Please cite this article in press as: Yousefifard M et al. Neural stem/progenitor cell transplantation for spinal cord injury treatment; A systematic review and meta-analysis. Neuroscience (2016), http://dx.doi.org/10.1016/j.neuroscience.2016.02.034

Neuroscience xxx (2016) xxx–xxx

NEURAL STEM/PROGENITOR CELL TRANSPLANTATION FOR SPINAL CORD INJURY TREATMENT; A SYSTEMATIC REVIEW AND META-ANALYSIS

M. YOUSEFIFARD,[a] V. RAHIMI-MOVAGHAR,[b] F. NASIRINEZHAD,[c] M. BAIKPOUR,[d] S. SAFARI,[e] S. SAADAT,[b] A. M. JAFARI,[f] H. ASADY,[g] S. M. T. R. TOUSI[a] AND M. HOSSEINI[b,h,i]*

[a] *Department of Physiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[b] *Sina Trauma and Surgery Research Center, Tehran University Medical Sciences, Tehran, Iran*

[c] *Physiology Research Center, Department of Physiology, Iran University of Medical Sciences, Tehran, Iran*

[d] *Department of Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[e] *Department of Emergency Medicine, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[f] *Department of Emergency Medicine, School of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran*

[g] *Department of Occupational Health Engineering, Faculty of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

[h] *Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

[i] *Pediatric Chronic Kidney Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran*

Abstract—Despite the vast improvements of cell therapy in spinal cord injury treatment, no optimum protocol has been developed for application of neural stem/progenitor cells. In this regard, the present meta-analysis showed that the efficacy of the neural stem/progenitor cell (NSPC) transplantation depends mainly on injury model, intervention phase, transplanted cell count, immunosuppressive use, and probably stem cell source. Improved functional recovery post NSPC transplantation was found to be higher in transection and contusion models. Moreover, NSPC transplantation in acute phase of spinal injury was found to have better functional recovery. Higher doses ($> 3 \times 10^6$ cell/kg) were also shown to be optimum for transplantation, but immunosuppressive agent administration negatively affected the motor function recovery. Scaffold use in NSPC transplantation could also effectively raise functional recovery.

Key words: spinal cord injuries, neural stem cells, functional recovery, neuropathic pain.

INTRODUCTION

Spinal cord injury (SCI) which is one of the most dangerous nervous system disorders, commonly affects younger population, and causes persistent and long-term disabilities. Unfortunately, about 90% of the patients suffer from long-term motor dysfunctions and approximately 78% experience moderate to severe pain. SCI and its complications impose great direct and indirect financial burdens; the annual treatment cost for each patient is estimated to be 26,270 dollars (Mann et al., 2013).

SCI is regarded as one of the main causes of motor dysfunction and neuropathic pain. There is no cure for it and most of the therapeutic modalities are only symptomatic (Finnerup, 2012; Sharp et al., 2012; Kumru et al., 2013; Nasirinezhad et al., 2015b). Pharmacotherapy holds the base of current treatment with little influence on functional recovery with only 30–40% decrease in neuropathic pain symptoms (Finnerup et al., 2005; Backonja et al., 2006). Besides, numerous medication adverse side effects are the major obstacles for the long-term use (Marineo et al., 2012; Hosseini et al., 2014; Nasirinezhad et al., 2015a). Motor dysfunction and neuropathic pain will persist unless the injured region recovers or pain control pathways reinforce. However, neurogenesis rarely occurs in central nervous system and self-healing in injured cells is rather limited. Accordingly, researchers are investigating to find methods to improve cell restoration. Currently, cell transplantation is considered as an appropriate choice for treating SCIs. According to the recent studies, cell therapy can create new neural connections which would then lead to neuropathic pain alleviation and improved functional recovery (Guenot et al., 2007; Hama and Sagen, 2007).

Various cell populations can be used for SCI treatment. Survival and differentiation of the transplanted cells are mainly influenced by host-related factors as well as innate properties. For instance, having been injected in brain neurogenic regions, such as the hippocampus or sub-ventricular zones, neural stem/progenitor cells (NSPCs) exhibit acceptable differentiation (Sun et al., 2011); but when transplanted in other parts of the nervous system, low survival and differentiation are observed (Mark Richardson et al.,

*Correspondence to: M. Hosseini, Department of Epidemiology and Biostatistics School of Public Health, Tehran University of Medical Sciences, Poursina Avenue, Tehran, Iran. Tel: +98-2188989125; fax: +98-2188989127.
E-mail address: mhossein110@yahoo.com (M. Hosseini).
Abbreviations: NSPC, neural stem/progenitor cell; SCI, Spinal cord injury; SMD, standardized mean difference.

http://dx.doi.org/10.1016/j.neuroscience.2016.02.034
0306-4522/

2005). Based on these findings, one may conclude that *in vivo* transplanted cell outcome is determined by innate characteristics and transplantation location.

Studies have shown that NSPCs are subject to renewal and can produce main neural cell phenotypes (neurons, oligodendrocytes and astrocytes) after transplantation in injured spinal cord (Tarasenko et al., 2007). These cells can also modulate immune and inflammatory responses (Lee et al., 2008a; Bacigaluppi et al., 2009; Ottoboni et al., 2015). Hence, as proposed by many studies, NSPCs may be the best choice in transplantation treatment for physiologic repair of the lesion, functional recovery and neuropathic pain relief in patients with SCIs (Bottai et al., 2008; Abematsu et al., 2010; Amemori et al., 2013). On the other hand, some researchers believe that these cells are not significantly effective in spinal lesion treatment (Macias et al., 2006; Nutt et al., 2013). These discrepancies might be due to the differences in treatment protocols, number of transplanted cells, application of co-treatments, source of extracted cells, and etc. In this regard, a systematic review showed that no consensus has been reached on the optimal source of NSPCs and their application in various models of spinal cord injuries, severity of injuries, and treatment protocol (Tetzlaff et al., 2011).

So, there is no reliable and comprehensive review to judge whether NSPC transplantation is really a suitable therapeutic protocol for SCIs. Conceivably, a meta-analysis seems to be an appropriate alternative solution for this problem. Recently, few meta-analyses were performed on the subject but none evaluated neural stem cells. In the previous meta-analysis we showed that bone marrow-derived mesenchymal stem cell application improved mechanical allodynia but had no significant effects on hyperalgesia (Hosseini et al., 2015). Accordingly, this study aimed to conduct a systematic review and meta-analysis to assess the efficacy of NSPCs on functional recovery and neuropathic pain relief in animal models of SCI.

METHODS

Search strategy

Two independent reviewers carried out an extended search in electronic databases of Medline (via PubMed), EMBASE (via OvidSP), CENTRAL, SCOPUS, Web of Science (BIOSIS), and ProQuest finding papers published until the end of December, 2015. Search strategy was based on keywords related to ‘‘neural stem cells", ‘‘neural progenitor stem cell” and ‘‘neural precursor cell” in combination with terms related to ‘‘spinal cord injuries". The combined terms in two databases of Medline and EMBASE are presented in Panel 1. In order to prevent omission of related studies, keywords were chosen as extensive as possible. Keywords were extracted from Mesh, EMTREE, and via manual search in titles and abstracts of the articles.

Additionally, PubMed search was not limited to Medline. Archived articles in PubMed Central were also screened. In order to further include non-indexed reports, search was also conducted in Google search engine and Google Scholar. Two strategies were pursued to gather gray literature: (a) authors of related articles were contacted via email to ask for unpublished data or dissertations and unrecorded data, (b) ProQuest database was meticulously searched for related dissertations. In cases where the article was not available online, the author was contacted. If there were no answers, a reminder was sent to the author, one week later. In case of no reply, other authors of the article were contacted through social networks including ResearchGate and LinkedIn, asking for the data. Two studies were obtained using this method.

To find additional articles, hand-search was performed in the bibliographies of relevant studies which yielded inclusion of two more articles. Moreover, journal hand-searching was also carried out. To do so, gathered studies were entered the EndNote X7 software and a list of highly focused journals with the highest number of articles on the subjects of stem cell therapy, neuroscience and spine was provided. All issues of the selected journals were manually screened and three more articles added to this strategy.

Panel 1. Keywords used for search in MEDLINE and EMBASE databases

Database	Search terms
Medline (PubMed)	‘‘Neural stem cells”[MeSH] OR (Progenitor cell*[tiab] OR Neural progenitor stem cell*[tiab] OR Neural precursor cell*[tiab] OR Spinal cord stem cell*[tiab] OR Brain stem cell*[tiab] OR Brain derived stem cell*[tiab] OR Spinal derived stem cell*[tiab] OR Embryonic-derived neural stem cell*[tiab] OR Embryonic neural stem cel*l[tiab] OR Induced pluripotent stem cell*[tiab] OR NSC[tiab] OR NSPC[tiab]) AND ‘‘Spinal cord injuries”[MeSH] OR (Spinal cord contusion[tiab] OR Spinal cord transection [tiab] OR Injured spinal cord[tiab] OR Spinal Cord Traum*[tiab] OR Spinal cord Hemisection[tiab] OR Spinal compression [tiab] OR Traumatic Myelopath*[tiab] OR Spinal Cord Laceratio*[tiab] OR Post-Traumatic Myelopath*[tiab])
EMBASE (OvidSP)	exp Neural Stem Cells/ or (Neural Stem Cells or Progenitor cells or Neural progenitor stem cell or Neural precursor cell or Embryonic-derived neural stem cell or Embryonic neural stem cell or Induced pluripotent stem cell$ or NSC or NSPC).ti, ab. and exp Spinal cord injuries/ or (Spinal cord injur$ or Spinal cord contusion or Spinal cord transection or Injured spinal cord or Spinal Cord Traum$ or Spinal cord Hemisection or Spinal compression or Traumatic Myelopath$ or Spinal Cord Laceration or Post-Traumatic Myelopath $).ti,ab.

Inclusion criteria

In the present survey, all controlled studies evaluating neural stem cell effects on functional recovery and sensory improvement after SCIs were included. No