

# Spinal Cord Injury and Its Future Therapy - A Perspective

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## ABSTRACT

**Abbreviations:** CNS: Central Nervous System; SCI: Spinal cord injury; CSPGS: Chondroitin Sulphate Proteoglycans, OMGP: Oligodendrocyte Myelin Glycoprotein; MAIS: Myelin Associated Inhibitory Proteins; NTF: Neurotrophic Factors; PNS: Peripheral Nervous System

## Mini Review

Human and animal body comprises of various systems. These body physiological functions coordinated and regulated centrally and peripherally by central nervous system and peripheral nervous system respectively. The Central Nervous System (CNS) consists of brain and spinal cord. This nervous system is complicated network of mechanism which is the central processing unit of an entire nervous system. The nervous system is made up of neurons and neuroglia. The neurons are a specialised cell with membrane ability to generating electrical impulses. Neuroglia are an abundant cell type than neuron in CNS which provides more supports for neurons. Our body system knows about the significance of these cells, so only brain and spinal cord are protected by armour cover of cranium and vertebral column. Because limited regenerative capacity of a neuronal cells [1].

The CNS injury is mainly divided into traumatic and non-traumatic. Traumatic CNS is the largest causes of death and disability, leading to suffering by, and costs to, the individual, their family and society [2]. The traumatic spinal cord injury is a result of primary insult of mechanical injury and consequently leads to cascade of secondary injury mechanisms. The manifestation of spinal cord injury is comprising of motor, sensory and autonomic dysfunctions, which dysregulate body homeostasis. The complications are neurogenic shock, changes in cardiovascular haemodynamics, respiratory failure, bladder dyssynergia, muscle spasticity and wasting, anxiety, depression and sexual dysfunction.

Diagnosis of spinal cord injury is appropriate and possible known well with the advancement of diagnostic imaging techniques. There are various therapeutic modalities encountered for treatment of traumatic spinal cord injury. The most of treatment strategies are mainly minimizing the progression of primary injury and preventing secondary injury mechanisms [3].

## Spinal Cord Injury (SCI) Incidence

Spinal cord injury (SCI) regarding in humans, getting an accurate incidence and prevalence is difficult because most of the developing countries not having separate spinal injury trauma unit and lack of national data entry. Recent year's spinal cord injury incidence rapidly increases due to modernisation and rapid industrialisation. Worldwide incidence expected to be 250000-500000 cases every year [4]. In developing countries like India road accidents will be most disabling condition by 2020. Wide world the average prevalence of SCI estimated to be 1:1000 and mean incidence proposed to be 4 and 9 cases per one lakh population per year. Spinal cord injury is a globally still incurable medical ailment conditions associated with mild to extreme severe disability of motor-sensory, autonomic functions of the body. Although much development and research activities happening in medical field, neither complete cure of spinal cord regeneration nor restore the physiological functions. So, we need to extend research of preclinical study in order to translate to humans.

## Faithful Model of SCI

Rat is a faithful animal for neuroscience, behavioural research and regenerative research for preclinical studies. The greater size of rat provides much more advantages than mice especially borne to surgical procedures and in studies of spinal cord injury, where rat models have been higher translational value [5]. It is much easier to handle and less stressed by human approaches than mice [6]. In the recent decades gene based neuroscience research growing with mice but rat and mice show drastic differences in basic studies like cognition, addiction, impulsive, social behaviour and demonstrate differences in extent of neuroregeneration, demonstrating the significance of appropriate model for a human wisely [7], moreover SCI injury changes in rats are similar to humans [8]. Human spinal cord injury much more complex than experimentally produced rat models although anatomical differences of axonal tracts should be taken into account with human, Rat is to be convenient model of spinal injury due to low incidence of surgical affections and well-established functional analysis techniques [9].

## Type of Spinal Cord Injury Models in Rat

Still what we know about spinal cord injury pathophysiology mechanism is very little. So to know pathophysiological aspects of spinal cord injury and to evaluate CNS spinal cord regeneration, many model has been created for spinal cord injury related to interest [10], for example weight drop model that first described by Andrew [11], aneurysm clip compression [12], calibrated forceps compression [13], contusion [14], complete transaction model [15], excitotoxic model via chemically mediated [16], tractive model [17], epidural balloon inflation compression model [18], hemi-transaction model [19]. This hemi transaction model commonly used to investigate nerve grafting in biomaterials research [20]. This partial transaction model simulates an injury more likely to be seen clinically than complete transaction and provides comparison between injured and healthy fibres in same animals [21]. This model relatively controlled injury environment, low morbidity, and the full transaction or crush injury models. Hence biomaterial scaffold, nerve grafting studies its being good model of choice [22].

## Spinal Cord Injury Pathophysiology

Spinal cord injury is a mechanical insult from externally as a primary injury comprises of various mechanisms and degree of injury with compression, laceration, shearing and distraction followed by cascade of secondary injury from seconds haemorrhage, decreased ATP, lactate acidosis [23]. These in turn neuron inflammation leads to degeneration of neurons by reactive astrocytes and these reactive astrocytes forming a glial scar [24]. Astrocytes are double edged weapon or remedies, earlier days astrocytic glial scar is a major limitation in spinal cord regeneration by inhibitory molecules Chondroitin Sulphate Proteoglycans (CSPGs), but this is not only by astrocytes, other cellular products also [25] in the sense these scar form a boundary to avoid further

neuronal damage. But it aids in CNS axon regeneration by expressing multiple axon growth support molecules [26]. Although intrinsic factor of neurons [27] and multiple growth inhibitory molecules limits axonal regeneration, mainly glial scar and Myelin Associated Inhibitory Proteins (MAIs). These MAIs include many notably Myelin Associated Glycoprotein (MAG), Oligodendrocyte Myelin Glycoprotein (OMgp), ephrin-b3, etc [28]. Glial scar containing CSPGs members are neurocan [29], versican v2 [30], brevican [31].

## Conventional Therapy In SCI

Conventionally, clinically methylprednisolone, cox-2 inhibitors, vitamins, calcium channel antagonists, hormones like thyroid releasing hormone, nutritional supplements like selenium, zinc, and magnesium and anti-excitotoxic agents are used [32]. A major focus over years has been on methyl Prednisolone as a therapeutic agent for treatment of SCI in humans. Unfortunately, data available from different clinical trials are controversial and qualitative. In addition to above drug, none of the treatments such as TRH, opioid antagonist and free radical scavengers in preclinical and clinical studies have been proven to be a major advantage in treatment of SCI [33]. In the experimental level, biologically active peptide gamma 1 chain of laminin 1 promotes axonal guidance by neuron outgrowth factors promotion [34], anti-no-go-A blocking agents/antibodies 11c7, 7B12 increase regeneration, plasticity of the lesioned CNS by increasing cellular cAMP [35]. Cethrin is an inhibitor of Rho signalling pathway which is having neuroprotective and neuroregenerative properties [36]. Cordaneurin drug is a scar preventing substance approved for acute spinal cord injury by European Union-2004. Ephrin A4 antagonist and apoptosis inhibitors (caspase inhibitors, potassium channel blockers (fampridine), Na channel blockers rizole, phosphor diesterase inhibitors involved in molecular interventional therapy of SCI [32].

## Neurotrophins in SCI

Another approach of SCI therapy is borne to neurotrophins. It is the growth factor form the CNS, promotes the normal development and functional maintenance. Neurotrophins enhance neuronal survival, remyelination, axonal growth [37]. Notably brain derived neuronal factor [38], NT-3 and GDNF are contribute neuron survival with synaptic transmission, axon sprouting and remyelination respectively [39]. Neurotrophic Factors (NTF) having short half-life so exogenous delivery of NTF low efficacy due to blood brain barrier, so cell mediated delivery of NTF will be the ideal [40]. On the other hand, in the neurotrophies group, nerve growth factors also produce detrimental effect like hyperalgesia and chronic pain [41]. The consideration of advantages of neurotrophic factors various studies underwent like implantation of NT soaked gel foam with laminin, fibronectin, NT delivery by mini osmotic pumps [42], injection with recombinant virus mediated gene therapy with NT genes [43]. The disadvantage of neurotrophic is that proneurotrophins binds to p75 NTR receptor and leads to apoptosis of the cell [44].

## Cell Based Approaches in SCI

Cell based approaches in SCI mainly by two concepts (1) directly replace the cells lost due to injury (oligodendrocytes or neurons or meningeal cells), (2) providing hospitable environment in such a way that either enhance or aids axonal regeneration and provide neuroprotection [45]. Schwann cells myelinating glial cells of the Peripheral Nervous System (PNS). Peripheral nerve grafts transplantation is the evidence of Schwann cell support axonal regeneration of CNS neuron [46,47]. The Schwann cell transplants also enhances remyelination and support axon growth [48] but axons do not extend beyond growth permissive graft so the remyelination of spared demyelinated axons and no functionally meaning full synaptic connections [49] leads to doubtful about therapeutic utility of Schwann cell in humans.

Schwann cell transplantation has neither neurological worsening nor improvement [50,51]. Olfactory ensheathing cell is a pluripotent olfactory nerve Schwann cell. This cell supports the axons leaves the olfactory epithelium and project through the PNS into olfactory bulb of CNS [52]. These olfactory ensheathing cells aids in axon regeneration and functional improvement in SCI rats [53]. This OEC does not form myelin [54], but it is creating environment for axonal growth and neurotrophic support [55,56]. Although in human study OECs failed to provide significant utilities [57]. Transplantation of olfactory bulb cells has been reported successful in 38-year-old SCI patient [58].

## Stem Cell-Based Approaches In SCI

Stem cells are capable of prolonged self-renewal and having ability to differentiate into multiple cell types [59]. The stem cells in neurological therapy with great concern by its property mainly transplanting cells act as bridge at lesion area and scaffolding for regrowing fibres to rejoin via secreting growth and neurotrophic factors [60]. The stem cells also having neuroprotective ability by secreting certain substances like cytokines, growth factor and trophic factor; the true stem cell is a totipotent. Many researchers considered zygote is a true stem cell because they can differentiate into any cell in favourable medium it can make a whole organism [61,62]. Other than zygote, stem cells broadly taxonomized into two types-one is somatic stem cells which is undifferentiated cells among the differentiated cells of specific tissue population after birth [59] second one is Embryonic Stem Cells (ESCs) which is in the inner cell mass of blastocyst [63]. In spinal cord injury, engrafting of ESC-derived stem cell is a strategy with a unique property of stem cell especially appropriate combination of growth factors; it can be used to obtain neurons and glial cells [64]. As stated, earlier demyelination of an intact axon is a major sequence of SCI [65]. Remyelination is needed for locomotor improvement and restore the salutatory conduction of neuron [66].

Notably human embryonic stem cell derived oligodendrocytes progenitor cells transplant remyelination and restore locomotion after spinal cord injury [67]. The problem of ESC derived immature

lineage cells is ability to induce teratoma after transplantation [68]. But with the high purity production of ESC derived cells it can limit the tumour inducing potential of ESC [69]. Neural Stem Cells (NSC) are multipotent, having ability to produce complete neural lineages [45]. The NSC is a remnant of neuroectoderm present in the brain and spinal cord. In adult the source of NSC cell is Sub Ventricular Zone (SVZ) lining the lateral ventricles and the Subgranular Zone (SGZ) within the Dentate Gyrus (DG) of the hippocampus and spinal cord [70]. These NSC contributes the remyelination [71] and in turn improves axonal conduction. In a different study on human neural stem cell transplants is found effective for SCI in primates [72] the limitation of NSC is that obtaining cells [73]. Other approach is to stimulate endogenous NSC, but in vivo microenvironment not good to stimulate NSC regeneration [74]. Although ESC derived NSC/NPC is an exogenous source, obtaining high purity is a matter.

Another type of somatic stem cell widely studied is mesenchymal stem cells. There are various sources for mesenchymal stem cells likely Wharton jelly of umbilical cord [75], bone marrow derived mesenchymal stem cells [76] and Dental pulp [77]. Human Dental Pulp Derived Stem Cells (DPSCs) having neuroprotective, neuroregenerative, neurotrophic support in preclinical study [78]. This neural crest originated DPSCs could be an ideal stem cell candidate for treating neurological and neurodegenerative diseases [79]. Although, no reports of clinical study in human spinal cord injury, transplantation of human immature dental pulp in spinal injured dogs showed improvement [80]. So many things have to take into account required stem cell density and availability, desirable strategies, for their use. For example, DPSCs or exfoliated deciduous tooth stem cells are not available throughout a patient's lifetime. Stem cell banking can overcome that, it is time-consuming and costly limits their use in clinical applications [81]. Human umbilical cord blood and Wharton's jelly isolated MSC transplantation reduces neuropathic pain [19] and improved sensory recovery [82] of SCI in rats.

The limitation of human UC blood isolated MSC is maternal cell contamination which negatively influence the utilization of this material for cell-based therapy due to Graft-Versus Host Disease (GVHD) [83]. Adipose tissue derived mesenchymal stem cells are easily can harvest from abundant adipose tissue [84]. These MSC secretes neurotrophic factor [85] which aids neuroprotection in ischemic spinal cord injury [86]. Bone marrow derived mesenchymal stem cell is a currently widely using MSC in spinal cord injury and regeneration due to its wide variety of study reports [87]. It lacks tumorigenic potential [88], neuroprotective ability [89] through expression of various kinds mRNA related to neurotrophic factors [90], immunosuppressive by low expression of MHC anti-inflammatory, aiding in axonal regeneration, endogenous stem cell activating property [91] unlike ESC no ethical problem and induce remyelination [92]. The BMSC administration is safe and feasible [93]. The limitation of MSC is that it needs substrate to attach which will improve survivability because anchorage dependant property

[94]. Hence MSC with scaffold increase survivability and overcome above stated limitation.

### Stem Cells & Nerve Growth Factors (NGF)

Another approach is stem cell and NGF. Advantage of this approach is that the stem cell secretes certain neurotrophic factors which are substantial neuronal recovery from spinal cord injury. Exogenous neurotrophic factor or over expressing NGF secreting cells are adding stem cell survivability [95,96] and helps in endogenous protective mechanism [97]. MSCs and NGF synergistic effect in promote axonal regeneration and improve functional recovery [98]. Limitation of this approach is that the injury site is not hospital environment for stem cell survival and attachment because injury site ECM related molecules and pathological state hampers advantage of this approach although various studies with significant results.

### Biomaterial & Stem Cells + Nerve Growth Factors

Biological scaffold materials composed of Extra Cellular Matrix (ECM) which assists the constructive remodelling of many different tissues in both preclinical animal studies and in human clinical applications. The composition of the biological scaffolds consists of a complex mixture and paternally arranged molecules in unique three-dimensional (3-D that mediate structural and/or biological properties patterns. So, it's an ideally suited to the tissue from which the ECM is harvested [99]. For example, acellular sciatic nerve scaffold in spinal injury favours environment for axon regeneration, but alone showing insufficient axon regeneration and low locomotor recovery combination with BDNF showing benefits [100]. Notably acellular spinal cord seeded with mesenchymal stem cell improves robust long-distance axonal regeneration in spinal cord injured rodent study [101].

### Conclusion

The spinal cord injury is a very complex mechanism so simply targeting a single mechanism does not give a good translational value. To improve the therapeutic strategies in spinal cord injury making lesion site like in vivo or mimic like environment by tissue engineering technology is focusing area. So the optimal multi-disciplinary approach combining biomaterials, stem cells, and bio molecules offers a promising treatment for repairing the injured spinal cord [102]. From above review lack of combined therapeutic strategy are noticed regarding spinal cord injury strategy. Hence to fill the limitation, we hypothesis that the nerve growth factor enriched spinal cord tissue derived hydrogels combined with Stem Cell Therapy (MSC) may be good approach in treatment of spinal cord injury.

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