NARRATIVE REVIEW

Stem Cells for Spinal Cord Injury – Are we Closer to Clinical Application in Humans?

Saqib Kamran Bakhshi, Rashid Jooma

Abstract

Recovery after spinal cord injury (SCI) is highly variable, often leaving the victim disabled for life and having to deal with the complications of paraplegia. Stem cell therapy is a potential hope for these patients. Most of the research on use of stem cells for SCI has been on animal models in laboratories. Some recent clinical trials involving human subjects have shown positive outcomes with regards to tissue growth after transplantation, but meaningful functional recovery is yet to be seen. The emergence of lumbar cord simulation is a new approach and the recent identification of recovery organizing interneurons points to a pathway that could integrate neuromodulation with cellular therapy.

Keywords: Spinal Cord, Paraplegia, Stem Cell, Transplantation, Interneurons.

DOI: 10.47391/JPMA.AKUS-14

Introduction

Paraplegia secondary to spinal cord injury (SCI) is a life-altering condition for the victims and has frustrated treating physicians since the time of Hippocrates. The focus of treatment has in the main been directed towards mitigating the effects of secondary injuries including oedema, haemorrhage, necrosis and demyelination, and to salvage any viable neural tissue.[1, 2] Functional neural regeneration is limited by scar formation and gliosis, due to the activities of the cord's microglia, fibroblasts and reactive astrocytes.[3,4] Stem cell-based therapies have been developed over the past three decades and continue to hold promise for SCI.[4]

Donald Orlic's group at NIH demonstrated regeneration of infarcted myocardium with bone marrow derived haematopoietic cells[5] and since then, stem cells have widely been employed for other organ systems. Despite the biological variability of the different lines of stem cells, they have three uniform effects[6] : First and foremost is their ability to replace the damaged necrotic cells utilizing their multi-differentiation potential; Second, they also possess the capability to produce and secrete anti-inflammatory factors that contain the inflammatory response in the damaged microenvironment and thirdly they produce many cytokines, growth factors and cell adhesion factors that promote tissue regeneration.[7]

These remarkable characteristics of in experimental settings and engendered the expectation that the neuro-regenerative effects of stem cells can represent therapies that would achieve promising outcomes in SCI patients.[8] However, the encouraging results from laboratories have so far not translated into real results in these patients. We reviewed the medical literature to assess the progress made so far on the use of stem cells for SCI.

Review of Evidence

In our review of the literature on the biology of spinal cord regeneration we have discerned 5 themes documented by research groups working on the facilitatory microenvironment for restoration of anatomical and functional connectivity.

Stem Cell Therapies

There can be two wide-ranging therapeutic cellular categories for SCI: non-neural stem cells, and neural stem cells. The non-neural stem cells include umbilical cord mesenchymal stem cells (MSCs), bone marrow MSCs, and adipose tissue-derived MSCs.[9-11] The MSCs can be administered via intravenous or intrathecal route. The cells are then taken up by the injured tissue under the influence of neurotrophic factors released by the MSCs.[12,13] After coming in contact with the injured tissue, they can potentially differentiate into neural cells, but with a high attrition rate which can significantly impact beneficent outcomes. The MSCs, also referred to as 'supportive stem cell therapy', are easy to acquire, culture and administer, therefore, despite mostly unfavourable outcomes, the non-neural stem cells have been widely used for trials and clinical research.[14,15]

The second type is based on neural crest generating stem cells, also referred as loading stem cell therapy. These include neural stem progenitor cells (NSPCs), neural progenitor cells (NPCs) and olfactory ensheathing cells

Department of Neurosurgery, Aga Khan University, Karachi Pakistan.
Correspondence: Rashid Jooma. Email: rashid.jooma@aku.edu

(OECs).[9,16] These cells require complex preparation procedure, and later direct transplantation at the injured spinal cord site via surgery. The final yield of functional neural cells from this therapeutic strategy is better than the MSCs, but procedural complexity has retarded their use for research.

Neuronal Regeneration after SCI

Neurons have limited regenerative potentials to compensate after an injury, thus, the reformative and recovery process after SCI is not spontaneous. Even the Wallerian degeneration of injured axons is highly variable and unpredictable. The proliferating astrocytes mainly mark a glial border, the oligodendrocyte progenitor cells mostly differentiate into oligodendrocytes which myelinate regenerating axons. The growth limiting factors are i) decreased intracellular cyclic adenosine monophosphate (cAMP) ii) absent neurotrophic elements and physical substrate for growth of axons in the injured space and iii) high concentration of inflammatory cells.[17,18] The tissue injury response favours formation of scar tissue by fibroblasts, foamy macrophages and reactive astrocytes but unlike other tissues where injury reaction promotes growth, it is mostly detrimental for regeneration in the nervous system.

In animal models of incomplete SCI, the preserved contralateral white matter tracts have been shown to extend axons across midline, and reshape the circuit. This has been observed for corticospinal, rubrospinal and reticulospinal tracts.[19] The length of dendrites also increases after administration of glial cell-derived growth factor. These adaptive changes have raised hopes for recovery after incomplete SCI, and it can potentially be further optimized if a growth permissive environment is provided in the form of stem cell implantation. However, there is still no substantial evidence to support the idea that this favourable growth environment theory will also translate into functional recovery after complete SCI.

Neurotrophic Factors

There are several neurotrophic factors with profound positive effects on neural regeneration.[9] Laboratory experiments have shown that stem cells decrease the accumulation of neutrophils and activated macrophages, and release these neurotrophic factors, when implanted in the acute and subacute phase after SCI. This significantly reduces secondary injury due to inflammation, stabilizes blood-spinal cord barrier, promotes cell growth and has a neuroprotective effect for injury-spared neural tissue.[11]

Remyelination

An important aspect of SCI recovery is to remyelinate partially or completely demyelinated axons. In the presence of functionally viable oligodendrocytes, after SCI, the supportive stem cell therapy provides a favourable environment for myelination.[20] This is a slow process requiring at least 3 weeks for myelin to ensheath a single axon. It also has a potential role in patients with multiple sclerosis, in which there is loss of myelin binding protein (MBP). In cases where oligodendrocytes are not preserved, the loading stem cell transplantation can provide substrate of cells that can differentiate into mature oligodendrocytes. Laboratory studies have shown reduced therapeutic effect if stem cells deficient in MBP are transplanted after SCI. There are some reports which contradict the importance of myelination in meaningful recovery after SCI, so further research is warranted.[21]

Relay Mechanism

Recovery after SCI also involves formation of new circuits connecting brain with spinal cord, as well as intraspinal connections. The transplanted cells labelled by β-III tubulin and hNu antibodies have been shown to cause juxta positioning of neurites and the presynaptic regions of host neurons in the spinal cord.[22] The regeneration of this relay mechanism is as important as regeneration of the neurons for good functional recovery. It has only been observed in laboratory research, where it is a very slow process, and it cannot be predicted how long it will take in human subjects. Considering the evidence from animal models, the relay mechanism and formation of new circuitry is vital for developing connections between old and new neurons and requires further research.

Recent Clinical Trials on Stem Cells for SCI

During last decade, several clinical trials have been conducted using stem cells acquired from different sources, in patients with SCI. Most of the researchers used MSCs derived from bone marrow or umbilical cord as stem cell source for transplantation. Others reported using neural stem cells, OECs, blood cells from human umbilical cord or Schwann cells. While all these studies resulted in substantial increment in knowledge and understanding of stem cell therapy, there were several limitations influencing generalizability and acceptance of results. The most recent phase 2 study published by Honmou et al. infused autologous MSCs intravenously in 13 SCI patients and reported variable functional improvement in 12 patients at 6 months after intervention.[23] They were able to show the safety and feasibility of their intervention, however, the study was

unblinded, lacked a control group as well as serial imaging and histological testing which hindered them from establishing a causal relationship.[23] Damianakis et al. did a review and studied 18 publications on stem cell therapy transplantation in human subjects.[23] They concluded that all these trials lacked inter-study standardization for source of stem cells, mode of administration, timing of transplantation and dose of cells.[24] These studies also differed in the characteristics and categories of SCI patients, and the follow-up patients.[23]

Stem Cell Therapy and Modified Rehabilitation

Clinical trials have shown an enhancing effect of adding intensive physical rehabilitation to stem cell therapy in mouse models of SCI, and cellular transplantation targeted at the lumbar enlargement improved spinal conductivity and central pattern generator activity[25]. Functional electrical stimulation (FES) via wearable devices have been shown to improve functional status of SCI patients. This has been referred to as modified rehabilitation technique and is intended to modulate neural circuits. The Hybrid Assistive Limb (HAL) devices and suits have been reported to expand the small stimulations in incomplete SCI patients, and convert them to large stimuli using exoskeleton, and mechanically support joint movement.[26] In the past decade much attention has been received by epidural spinal stimulation (ESS) of the lumbosacral spinal cord segments with a number of groups reporting return of motor function with assisted walking in patients with paraplegia[27]. The biggest benefits in these studies have been the least visible — improvements in blood pressure, bladder and bowel control, sexual function and temperature regulation.[28]

While it is yet to be determined if EES would have a synergistic effect with stem cell therapy,[29] a recent publication from Lausanne raises this intriguing possibility by identifying a subpopulation of spinal interneurons that are activated by the spinal injury and subserve return of ambulation with EES.[30] This suggests that stem cell therapies could one day augment the crucial populations of recovery-organising neurons activated in spinal-cord injuries.

Conclusion

While laboratory models and clinical studies on human subjects have shown promising results for stem cell transplantation after SCI, strong evidence for functional recovery is still not present. The increasing number of human clinical studies during last decade raise the hope of achieving meaningful breakthrough in improving functional outcomes after stem cell transplantation in SCI patients particularly with an important and evolving role for electrical neuromodulation.

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Disclosure: None to declare.

References

1. Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg 1991;75:15-26. doi: 10.3171/jns.1991.75.1.0015.
2. Guertin PA. A central pattern generator in the spinal cord for the central control of micturition: an opportunity for first-in-class drug treatments. Asia Pac J Clin Trials Nerv Syst Dis 2019;4:1-2. doi: 10.4103/2542-3932.251477
3. Silver J, Miller JH. Regeneration beyond the glial scar. Nat Rev Neurosci 2004;5:146-56. doi: 10.1038/nrn1326.
4. Donnelly DJ, Popovich PG. Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. Exp Neurol 2008;209:378-88. doi: 10.1016/j.expneurol.2007.06.009.
5. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, et al. Bone marrow cells regenerate infarcted myocardium. Nature 2001;410:701-5. doi: 10.1038/35070587.
6. Shao A, Tu S, Lu J, Zhang J. Crosstalk between stem cell and spinal cord injury: pathophysiology and treatment strategies. Stem Cell Res Ther 2019;10:238. doi: 10.1186/s13287-019-1357-z.
7. Neves J, Sousa-Victor P, Jasper H. Rejuvenating Strategies for Stem Cell-Based Therapies in Aging. Cell Stem Cell 2017;20:161-75. doi: 10.1016/j.stem.2017.01.008.
8. Jooma R. Towards a cure for traumatic paraplegia--is there cause for hope? J Pak Med Assoc 2006;56:599-602.
9. Hawryluk GW, Mothe A, Wang J, Wang S, Tator C, Fehlings MG. An in vivo characterization of trophic factor production following neural precursor cell or bone marrow stromal cell transplantation for spinal cord injury. Stem Cells Dev 2012;21:2222-38. doi: 10.1089/scd.2011.0596.
10. Gu W, Zhang F, Xue Q, Ma Z, Lu P, Yu B. Transplantation of bone marrow mesenchymal stem cells reduces lesion volume and induces axonal regrowth of injured spinal cord. Neuropathology 2010;30:205-17. doi: 10.1111/j.1440-1789.2009.01063.x.
11. Abrams MB, Dominguez C, Pernold K, Reger R, Wiesenfeld-Hallin Z, Olson L, et al. Multipotent mesenchymal stromal cells attenuate chronic inflammation and injury-induced sensitivity to mechanical stimuli in experimental spinal cord injury. Restor Neurol Neurosci 2009;27:307-21. doi: 10.3233/RNN-2009-0480.
12. Pinho AG, Cibrão JR, Silva NA, Monteiro S, Salgado AJ. Cell Secretome: Basic Insights and Therapeutic Opportunities for CNS Disorders. Pharmaceuticals (Basel) 2020;13:31. doi: 10.3390/ph13020031.
13. Vawda R, Badner A, Hong J, Mikhail M, Dragas R, Xhima K, et al. Harnessing the Secretome of Mesenchymal Stromal Cells for Traumatic Spinal Cord Injury: Multicell Comparison and Assessment of In Vivo Efficacy. Stem Cells Dev 2020;29:1429-43. doi: 10.1089/scd.2020.0079.
14. Dai G, Liu X, Zhang Z, Yang Z, Dai Y, Xu R. Transplantation of autologous bone marrow mesenchymal stem cells in the treatment of complete and chronic cervical spinal cord injury. Brain Res 2013;1533:73-9. doi: 10.1016/j.brainres.2013.08.016.
15. El-Kheir WA, Gabr H, Awad MR, Ghannam O, Barakat Y, Farghali

HA, et al. Autologous bone marrow-derived cell therapy combined with physical therapy induces functional improvement in chronic spinal cord injury patients. Cell Transplant 2014;23:729-45. doi: 10.3727/096368913X664540.

16. Richter MW, Fletcher PA, Liu J, Tetzlaff W, Roskams AJ. Lamina propria and olfactory bulb ensheathing cells exhibit differential integration and migration and promote differential axon sprouting in the lesioned spinal cord. J Neurosci 2005;25:10700-11. doi: 10.1523/JNEUROSCI.3632-05.2005.
17. Lu P, Yang H, Jones LL, Filbin MT, Tuszynski MH. Combinatorial therapy with neurotrophins and cAMP promotes axonal regeneration beyond sites of spinal cord injury. J Neurosci 2004;24:6402-9. doi: 10.1523/JNEUROSCI.1492-04.2004.
18. Filous AR, Silver J. "Targeting astrocytes in CNS injury and disease: A translational research approach". Prog Neurobiol 2016;144:173-87. doi: 10.1016/j.pneurobio.2016.03.009.
19. Murray KC, Nakae A, Stephens MJ, Rank M, D'Amico J, Harvey PJ, et al. Recovery of motoneuron and locomotor function after spinal cord injury depends on constitutive activity in 5-HT2C receptors. Nat Med 2010;16:694-700. doi: 10.1038/nm.2160.
20. Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature 2012;487:443-8. doi: 10.1038/nature11314.
21. Fischer I, Dulin JN, Lane MA. Transplanting neural progenitor cells to restore connectivity after spinal cord injury. Nat Rev Neurosci 2020;21:366-83. doi: 10.1038/s41583-020-0314-2.
22. Kadoya K, Lu P, Nguyen K, Lee-Kubli C, Kumamaru H, Yao L, et al. Spinal cord reconstitution with homologous neural grafts enables robust corticospinal regeneration. Nat Med 2016;22:479-87. doi: 10.1038/nm.4066.
23. Honmou O, Yamashita T, Morita T, Oshigiri T, Hirota R, Iyama S, et al. Intravenous infusion of auto serum-expanded autologous mesenchymal stem cells in spinal cord injury patients: 13 case series. Clin Neurol Neurosurg 2021;203:e106565. doi: 10.1016/j.clineuro.2021.106565.
24. Damianakis EI, Benetos IS, Evangelopoulos DS, Kotroni A, Vlamis J, Pneumaticos SG. Stem Cell Therapy for Spinal Cord Injury: A Review of Recent Clinical Trials. Cureus 2022;14:e24575. doi: 10.7759/cureus.24575.
25. Tashiro S, Nishimura S, Iwai H, Sugai K, Zhang L, Shinozaki M, et al. Functional Recovery from Neural Stem/Progenitor Cell Transplantation Combined with Treadmill Training in Mice with Chronic Spinal Cord Injury. Sci Rep 2016;6:30898. doi: 10.1038/srep30898.
26. Wall A, Borg J, Palmcrantz S. Clinical application of the Hybrid Assistive Limb (HAL) for gait training-a systematic review. Front Syst Neurosci 2015;9:e48. doi: 10.3389/fnsys.2015.00048.
27. Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nat Med 2018;24:1677-82. doi: 10.1038/s41591-018-0175-7.
28. Rejc E, Angeli CA, Ichiyama RM. Editorial: Advances in Spinal Cord Epidural Stimulation for Motor and Autonomic Functions Recovery After Severe Spinal Cord Injury. Front Syst Neurosci 2022;15:e820913. doi: 10.3389/fnsys.2021.820913.
29. Shinozaki M, Nagoshi N, Nakamura M, Okano H. Mechanisms of Stem Cell Therapy in Spinal Cord Injuries. Cells 2021;10:2676. doi: 10.3390/cells10102676.
30. Kathe C, Skinnider MA, Hutson TH, Regazzi N, Gautier M, Demesmaeker R, et al. The neurons that restore walking after paralysis. Nature 2022;611:540-7. doi: 10.1038/s41586-022-05385-7.