Review Article

Rehabilitation Medicine Implications of Stem Cell Therapy in Spinal Cord Injury–A Review

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Abstract

The life expectancy in spinal cord injury has increased but no cure has been found yet. Stem cell therapy in the spinal cord injury stands high hopes of neural repair and regeneration and getting back to normal life. But for its fruitful result it is essential to know the pathophysiology of the spinal cord injury and also the treatment should be appropriately timed according to the stages of injury. Regular follow-up of these patients is very important as stem cell therapy alone without appropriate rehabilitation may not only result in failure of therapy but also patients may end up in complications such as UTI, bed sores etc. Role of rehab in spinal cord injury with respect to physiological and task oriented neuroplasticity has shown benefits in animal studies. Rehabilitation programme integrated with the stem cell therapy may help to improve the functional outcome.

Key words: ***Spinal cord injury, stem cell therapy, rehabilitation.***

Introduction:

The incidence as well as prevalence of spinal cord injury has remained same with the increase in their life expectancy[1]. Spinal cord injury (SCI) results in loss or damage of the nervous tissue with loss of motor and sensory function below the level of injury and consequently loss of bowel and bladder sensation and control. This makes the affected dependant on others, with many of them going into depression and loss of employment, adding on to the burden. At present, there is no treatment that can repair the lost or damaged nervous tissue to restore normal life of the sufferer.

Stem cell therapy is one of the new modalities which once being the talk of the hour, is considered a glamorous technique of treatment. Treatment with stem cells may help in spinal cord repair or replacement and thus lays a potential scope for stem cell research in spinal cord injury. Stem cell by definition is a cell that is capable of both self renewal and differentiation. There are different varieties of stem cells which have been evaluated in animal models and humans. Stem cell therapy combined with rehabilitation in SCI patient may show better results than single therapy alone. To understand rehabilitation implications of stem cell therapy better, we need to first analyse the pathophysiology of spinal cord injury related basic sciences research and the relevant guiding principles for rehabilitation of persons with SCI who have received or are likely to receive stem cell therapy.

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Pathophysiology of Spinal Cord Injury:

After primary insult (physical injury) to spinal cord, secondary changes (the subsequent chain of events)[2] occur to curtail the primary injury but paradoxically causes damage at the cellular level. The secondary phase of injury includes inflammation, ischaemia, disruption of ion channels, axonal demyelination, massive cell death, oxidative damage, excitotoxicity, glial scarring (astrogliosis), secondary necrosis and/or apoptosis; which altogether can damage the remyelinating cells of spinal cord i.e. oligodendrocytes and other cells (Fig 1). This makes us understand that we need to use multiple

techniques to tackle this altogether and the necessity to treat at the right time. Time sequence of SCI is divided into three stages: acute (primary injury occurring seconds to minutes after SCI), subacute (secondary changes occurring minutes to weeks after SCI), and chronic stage. The treatment should confirm according to these stages. In the acute and subacute stages, the intention of treatment is neuroprotection (to prevent secondary changes) whereas in the chronic stage; it is neural repair and restoration[3]. Spinal cord has also been shown, in basic research on animal models, to have spontaneous neuroplasticity after injury which may occur at the level, caudal and rostral to the level of injury and in supraspinal pathways along with cortical reorganisation. This occurs in the form of axonal sprouting and cellular proliferation. This neuroplasticity may aid in spontaneous recovery seen in a few of the injured.

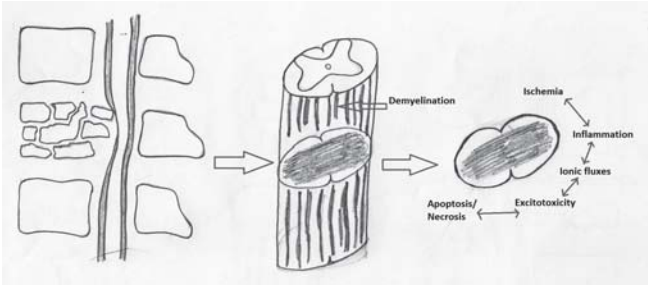

Fig 1- *Pathophysiology of Spinal Cord Injury*

Stem cell–Past, Present and Future:

Stem cells can be allogenic or autologous. Various sources of stem cells include embryonic stem cells[4], neural stem cells from adult brain[5], mesenchymal stem cells (MSCs) from bone marrow[6] and other organs (foetal blood, adipose tissue, umbilical cord)[7] and non-stem cells like olfactory ensheathing cells[8] and Schwann cells[9]. With so many varieties of stem cell available and further being developed, the hope and expectations from the research are high but there are only a handful of clinical trials few of which are listed in Clinical Trials hosted by the National Institute of Health[10].

The stem cell therapy can be compared with Gartner's Hype Cycle (Fig 2) theory that every new technology experiences a period of continuous hype growth, followed immediately by a strong downward trend in the expectation and viability of that particular technology sector. Finally, there is a gradual increase towards the productivity[11]. Stem cell therapy was much hyped few decades back and there came a plateau phase and a phase when the adverse effects came into picture (cancerous growth/ no improvement with stem cells). Again a prolific approach is being considered now with combined therapies linked to functional outcomes, which shows some positive results and is likely to get better in the near future. No research technique can accomplish success without proving its odds out.

Fig 2- *Gartner's Hype Cycle*

Combination therapies are being tried for edging in the various stages of the injury and to enhance the growth or inhibit the apoptotic factors by adding some yet undefined factors along with stem cells like the use of growth factors, axonal guiding, overcoming inhibition, stimulating remyelination, multi cell transplant (Schwann, OEG, Stem cell implants). Regeneration, remyelination and restoration of spinal cord function are taken care of by different methods using combination therapies and thus seem more likely to be successful. The pros and cons of the stem cell types have been described elsewhere[12]. But what we also need to pay attention to is when exactly the stem cells can be implanted in a patient of spinal cord injury.

Timing and Site of Stem Cell Transplantation:

Optimal timing would mean better stem cell survival and thus better clinical outcome. Neural stem cells (NSC) transplantation rostral to the site of injury at the subacute stage showed less macrophage infiltration at 4 weeks post operation suggesting better engrafted NSC survival and host behavioural response[13]. Optimal time for NSC transplantation would result in its high survival ratio and efficient differentiation[14]. Okano *et al*[15] also suggested that optimal time for NSC transplantation should be 7-14 days post injury, as acute inflammatory stage lasts for 1 week and glial scar formation would occur by 3 weeks post injury. Optimal timing would also mean better clinical neurological recovery and to support this; Mac

Donald *et al*[16] found that there was partial recovery in coordination of hind limbs and in weight bearing when NSC transplantation was done on 9th post op day. Although clinically it is seen that the recovery and regeneration process that occurs naturally also is responsible for the considerable functional improvement and it is difficult to isolate the two in case of early approach. The studies done on chronic SCI patients highlights the challenges in the stem cell therapy outcomes.

Rehabilitation Implications with Stem Cell Therapy: Learning from Research in Basic Science:

Apart from the spontaneous neuroplasticity occurring in CNS after SCI, task oriented training or physical exercise has been studied to cause various changes in CNS which may help in spinal reorganisation. It (1) increases neurotrophic factors and their receptors in spinal cord[17,18], (2) increases dentate gyrus (neuronal cells) in adult rats and cortical reorganization[19], (3) causes reorganisation of locomotor networks along the spinal cord generating new patterns of muscle activity[20], (4) stimulates serotonergic fibre growth[21], (5) increases ependymal cell (endogenous stem cells) proliferation[22]. Spinal cord is not just a bundle of tracts but has dynamic neuroplasticity which helps in regaining function. Human locomotion is controlled by mainly supraspinal pathways, which differ from rats/cats and so motor neuron pools below the lesion may be unable to generate activities to support body weight and propel the limb forwards. This suggests that humans develop new compensatory strategies to replace lost function. This was proved by recording neuroplastic redistribution of activity across most of the rostro-caudal extent of spinal cord generating new patterns of muscle activity, which seem to be motor equivalent of normal people in the treadmill trained SCI. Body weight support used in these was 75% of body weight. Though it was done on only 11 patients, they noted change in ASIA score in incomplete paraplegia (ASIA C to D) but not in complete paraplegia (ASIA A). Neuroplastic redistribution of activity was recorded in all these. Further, adult neural stem cells have been isolated from subventricular zone and ependymal cells from around cord central canal which in vivo develop to glial scar tissue after a SCI but in vitro these can be processed to develop to neural progenitors. Ependymal cells found around the central canal of adult spinal cord are endogenous stem cells and these have been shown to proliferate with physical exercise (treadmill training) in a study by Foret *et al*[22]. 5HT descending fibres have been shown to disappear 1 month post-transection below the level of lesion. 5HT has been proposed to originate from autonomic regions of brainstem raphe, with only 2-10% intrinsic to spinal cord. Thus identification of 5 HT fibres rostral to the lesion may indicate regeneration though it's not proven till.

Task oriented training produces improved function which is lost in subsequent change in the training[23]. One study[24] show the motor response to the rate of application of sensory input to the human spinal cord during stepping using body weight supported treadmill and proposed that human spinal cord can interpret complex step-related, velocity-dependent afferent information to contribute to the neural control of stepping, thus supporting the task oriented training theory.

Carvalho *et al*[25] in their trial on the combination of bone marrow stem cell therapy (CD45(+)/CD34(-)) and exercise in functional outcome after SCI found that the combination therapy resulted in significant functional improvement in acute SCI than with single or no therapy. Ying *et al*[26] did MSCs transplantation combined with electroacupuncture (EA) treatment and found that this could promote axonal regeneration and partial locomotor functional recovery in the transected spinal cord in rats and indicate a promising avenue of treatment of SCI. Bone marrow mesenchymal stem cells electro-acupuncture downregulate the inhibitor molecules and promote the axonal regeneration in the transected spinal cord of rats[27]. This was also supported by another study by Z Yiu *et al*[28] who also proposed from their study that combined strategy could promote a better structural and functional recovery of injured spinal cord, as electro-acupuncture may activate the process of cell metabolism, and initiate synthesis and secretion of endogenous neurotrophic factors in the ambient tissues at the lesion site of spinal cord.

OEG tranplantation improves hindlimb stepping in paraplegic rats and task specific training enhances the effect[29]. Exercise increases neurotrophic factors and their receptors in spinal cord. The neurotrophic factors like BDNF which are also secreted by the stem cells like OEG has been shown to facilitate intrinsic spinal cord reorganisation; thus exercise and stem cells may have synergistic effects. For example, in a study by Kubasak *et al*[29]; OEG tranplantation improved hindlimb stepping in paraplegic rats and task specific training enhanced

Table 1: *Integrative Approach in Spinal Cord Injury. MSC- Mesenchymal Stem Cells*

Study	Intervention	Result
Foret A et al	Treadmill training (physical exercise)	Endogenous stem cell proliferation --à can promote regeneration
Janell A et al (Task oriented training)	Body weight supported treadmill training	Motor response to the sensory stimuli increases in spinal cord
Carvalho et al	Bone marrow stem cell and exercise	Significant functional improvement
Yin et al	MSC implantation and electroacupuncture application	Axonal regeneration and partial locomotor recovery
Z Yiu et al	Stem cell and electroacupuncture	Significant functional improvement
Kubasak et al	OEG transplantation and step training	Improves hindlimb stepping
Yoshihara H et al	Passive motorized cycling and stromal cell transplants	No recovery in incomplete contusive injury
Harvey P J et al	Electrical stimulation with peripheral nerve grafts	No rubrospinal tract regeneration
De Leon RD et al	Robotic assisted locomotor training on treadmill and quipazine (5 HT agonist)	No locomotor recovery

the effect. Repair strategies must be coupled with rehabilitation therapies that drive activity dependent plasticity for walking, reaching and grasping, bowel and bladder control, prevention of pain and dysautonomia[30]. CNS responds negatively to the suboptimal rehab strategy and training in one behaviour can negate the consequences on other behaviours[31,32]. Few of combination therapies have shown no positive results[33-35]. Exercise, being a broad term, raises query as to what type of exercise helps in recovey. Lynskey *et al*[36] reviewed role of passive exercise, active exercise and neuroprosthesis in promoting plasticity and recovery. Because of loss of modulation by supraspinal fibres after SCI, spinal circuitry depends on peripheral input as stimulation, which may be the cause of spasticity[37,38]. Passive exercise through joint movements activates H reflex via group 1a afferents and with repetition of movements conditions the spinal cord to normal motor neuron electrophysiology[39] and help reduce spasticity and also influence dendritic morphology[40]. Active exercise in incomplete SCI (ex- partial weight supported treadmill training) has been found to cause task specific changes[41,42] apart from causing task oriented changes. It decreases inhibitory molecules[43] and enhances neurotrophic factor (BDNF) expression[44], causes cortical motor reorganisation, collectively enhancing recovery. It increases corticospinal drive to the muscles of lower limb[45,46]. Neuroprosthesis is another type of modality being tried in SCI. It uses electrical stimulation to activate neural structures. The types of neuroprosthesis include functional electrical stimulation (FES- stimulates the peroneal nerves to elicit a flexion withdrawal reflex and thereby cause limb movement), Functional neuromuscular stimulation (FNS- stimulates multiple leg muscles at their motor points in an appropriate sequence to produce coordinated functional movements, such as grasping, standing, or rhythmic leg movement) and epidural spinal cord stimulation (ESCS- stimulates the dorsal aspect of the spinal cord at a particular spinal level using implanted electrodes). The mechanism by which it helps in recovery is not known exactly but it may cause plastic changes at cellular and neural circuitry level. It also enhances BDNF factor and its receptor expression, promoting axonal regeneration[47-49].

Stem Cell Therapy in Other Aspects of SCI:

Few patients of SCI, who have accepted their condition but are held back because of complications, may want improvement in these aspects only. Stem cells can be tried to improve at least some aspects if not completely restore the condition back. Gonzalez Sarasua *et al*[50] did a preliminary study on the use of bone marrow mononuclear cells (BM-MNCs) to treat pressure ulcers in terms of clinical outcome, procedure safety, and treatment time. Their data indicate that cell therapy using autologous BM-MNCs could be an option to treat type IV pressure ulcers in patients with SCI, avoiding major surgical intervention, which also decreased the duration

of hospital admission and wound care time. Stem cell therapy has also been tried in neuropathic pain associated with SCI and found to have effective results. Three cycles of allogenic MSC treated CD 34 cells given over 14 months to a subject of incomplete SCI showed significant reduction in neuropathic pain and also resumption of motor and sexual activities[51]. But in a study, early exercise in spinal cord injured rats induced allodynia through TrkB signalling[52]. In another open labelled case control study taking 64 patients of SCI treated with monthly MSCs for 6 months; more than half of the patients developed neuropathic pain[53]. So, it can act as double edged sword; one should be cautious while treating a patient and also while choosing an appropriate patient.

Long Term Results with Stem Cell Therapy:

Park *et al*[54] in their human clinical study on long term effects of SCI therapy using mesenchymal stem cells concluded that 3 of 10 patients showed improvement in motor power of upper extremities and in activities of ADL along with significant MRI and electrophysiological changes on long term follow-up.

Present Status Regarding Stem Cell Research and its Rehab Implications:

The stem cell clinical trials done until now are mainly on rats and only a few on humans. The sample size in each is small. Mode of injury incurred on the rats are through weights or balloon dilatation, that are not similar to forces involved in human SCI which also includes rotational and shearing component; chances of incomplete injury are high in rats which may naturally recover over a period of time. Safety standards have to be maintained in the labs while preparing the stem cells before putting humans under trial. Dobkin *et al*[55] concluded from their observational study on cellular transplants in SCI done in China; that perioperative morbidity and lack of functional benefit were identified as the most serious clinical shortcomings and the procedures observed did not attempt to meet international standards for either a safety or efficacy trial. Kwon *et al*[56] also suggested for more preclinical trials before translation into humans. They did a comparison of opinion between researchers and spinal cord-- injured individuals on the preclinical evaluation of novel therapies for SCI. They found that SCI individuals had high expectations in the level of pre-clinical evidence required before proceeding with the clinical trials and their expectations should be kept in mind before doing the clinical trials.

Tator[57] in his review article on trials in human SCI states that stem cells have unproven effectiveness and proven effective are methyl-prednisolone (controversial) and gravity assisted ambulation training, thus emphasising the rehab component.

There have been few studies quoting time taken for recovery after treatment with stem cells and poststem cell therapy management. There has been no study regarding the number of sittings with the exact duration of gap between each sitting required for the stem cell treatment. And also how the rehabilitation programme be structured to these patients. The complacence on part of physicians administering the stem cell therapy could be counterproductive as waiting for recovery may in fact hinder the rehab protocol and worsen the functional outcome or may even cause complications like pressure ulcers, UTI etc. Adding to it is the fact that patients who have received the stem cell therapy are reluctant participants in rehabilitation and are too hopeful even if some sensory improvement is seen and often become too resentful if there is no benefit from the procedure. It is observed that they often think that cell transplant therapy is the quick-fix to their all problems related to SCI. We have to put a lid on expectation from stem cell therapy alone and encourage the patients to continue with the rehab prescript. Patients often incur huge debts and have sold everything in hope of walking back normally after the procedure and eventually do not get rehabilitation done and further deteriorate. Media hype fuels the expectations and gives rise to increased vulnerability of patients to fall for non-standardised cell therapies.

It is therefore imperative that rehab should be continued even after stem cell treatment and it should be a part of the clinical trials and these clinical trials should be aimed related to functional goals, so that functional outcome may be better related to the stem cell therapy. More clinical trials should be done focusing on integrative approach of stem cell with rehabilitation to clear the concepts and help the individual. People should not fall victim for these stem cell trials without proper structured rehab facility; since these can not only worsen there condition but can also lead to financial loss with waste of time which may add on to their frustration and depression. Since most of the clinical trials on stem cell therapy in SCI are still in initial phases, it would be more

beneficial if we club these trials along with structured rehab programmes for a better clinical outcome.

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Abbreviations:

SCI – Spinal cord injury

MSC – Mesenchymal stem cells

ASIA – American Spinal Injury Association

BDNF – Brain derived neurotrophic factor

UTI – Urinary tract infection

BM MNCs - Bone marrow mononuclear cells

OEG – Olfactory ensheathing glia

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