for SCI. Further optimization of cells and their recipient environment will likely be required to achieve greater recovery.

A similarly strategy has been the differentiation and transplant of oligodendrocyte precursor cells (OPCs) which are multipotent CNS cells with a preference for becoming myelinating oligodendrocytes. After promising data from preclinical studies, a Phase I/II trial (NCT02302157) by Asterias Biotherapeutics Inc. (Fremont, CA, USA) is underway assessing their AST-OPC1 line for changes in long-term sensorimotor scores. Results are expected by 2018.[22]

Mesenchymal stem cells (MSCs) are a multipotent cell type that have been shown to enhance regeneration and locomotor function after both acute[70] and chronic[71] SCI in rodents. The mechanism of action is thought to be mediated primarily through local and systemic immunomodulation and trophic factor support. A phase II/III trial of autologous MSCs administered intraparenchymally and intrathecially into patients with AIS grade B injuries is currently underway by Pharmicell Co. (NCT01676441) (Seoul, Republic of Korea). The study is expected to conclude in 2020.[22]

Schwann cells (SCs) provide myelination of axons in the peripheral nervous system where they provide a robust pro-regenerative conduit for nerve regeneration. They have also been used for transplantation after SCI in multiple animal models where they were found to promote axon remyelination, reduce cavitation, and improve recovery.[72] Important ongoing clinical trials investigating the use of autologous Schwann cells harvested from the sural nerve of SCI patients in the subacute and chronic period after injury are currently underway (Miami Project; ClinicalTrials.gov Identifier: NCT01739023, ClinicalTrials.gov Identifier: NCT02354625).[22]

Polymer Scaffolds and Hydrogels

Biodegradable polymer scaffolds and hydrogels can provide structural support, guide cell migration and neurite outgrowth, and facilitate the delivery of therapeutic agents in the setting of SCI. Multiple pre-clinical laboratory studies have shown promising results using synthetic peptides (e.g. QL6[73]), human protein matrices (e.g. fibrin-thrombin complexes[74]), polymers (e.g. Neuro-Spinal Scaffold), and other naturally-occurring materials (e.g. chitin and methylcellulose[75]). A study by InVivo Therapeutics (Cambridge, MA, USA)

investigating the efficacy of a Neuro-Spinal Scaffold in patients with AIS grade A thoracic SCI is currently ongoing (NCT02138110).[22]

Cethrin

The Rho-ROCK (Rho-associated protein kinase) pathway has long been implicated in the inhibition of axonal growth after injury. Antagonism of this pathway has shown promise in pre-clinical studies of SCI by enhancing neurite outgrowth and behavioural motor outcomes.[76] In a mixed cervical/thoracic phase I/IIa clinical trial, treatment with Cethrin, a potent Rho inhibitor, led to a 27.3±13.3 point improvement in ASIA motor score at 12 months for individuals with a cervical injury. Furthermore, 66% of cervical SCI patients converted from ASIA A to ASIA C or D.[77] Given these results, a phase II/III trial is now underway to assess the efficacy of Cethrin for acute cervical SCI.[22]

Neurorehabilitation

Conventional physical rehabilitation to strengthen muscles, improve range of motion and induce cardiorespiratory loading is increasingly being augmented by the technologies discussed below.

Functional Electrical Stimulation

SCI leads to a loss of central control of the neuromuscular system resulting in motor paralysis. Functional electrical stimulation (FES) relies on the principal of providing electrical currents to the nerve and muscles that provide key movements in order to enhance their activity for the short and long term. FES can be used as a supplement during rehabilitation training to augment movements thereby increasing sensory feedback, muscle use, and providing a degree of cardiorespiratory conditioning.[78] Stimulation of trunk muscles using FES has also been shown to enhance trunk posture and stability.[79] A phase II trial examining upper limb FES in patients with cervical SCI is currently underway to assess improvements in long-term functional independence and motor skills (ClinicalTrials.gov Identifier: NCT01292811). Other trials assessing the cardio-metabolic benefits of FES and lower limb function are also ongoing.[22]

Epidural Spinal Cord Stimulation

Epidural spinal cord stimulation supplies rhythmic electrical current to the cord via an epidural electric with the aim of activating central circuits that mediate locomotion, pain and/or cardiorespiratory systems. Epidural stimulation has also shown its ability to modulate pharmacologically refractory neuropathic pain,[80] enhance locomotion in select patients,[81] and improve urinary bladder control[82] after SCI.

Exoskeleton

Exoskeletons are external motorized orthoses that can be used to enable locomotion in paralyzed or paretic individuals. Control may be via a hand controller, mouth controller, and/or detection of micro movements with development ongoing towards direct CNS-machine interface based control. A meta-analysis including 14 studies examining the use of exoskeletons for SCI demonstrated improved ambulation with the use of these device.[83] Multiple additional clinical trials are ongoing investigating exoskeletal-assisted walking devices in patients with SCI including Ekso™ (Richmond, CA, USA; ClinicalTrials.gov Identifier: NCT01701388), Indego® (Parker Hannifin Corp., Cleveland, OH, USA; ClinicalTrials.gov Identifier: NCT02202538) and ReWalk™ (ReWalk Robotics, Inc., Marlborough, MA, USA; ClinicalTrials.gov Identifier: NCT02658656).

Conclusion

SCI is a complex condition associated with substantial disability, reduction in quality of life, and costs. A large emphasis has now been placed on the concept of 'time is spine' where early, streamlined interventions in the immediate post-injury phase are essential for improving long-term outcomes. While some require advanced levels of expert care (e.g. surgical decompression), others can be feasibly employed at field or regional hospital (e.g. methylprednisolone, modest blood pressure augmentation). Although there are currently very few widely-accepted neuroprotective strategies for SCI and no neuroregenerative strategies, multiple promising therapies are actively being explored along the basic science and translational research pipeline. Pharmacologic treatments, cell-based therapies, and other technology-driven interventions will likely play a combinatorial role in the evolving management of SCI for both civilians and military service members.

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