Stem Cell Therapy in Spinal Cord Injuries: Current Concepts

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Need for Stem Cell Therapy

The future of medicine is regenerative medicine wherein stem cell therapy is going to play a major role. Although there is a lack of clarity on stem cell therapy, the scientists are confident that at some stage in future, stem cell therapy will be recognized as a definitive management strategy for various debilitating conditions. The stem cells can be taken from a variety of sources including umbilical cord blood and bone marrow.

Historical Basis

Many unanswered questions were answered later in the field of spinal injuries. Nevertheless, there is one consensus that it is a devastating ailment. It had been described as ‘An ailment not to be treated.’ It was only during the World War period that Sir Ludwig Guttmann (United Kingdom) and Sir George Bedbrook (Australia) showed that if properly rehabilitated, these people could lead a near normal lifestyle.

The developed countries certainly took the challenge, and a number of spinal injury centers came up. However, in the developing countries, the issue remains neglected even till now. Ironically, this often-neglected area had the most media attention in the past few years, largely due to claims of stem cell therapy as a viable option in improving the quality of life of such patients. A literature review on the developments with regard to stem cell therapy as a therapeutic option in patients affected by spinal cord injuries can throw light on the exact status of the developments in this particular field.

Myelinated fiber tracts of the adult central nervous system (CNS) have a complex and regular arrangement of three types of glial cells, namely, astrocytes, oligodendrocytes and microglial cell. As early as in 1928, Ramon Cajal historically stated that neurons have the potential to regenerate and in fact showed that at some stage in future, stem cell therapy will be recognized as a definitive management strategy for various debilitating conditions. The stem cells can be taken from a variety of sources including umbilical cord blood and bone marrow.

Current Perspectives

Cell-based therapies for spinal cord injury are of two types:

• Regenerative cell therapy.
• Replacement cell therapy.

The regenerative cell therapy has focused on restitution of the white matter along tracts, whereas the replacement cell therapies are focused on neuronal or oligodendrocyte replacement.

Replacement Cell Therapies

The replacement cell therapy is based on the replacement of cells with a view to regenerate axons and myelination of the regenerated axons. Myelination is considered because there are a substantial number of neurons that are demyelinated at the site of injury. Any effect with respect to helping the myelination of these fibers may help in substantial neurological recovery.

The various methods tried in replacement cell therapy include:

• Stem cells from xenografts.
• Embryonic and fetal stem cells.
• Umbilical cord blood stem cells.
• Adult stem cells.

Stem cells from xenografts

In 2001, the study of porcine stem cells was undertaken in Washington University, but the results have not been published so far. Hence, the role of porcine stem cells in spinal injuries remains undetermined.

Embryonic and fetal stem cells

With respect to trials using human fetal spinal cord cells, there have been independent trials that have been hence completed and closed. Trials in Sweden, Denver, Russia and Gainesville focused on spinal cord injury patients with posttraumatic syringomyelia. In the Russian trial,1 there were five patients and in the Gainesville trial there were eight patients. In these trials, human fetal spinal cord cells from 6- to 9-week-old aborted fetus were used. The fetal spinal cord was minced and transplanted into the cyst cavity following a myelotomy. Only the safety of the procedure could be documented. Although the magnetic resonance image scanning subsequently showed that the cavity is filled up, the trial suggested that it was premature to draw any conclusions.

Umbilical Cord Blood Stem Cells

In 2004, the Korean researcher (Chosun University Professor Song Chang-Hun) claimed to have used multipotent stem cells from umbilical cord blood stem cells in a 37-year-old female patient after spinal cord injury. The claims related to this stem cell research were relegated 1 year later.

Recently, the China spinal cord injury Net is conducting a human multicentric clinical trial using umbilical cord blood stem cell with the guidance of Wise Young.

Adult stem cells

Adult neural stem cells

At the Irvine Reeve-Irvine Research Center, the adult human neural stem cells were used to successfully regenerate the damaged spinal cord tissue and improve mobility in mice.2 These transplanted stem cells differentiated into new oligodendrocyte cells that restored myelin around damaged mouse axons. Additionally, transplanted cells differentiated into new neurons that formed synaptic connections with mouse neurons. They demonstrated that not only oligodendrocyte cells were formed,

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but these cells also differentiated into new neurons. However, experiments in animals do not necessarily translate into humans. So far, there has been no human trial using these cells and the outcome in human spinal cord repair remains to be explored.

**Adult Autologous Marrow Stem Cells**

Generally, the autologous source has been used to harvest adult marrow stem cells because it is very easy to obtain. They are either injected intravenously or implanted intramedullary. Once again, the mechanism of action still remains unclear. In recent times, various trials that are drawing attention include that in Prague, and ongoing trials in Brazil, Turkey and a similar trial in AIIMS. But in AIIMS, the trials were mainly focused on cardiovascular and other problems.

Sykova et al. in 2006 reported the transplantation of unmanipulated autologous bone marrow in 20 complete spinal cord injury patients, 10–467 days post injury. They compared intra-arterial with intravenous route of administration. They concluded that it is a safe procedure but longer follow-up is required and hence cannot comment on beneficial effects due to this cell therapy.

Park et al. in 2005 reported autologous bone marrow therapy at the site of injury in six complete spinal cord injury patients. Improvement was seen in all subjects [adolescent idiopathic scoliosis (AIS) - A to C in five and AIS - B to C in one subject]. Serious complications were not found.

Yoon et al. in 2007 had conducted an open-label, nonrandomized study on 35 complete spinal cord injury patients. Bone marrow transplant was injected into the area surrounding spinal cord injury site within 14 injury days, between 14 days and 8 weeks and more than 8 weeks after injury. Improvement was seen in 30.4% acute and subacute patients.

No significant improvement was seen in chronic patients. No adverse event was reported in any of them. The authors concluded that long-term and large-scale multicenter clinical study is required to determine its precise therapeutic effect.

**Embryonic Cell Therapy vs. Adult Neural Stem Therapy**

The advantage of embryonic stem cell therapy over adult neural stem cell therapy is that these cell lines can be cultivated in vitro for further use; but the disadvantage is that it is not autologous. There are risks of immunological rejection, tumor or teratoma formation.

The available literature also supports the fact that there have been tumorous proliferations owing to this unproliferated growth. Also there are risks of mutations, dedifferentiation and transdifferentiation and infections. The risk of infection is related to the direct injection of the cell lines into the meninges. The mechanism of differentiation is unknown, and there are major ethical issues regarding the use of live human embryos.

The greatest challenge in stem cell research is the inability to uncover the extracellular and intracellular mechanisms that determine and control the self-renewal and differentiation properties of stem cell in physiological and host environment. There is no means by which cell differentiation and the rate of cell renewal can be controlled. In the process, it has been shown that most of them rather become scar cells and this is perhaps one of the reasons for the very high incidence of increased pain in these patients.

On the other hand, adult stem cell therapy has the advantage of having an autologous or allogenic source, with a low risk of immune rejection, and thus the need for immunosuppression can be avoided. Also, there is no risk of tumor or teratoma formation and no major ethical issues.

**Regenerative Cell Therapy**

The objective of regenerative cell therapy is axonal elongation, restoring myelin and complete integration into the host environment. The methods used in regenerative cell therapy in spinal cord injuries include:

- Peripheral nerve grafts.
- Highly enriched Schwann cell suspension.
- Activated macrophages.
- Olfactory ensheathing glial (OEG) cells.
- Oligodendrocyte precursor cells.

**Peripheral nerve grafts**

Clinical trials using peripheral nerve grafts are of two kinds, namely:

1. Using nerve grafts to bridge the gap in the spinal cord with some form of glue, which would release growth factors.
2. Bypass surgeries, where various forms of nerves like the ulnar nerve are rerouted into the distal part of the injury hoping that this would stimulate, form a bypass and have a neurological recovery. In the second case, researchers have also used intercostal nerves to bypass the defect. Except for one trial, where the spasticity was reduced, the published literature so far has failed to document any usefulness of the procedure.

**Schwann Cell Cultures**

There have been trials using Schwann cell cultures. It was found that they integrate into the host tract glial structure, and that it greatly increased axon sprouting in the corticospinal tract, but very few sprouts reenter the distal tract. Regrettably, no data are available with respect to the functional recovery.

**Activated Macrophages**

These trials were based on the presumption that transplanting activated macrophages would allow the control of the secondary mechanisms. A Food and Drug Administration-approved clinical trial on activated macrophages was started in 1999 as a phase I study in various hospitals. Knoller et al. reported in 2005 a Phase I, open-label, nonrandomized study in which monocytes were isolated from blood, incubated ex vivo with autologous dermis and injected into spinal cord immediately caudal to the lesion within 14 days of injury. Three subjects improved significantly (AIS A to C) and the technique was well-tolerated. They concluded that further clinical trials were warranted. The phase II study was started in 2004. However, subsequent trials had to be closed.

**Olfactory ensheathing glial cells**

The major problem in cellular therapy for spinal cord injury was that the axon sprouts were reluctant to leave the Schwann cell environment of the transplant and reenter the glial involvement of the distal corticospinal tract. This largely paved a way for the promising technique in which olfactory ensheathing glial (OEG) cells are used.

While studying the olfactory system, it was seen that there is a continuous physiological mechanism of regeneration and reconnection occurring between the peripheral nervous system and the CNS. The entry point of the olfactory axons into the olfactory bulb is associated with special glial cells, which are
known as the OEG cells. It was found that they permit the growing axons from neurons of the nasal cavity olfactory mucosa to reenter the olfactory bulb and synapse with second order neurons. This process continues to happen throughout the life.

Some trials were undertaken in which the olfactory ensheathing cells were isolated from the respective adult human olfactory bulb. These trials revealed that OEGs can be grown in tissue culture with high viability and they have the ability to form myelin sheaths following transplantation into the areas of persistent demyelination in the adult rat CNS. It was also reported that they could promote substantial neurological recovery in mice.

Mackey-Sim et al. in 2004 comprehensively reviewed the OEG cell therapy. They stated that it had been 20 years since the first paper was published. In the first 10 years, there were 13 research papers. In the subsequent 7 years, 50 papers were published describing mainly OEG transplantation, 51 describing biology and 31 were review articles.

The source has been either from the olfactory bulb of the dead aborted fetus or an adult donor or the olfactory mucosa. The route of administration has been either intrasurgical surgical implantation with or without removal of the scar tissue or intrasurgical image guided injection.

The advantages of OEG cell transplantation are:

- It has been extensively studied with substantial data to support the regenerative properties;
- It is easy to obtain;
- There are lower risks of rejection;
- No major ethical considerations are involved.

It is due to these reasons that there have been a lot of clinical trials using these cells.

In 2006, Huang et al. reported their prospective study on 16 chronic spinal cord injury patients. Olfactory bulbs were harvested from 3- to 4-month-old aborted human fetus and single fetal OEC cells were cultured for 12–17 days. A suspension containing about $1 \times 10^6$ fetal OECs was transplanted through an injection into the subject’s spinal cord. No cell-related adverse effects were reported. They concluded that their protocol is feasible and safe to treat patients with chronic spinal cord injury within 38 months after the injury.

In 2006, Lima et al. reported their human pilot study in AIS A subjects between 18 and 32 years of age, 6 months to 6.5 years post injury. Olfactory mucosa autografts were transplanted into lesions after a myelotomy and scar removal. Only mild adverse events were noted. They concluded that the study was feasible, relatively safe and potentially beneficial procedure. Long-term follow-up was required to rule out delayed side-effects and assess any further improvements.

In 2005, Feron et al. reported their study on six complete spinal cord injury subjects with injury at least 2 years prior to autologous bone marrow transplantation. This phase I/IIa design study had a control group in which no surgery was done. No adverse findings were reported till 3 years of follow-up, but no significant functional or neurological changes were found either. They concluded that the procedure was feasible and safe up to 3 years post implantation. However, this was a preliminary conclusion because of the small number of trial subjects.

In 2009, Chhabra et al. published a prospective pilot study with five chronic, motor, complete spinal cord injury subjects with neurological level C5–T12. Autologous olfactory mucosal transplantation was done after a myelotomy and removal of scar at the injured site in the spinal cord. This technique had been reported by Lima et al. They concluded that the study was relatively safe and feasible in AIS A participants with thoracic-level injuries at 18-month follow-up. No efficacy could be demonstrated which could be attributed to the procedure. It may not be possible to conclude regarding the efficacy of the procedure due to the limitations of the study.

Indian Contribution to Stem Cell Research

There have been a lot of claims in the Indian media about success in cellular therapies for spinal cord injury. However, only one Indian human trial (Chhabra et al. 10) has been published so far.

Another ICMR-approved study titled “Autologous Bone Marrow Cell Transplantation for Acute Spinal Cord Injury” by the same author is ongoing at Indian Spinal Injury Centre. Subjects with 10–14 days post injury are being divided into three groups. One arm will only be rehabilitated. The mononuclear cells harvested and processed from bone marrow from the iliac crest are being transplanted via direct route or intrathecal route in second and third arm, respectively. The subjects are being followed up for 2 years. The primary endpoint would be improvement in American Spinal Injury Association (ASIA) grade of at least one in 2 years or change from baseline of ≥6 points in total motor score of ASIA manual motor test. A number of secondary endpoints include walking index, sensory score, non-ASIA voluntary muscle score, EMG evaluation, urodynamics, etc. are also being considered.

Indian Council of Medical Research is also working on a national-level multicentric trial using the same technique.

Summary

The list of experimental therapies that have been developed in animal models to improve functional outcomes after spinal cord injury is extensive. Though preclinical trials have shown a good potential for cellular therapies in spinal cord injury, there is no documentary proof as of now that any form of cellular therapy definitely improves outcome in management of human spinal cord injury. The adverse effects of many such therapies are well-documented.

There is a need to conduct proper clinical trials. Some early-stage spinal cord injury clinical trials have recently been done and some have been started. However, some experimental therapies have been introduced into clinical practice without a clinical trial being completed. Undue hype by the media and claims by professionals have a profound psychological effect on the spinal cord injured and interferes in their rehabilitation. While we know that the future holds a good promise, this should not prevent patients from aggressively pursuing rehabilitation since we are not sure when a clinical breakthrough will be achieved.

References

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