

Student's Corner

Stem cell therapy in spinal cord injury: Hollow promise or promising science?

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Abstract

Spinal cord injury (SCI) remains one of the most physically, psychologically and socially debilitating conditions worldwide. While rehabilitation measures may help limit disability to some extent, there is no effective primary treatment yet available. The efficacy of stem cells as a primary therapeutic option in spinal cord injury is currently an area under much scrutiny and debate. Several laboratory and some primary clinical studies into the use of bone marrow mesenchymal stem cells or embryonic stem cell-derived oligodentocyte precursor cells have shown some promising results in terms of remyelination and regeneration of damaged spinal nerve tracts. More recently, laboratory and early clinical experiments into the use of Olfactory Ensheathing Cells, a type of glial cell derived from olfactory bulb and mucosa have provided some phenomenal preliminary evidence as to their neuroregenerative and neural bridging capacity. This report compares and evaluates some current research into selected forms of embryonic and mesenchymal stem cell therapy as well as olfactory ensheathing cell therapy in SCI, and also highlights some legal and ethical issues surrounding their use. While early results shows promise, more rigorous large scale clinical trials are needed to shed light on the safety, efficacy and long term viability of stem cell and cellular transplant techniques in SCI.

Key words: Spinal cord injury (SCI), spinal regeneration, stem cell therapy

INTRODUCTION

In the late nineteenth century, the eminent Spanish histologist and neuroscientist Ramón y Cajal established the central dogma of neurology: "In the adult centers, the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated."^[1] The belief that unlike other body systems, the adult central nervous system (CNS) is "fixed and immutable," and unable to regenerate neurons has prevailed for several years. This was based mainly on

clinical observations of nonrecovery in the patients affected by neurological pathologies, and on the theory that memory relies on the existence of stable, unchangeable neuronal circuits formed during learning.^[1] Today, this belief has been refuted by a number of studies showing that limited areas of the mature CNS are, in fact, capable of some regeneration.^[2-4] While the dogma may have been discredited, the reality remains that very little growth and repair follows CNS injury, and prognosis still remains bleak.^[5] In recent years, there has been a phenomenal

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interest in the generation of stem cells for the management of neurological disorders. CNS injury is believed to lead to a characteristic cascade of immune-mediated cytotoxic and apoptotic destruction, and a profound loss of neural cells. Stem cells, by definition, are capable of prolonged self-renewal, and usually retain the ability to differentiate into multiple cell types.^[6] The utilization of this multipotency may present a valuable solution for CNS disorders, by providing replacement neurons and glial cells to restore function.

The current feasibility, safety, and scope of stem cell therapy has been studied and reviewed for a variety of neurodegenerative and neurological diseases such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord injury (SCI), ischemic stroke, and multiple sclerosis.^[2] Despite some successful animal and cellular studies into stem cell transplant, their bedside translation still remains a distant prospect with regard to most neurological disorders. This is primarily due to difficulties in controlling the purity of the graft and its successful integration and interaction with the host environment, resulting in concerns regarding long-term complications and ethical issues.^[2,7]

According to "International perspectives on spinal cord injury," a 2013 report compiled by the World Health Organization (WHO), 250,000-500,000 people suffer from traumatic SCI each year. Nontraumatic causes of SCI also exist, which include musculoskeletal, congenital and immune mediated diseases, and infections.^[8] However, the incidence of these is less frequent.^[8] The socioeconomic implications of SCI disability are significant, with a two-five times drop in life expectancy, loss of employment and productivity, and high costs of treatment and rehabilitation. In low-income countries, the limited availability of medical and rehabilitation facilities contributes to social exclusion and leads to further economic and psychological damage.^[8]

I have chosen to study and evaluate the current research into stem cell therapy for SCI in this essay, as I feel this is a disability with widespread socioeconomic and psychological consequences in both developed and developing countries. Further, while rehabilitation, symptom management, and prevention of secondary complications are possible, no effective primary treatment solution exists for SCI. I will explore three types of stem cell transplant techniques that have achieved some success in recent SCI research: Mesenchymal stem cell (MSC) therapy, embryonic stem cell (ESC) therapy, and olfactory ensheathing cell (OEC) therapy. OECs, although not strictly classed as stem cells, share similar functional characteristics with transplanted stem cells with regard to the repair and regeneration of neural cells in SCI. By exploring the current state of preclinical and clinical research into these therapies, I will evaluate the evidence for their safety and efficacy, the medical, legal, and ethical concerns surrounding their use, and ultimately, their potential as a treatment option for SCI.

Pathophysiology of spinal cord injury

To develop an effective treatment strategy, understanding the mechanisms of cellular damage following SCI is essential.

Studying the local spinal environment following injury has highlighted two major phases of injury:

Primary (mechanical) phase

The primary phase essentially involves the mechanical disruption of the normal architecture of the spinal cord. Damage to neurons, glial cells, and demyelination of spinal tracts leads to anatomical discontinuity.^[9] The extent of the initial impact and degree of neuronal damage is the most crucial determining factor in functional outcome. Acute hemorrhage and edema are observed, which lead to systemic hypotension, ischemia, imbalance of ion homeostasis, and neurotransmitter accumulation.^[10] The excessive accumulation of glutamate, a major excitatory CNS neurotransmitter, causes drastic or complete axonal conduction block, and is a major contributor of motor and sensory deficits seen in patients with SCI.^[10]

Secondary (biochemical and vascular) injury cascade

Secondary injury may last from minutes to months, and results from ischemia and an acute inflammatory response whereby inflammatory cells including neutrophils, macrophages, microglia, and T cells invade. These cause free radical and apoptotic cell damage, and release proinflammatory cytokines, such as TNF- α , IL-1 β , IL-6, and growth factors.^[10] While helping to clear cellular debris, this cascade of reactions also exacerbates the injury by "killing" normal nervous tissue.^[10] "Astrogliosis," or the proliferation of astrocytes in the lesion site, results in the formation of a "glial scar," a region rich in growth inhibitory molecules, such as chondroitin sulfate proteoglycans, which prevent neuron regeneration at the injury site.^[11]

Ultimately, it is the extent and spinal level of injury during the primary phase that will determine the degree of functional loss and scope of recovery in patients with SCI. Apart from motor and sensory losses, a variety of multisystem impairments may be observed. Severe or fatal consequences may include chest infections and hypoxia due to respiratory muscle paralysis, asystolic cardiac arrest due to loss of sympathetic innervation to the heart, and autonomic dysreflexia (an uncontrolled rise in blood pressure).^[12] A majority of patients also experience bladder and bowel incontinence, thus requiring lifetime care and symptom management.

Current therapeutic interventions following spinal cord injury

The complex pathophysiology of SCI, with primary and secondary mechanisms, may explain why a suitable curative therapy is so difficult in clinical practice. Most current therapies are aimed at reversing the damage-enhancing effects of the secondary phase.^[10]

The current management of acute SCI may involve spinal immobilization, the administration of high-dose steroids to reduce inflammation, and early surgical intervention to prevent further injury.^[13,14] However, recent research into the clinical efficacy of steroid treatment has shown mixed results.^[9,13] One

systematic review on the effectiveness of methylprednisolone showed that if administered within 8 h after surgery, and for a period of 24-48 h, some improvement in neurological outcome up to 1 year post-incident was seen.^[15] However, the beneficial effects are not permanent. Further, no other steroid therapy has been proven efficacious in any Phase 3 randomized trial.^[15]

Numerous other techniques may target neuroinflammation, such as administration of immunomodulators (such as minocycline), antibodies against neutrophil cell adhesion molecules such as CD11d and CD16,^[16] Na⁺/Ca²⁺ channel blockers to target ionic imbalances, and glutathione promoters and iron chelators to reduce free radical damage.^[9,10,17] However, owing to the complexity of reactions following SCI, many of these therapies are ineffective on their own, and indeed their safety and efficacy is under much dispute in the SCI research community.^[17] Several papers seem to highlight that molecular techniques on their own are not a primary solution to the problem, but combined molecular and cellular techniques may provide a more effective treatment strategy in patients with SCI.^[9,10]

The role of stem cells in neurological therapy

Several concepts of promoting physiological recovery in SCI using cellular transplant techniques exist, and include:

- Transplanting cells to “bridge” axons in the damaged region, to act as a scaffolding for regrowing nerve fibers to rejoin, *via* the secretion of growth and neurotropic factors.^[18]
- Inducing stem cells to form oligodendrocyte precursors to remyelinate damaged axons.^[19]
- Removing or inactivating growth inhibitory factors and cells such as self-destructive immune cells.^[18]
- Promoting neovascularization to support axon regrowth.

Existing and emerging research into adult and embryonic stem cell therapy for spinal cord injury

Stem cells may be classified into two main subtypes:

- Adult or somatic stem cells* (ASCs), derived from differentiated adult tissue sources, are thought to support repair and regeneration of specialized adult tissue.^[6]
- ESCs*, derived from the inner cell mass of the early stage blastocyst,^[20] can be used to produce large quantities of neuron/glia precursor cells, which cannot be easily obtained from adult stem cells. However, unlike adult stem cell recipients, ESC recipients are genetically nonidentical to donors, and may thus need long-term immunosuppressive therapies, increasing the risk of opportunistic infections.^[21]

The clinical potential of the above classes of stem cells, with regard to SCI therapy, will be discussed in the following section.

Mesenchymal stem cell therapy

Mesenchymal stem cells (MSCs) are a type of multipotent adult progenitor cells that can be differentiated into several types of mesodermal tissues including bone, cartilage, muscle, and blood vessels. Bone marrow and umbilical cord blood are the richest

sources of MSCs, but other sources include adipose tissue, skeletal muscle, trabecular bone, and deciduous teeth.^[13] How can these mesenchyme-derived stem cells aid the regeneration of injured ectodermal neural tissue following SCI? True transdifferentiation of an MSC into a functional neuron would require reversion to pluripotent stage, differentiation to an ectodermal precursor, and subsequently, into a neuron.^[6] The mechanism of this type of differentiation is highly controversial.^[22] More widely accepted is the theory that MSCs can be induced to secrete neurotrophic factors.^[23] These may address the complex secondary processes occurring after SCI, promoting axon growth, angiogenesis, and anti-inflammatory actions. Thus, one can see how MSCs may provide a powerful therapeutic option in SCI, through the growth of new axons, reestablishment of blood supply to damaged tracts, and prevention of inflammatory cell activation. Moreover, as MSCs are adult stem cells, they are more readily accessible and less prone to immune rejection than ESCs.^[23] Further, as they may be derived from adult sources or from frequently discarded umbilical or placental tissue, they are less controversial from an ethical viewpoint. Despite their potential benefits, MSC transplantation following SCI presents some drawbacks, such as increased incidence of hematological and other malignancies and tumor metastases, perhaps due to their neovascularization potential.^[24]

In the field of SCI therapy, bone marrow stromal cells (BMSCs) appear to be the most frequently studied stem cells of mesenchymal origin in recent years, and given their well-established success in treating leukemia, amyotrophic lateral sclerosis, and multiple sclerosis, this is not surprising.^[25] Many studies involving BMSC transplantation into rodent models of SCI have shown improved functional recovery.^[25] One study showed that BMSCs induced along the Schwann cell lineage promoted extensive growth of motor and sensory neurons, such as calcitonin gene-related peptide (CGRP)-positive dorsal root sensory axons and rubrospinal axons, in the trauma zone of SCI rodent models.^[26] They also induced expression of vascular endothelial growth factor (VEGF), and significantly attenuated self-destructive astroglial and microglial immune reactions.^[26] In a recent randomized controlled trial comprising 40 patients with cervical SCI, the efficacy of bone marrow MSC transplantation in SCI patients was tested using the “American Spinal Injury Association Impairment Scale (AIS),” a multidimensional scoring system for motor and sensory impairment following SCI.^[27] Fifty percent (10 patients) of the treatment group showed significant motor and sensory improvements and improved bladder function. Six months on, no significant adverse reaction, such as tumor growth, was observed.^[27] The study appears to be one of good methodological quality, using a variety of methods such as spinal cord MRI, electromyography, and residual urine volume, besides observing clinical signs, to test the functional outcome after transplant. It seems safe to accept the trial conclusions that bone marrow MSC transplant has a clear role in improved neurological outcome following SCI.^[27]

Although several studies have demonstrated the efficacy and safety of bone marrow MSC transplantation in SCI, and positive evidence from other types of MSC therapy is

growing, some contradictory evidence still remains. It seems wise to continue to explore the clinical benefits of other types of MSCs, while remaining vigilant of the risks and adverse outcomes.^[25,27]

Human embryonic stem cell (hESC) therapy

The remarkable clinical potential of ESCs amidst the long-standing ethical concerns regarding their development and utilization, have made ESC therapy one of the most controversial and discussed subjects within the scientific community and beyond.

The pluripotency of ESCs have allowed researchers to study their potential as both oligodendrocyte and neuronal cell precursors, and ultimately, their role in remyelination and regeneration of spinal cord tracts after SCI. While research into their differentiation into CNS tissue is still in its infancy, many studies have highlighted their efficacy *in vitro* and in animal models. In one study, ESC-derived oligodendrocytes were produced in culture using the technique “Retinoic acid induction,” and these were seen to rapidly and successfully myelinate multiple axons in culture,^[28] restoring the normal nodal structure and distribution of voltage-gated Na⁺ and K⁺ channels. When transplanted into the spinal cords of myelin deficient *shiverer* adult rats, immunostaining indicated that the retinoic acid-induced ESCs differentiated primarily into myelin-forming oligodendrocytes, and successfully survived to form multilayered, compact myelin sheets in a majority (90%) of rats under study.^[28] Full functional recovery was observed, with no ESC-derived tumor formation. Another study by Keirsted *et al.*^[29] reported that injection of ESC-derived OPCs led to successful remyelination, reduced lesion pathogenesis, and restoration of locomotor function in mice models with spinal cord contusion.

Besides inducing functional recovery by the direct differentiation to oligodendrocytes, hESC-derived oligodendrocyte progenitor cells (OPCs) are thought to secrete trophic factors such as TGF- β 2, hepatocyte growth factor, brain-derived neurotrophic factor (BDNF) etc., which may play an important role in promoting axonal regeneration and neurite outgrowth from damaged neural tracts.^[19] This combination of oligodendrocyte differentiation promoting myelination and trophic factor secretion, promoting axon regeneration may explain the beneficial role of hESC-derived OPCs in patients with SCI.

The first clinical trial to study the safety and efficacy of hESC-derived OPC transplant in the patients with SCI was started in 2009 by the biopharmaceutical company, Geron.^[11] Two years later, no serious adverse issues were noted in the thoracic SCI patients who had undergone transplant. However, in response to criticism of the trial design, its limited and biased mode of patient selection, and to ethical concerns, the trial was terminated in 2011.^[11] Although unsuccessful, the trial was the first attempt at translating the successful preclinical research into hESC-derived OPCs, clinically.^[11] The methodological flaws of the study may inform future trials on how to improve their study design, safety, and ethics in order to evaluate the clinical potential of ESC-based therapy in SCI.

Olfactory Ensheathing Cell Therapy

Following the discovery of the unusual neuroregenerative capacity of the olfactory nerve fibers that arise from olfactory neurosensory cells, in 1985, Raisman *et al.*^[30] discovered a unique type of glial cell, the OEC that contributes significantly to the regenerative capacity of these fibers. OECs surround the unmyelinated olfactory fibers from their origin within the nasal mucosa to their synaptic terminals with olfactory bulb fibers in the anterior cranial fossa.^[31]

In vitro research has shown that OECs play an important role in guiding olfactory nerve fibers to their appropriate target cells within the olfactory bulb *via* the secretion of neurotrophic factors: Nerve growth factor (NGF), brain-derived neurotrophic factor, and glia cell-line derived neurotrophic factor (GDNF).^[32] Lipson *et al.*,^[31] in 2003, found that remarkable neurite outgrowth was seen from peripheral ganglion cells when these were cocultured with OECs. Reverse transcriptase-PCR studies demonstrated that the cultured OECs express mRNA for several types of neurotrophic factors, which, when secreted by OECs into the growth medium, stimulated dendrite growth in target neurons.^[31] It was concluded that while secretion of neurotrophic factors by OECs play an important role in neuronal growth, cell-cell interactions are necessary for such growth to occur. In other words, OECs themselves, and not just the secreted factor, must be present in order to stimulate neuron growth.^[31,32]

OECs have been shown to provide neurotrophic support to various neural cell types including adult retinal ganglion cells, embryonic and adult dorsal root ganglion neurons, and postnatal cerebrocortical and hippocampal neurons.^[31,33,34] Though the potential of OEC transplant therapy is remarkable, studies have shown mixed results in terms of its efficacy in patients with SCI. It has been suggested that the purity of the graft, and the subpopulation from which the cells are derived may determine treatment outcome.^[35]

In 2013, Raisman *et al.*^[36] conducted a preliminary phase 1 clinical trial to study the feasibility of mucosal OEC transplants in six patients with complete cord transection. OECs were extracted from olfactory mucosal biopsies and inserted into the severed region of the patients’ own spinal cords. One-year after surgery, all patients with transplants showed improved motor and sensory function and reconstitution of some white matter tracts at the site of injury. Moreover, no deterioration, tumor growth, infection, or neuropathic pain was observed.^[36] In the same year, a systematic review of 10 clinical trials into the subject showed no significant side effects such as sensory/motor deterioration, infections, aseptic meningitis, or death, within 3 h after surgery, and the overall adverse event rate was low, at 7.68%.^[37] The AIS improvement rate was significant at 39% (confidence interval: 28.1-51.1%), with low heterogeneity among the trials, suggesting that OEC transplant in the patients with SCI is of considerable benefit.^[37] However, despite the apparent success of OEC therapy, the limited methodological quality of some of the studies in this meta-analysis makes it

difficult to form confident conclusions regarding the efficacy of this type of therapy in SCI patients. There is a need for further research, and more rigorously controlled trials to evaluate to overall benefits and risks of OEC therapy in SCI patients.

Ethical and legal issues surrounding stem cell therapy

The use of hESC, despite some clinical success in some areas of medicine, continues to face major ethical objection, especially from religious and political groups who believe that human life begins at conception, and that extraction of the blastocyst for stem cell research is tantamount to murder.^[38] Countries differ in their laws regarding the use of stem cells for research. In the UK, the Human Fertilisation and Embryology (Research Purposes) Regulations (2001) and the Human Fertilisation and Embryology Act (2008) license the use of human embryos only if absolutely necessary for the purposes of research.^[39] Research can only be carried out on embryos created *in vitro*, and up to 14 days after fertilization. “Surplus” embryos after IVF may be used if full consent is obtained from the donor parents.^[39] ESCs hold great potential for SCI and other neurological disorders, but national and international policies and public opinion is likely to dictate whether this potential is harvested.

Developed by Japanese scientists in 2006, “induced Pluripotent Stem Cells” (iPSCs) present a viable and less ethically controversial alternative to pluripotent ESCs.^[40] iPSCs are generated by the genetic reprogramming of differentiated adult somatic cells introducing transcription factors to transform them back into their former pluripotent stage.^[40] iPSCs have been induced to form glia, neurons and neural precursor cells in various models of neurological and neurodegenerative disease; however, systematic reviews show disparity in overall results including their tumorigenesis potential, fate in grafts and efficacy.^[21] Perhaps with better technology to minimize the current risks of iPSCs, these cells may prove to be a novel and promising transplant therapy for SCI.

The rise in “stem cell tourism” highlights another significant ethical and safety concern surrounding stem cell therapy, endangering patients’ lives and the credibility of legitimate research. Stem cell therapy for a majority of conditions is still at a preclinical phase, yet many clinics worldwide routinely and illegally provide untested and dangerous stem cell therapy to desperate and vulnerable patients, for large sums of money.^[41] The International Society for Stem Cell Research has set guidelines for “ethical, scientifically based and medically and socially responsible” clinical translation of stem cell research, and provides information to the patients to make informed decisions.^[42] However, there is still a need for international regulation on the responsible transfer of stem cell lines, and stricter medical malpractice laws directly addressing stem cell therapy, to minimize the unethical exploitation of the patients through the use of unapproved therapies.^[43]

CONCLUSIONS

From my study into the current state of stem cell research for SCI, I have realized that although there is a significant amount of preclinical data supporting the potential of certain types of stem cell therapy, clinical research into the subject still remains a relatively uncultivated ground. While a fair number of clinical trials do exist, the methodological quality of many remains questionable. The low numbers of participants recruited, the paucity of randomized controlled studies, the short time periods of follow-up, and the shortage of data on the different types of SCI seem to lower the credibility of research. I feel there is a strong need for more trials of phase 2 and beyond, exploring the efficacy and clinical translation of preclinical data, and more systematic reviews to consolidate the existing clinical evidence.

A common reason for the lack of successful translational research is the failure of preclinical studies. Perhaps, the reason for the failure of some preclinical studies lies in the methods of extraction and purification of the cultured cells; as suggested by Ekberg *et al.*,^[35] the unintentional presence of other cell types within the transplant, for example, the presence of fibroblasts within a transplant of OECs, can dramatically alter the behavior of transplanted cells, and may lead to adverse events. Other reasons for graft failure may include extraction of cells from suboptimal areas. For example, studies have reported greater functional benefit of OECs extracted from the olfactory bulb compared to those extracted from olfactory mucosa. In a recent landmark paper,^[44] autologous transplant of olfactory bulb-derived OECs with peripheral nerve bridging demonstrated significant clinical recovery as well as functional regeneration of long distance fibers in a patient with complete SCI. Larger scale clinical as well as laboratory studies into the reparative potential of bulb-derived OECs in various conditions will further elucidate their clinical potential.

A therapy that allows the revival of motor and sensory function will give new life and hope to individuals and families left devastated by SCI. Do stem cells really have the potential to fill this role, or is their clinical application merely a hollow promise, as some scientists claim?^[45,46] Through my research I can conclude that ample preclinical evidence exists for the regeneration of neurons *via* stem cells, although there is conflicting evidence in some cases. Whether or not stem cell therapy is effective enough to be translated to clinical practice remains to be proven by more focused and collaborative research, rigorous trials, and honest scientific documentation. In the interests of the several thousands of individuals suffering spinal cord injuries each year, it can only be hoped that stem cell therapy is transformed from an uncertain scientific vision, to a life-changing reality.

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Conflicts of interest

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