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

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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 ($>3\times10^6$ 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, 2013; 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., 2005).

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Abbreviations: NSPC, neural stem/progenitor cell; SCI, Spinal cord injury; SMD, standardized mean difference.

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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

temporal or linguistic restrictions were considered. Included studies were *in vivo* animal models (non-human), in which SCI was induced through compression, contusion, hemisection or transection models with no age, gender or phylum restrictions. A four-week gap during the follow up period was considered as exclusion criterion, since the minimum amount of time needed for the cell therapy effects on functional recovery and sensory improvement is three to four weeks. Surveys lacking control groups (sham, saline-treated or vehicle treated groups) were also excluded.

Quality assessment and data extraction

Duplicate articles were removed using EndNote software (version X7, Thomson Reuters, 2011). Two of the authors (M.Y and S.S) independently examined the titles and abstracts of the articles and screened potentially eligible studies. Then, study full-texts were investigated and surveys met with the inclusion criteria were selected. Data extraction performed by researchers blinded to the author, journal and organization of the studies. Data recorded in a checklist designed based on PRISMA statement guidelines (Moher et al., 2009). The data included: (i) animal characteristics (number, recipient species, gender, weight), (ii) SCI model details including injury model, severity and location, (iii) cell therapy protocol as time interval between injury and treatment, delivery route, antibiotics application and immunosuppressive agents use, transplanted cell count, (iv) graft type (allogeneic or xenogeneic), (v) extracted neural stem cells characteristics including donor species, embryonic or adult source, (vi) follow-up duration (vii) outcome (motor function and neuropathic pain symptoms), and (viii) probable biases. Reviewers' disagreements were discussed with a third reviewer and settled through mutual cooperation (93% agreement). For quality assessment, each study was assigned a score of good, fair or poor, based on a 19-item checklist recommendation of Antonic et al. (Antonic et al., 2013) and Hassannejad et al. (Hassannejad et al., 2015) studies.

Data synthesis

Outcomes assessed included functional recovery and neuropathic pain symptoms (allodynia and hyperalgesia). Data were recorded as mean and standard error. In case data were presented as charts, the data extraction method proposed by Sistrom and Mergo was utilized (Sistrom and Mergo, 2000). When outcomes were reported in multiple stages of the survey, only the last reported figures were included. If multiple reports were given for the same population, the study with the largest sample size and the longest follow-up period would be included. In non-extracted data studies, the author was contacted and asked for the required information.

Statistical analysis

Data were summarized and entered in the STATA 11.0 statistical software in mean and standard deviation formats. In case standard errors were presented, standard deviations were calculated according to the study sample size. For each individual comparison, based on Hedges' g, a standardized mean difference (SMD) was calculated with a confidence interval of 95% (95% CI) and then a pooled effect size was presented. Publication bias was examined through Egger's and Begg's tests and funnel plots drawing (Egger et al., 1997). Heterogeneity was assessed using Chi-squared and I^2 tests. A p value of 0.1 or less and an I^2 greater than 50% were considered as existence of heterogeneity. Fixed effect model was used for homogenous studies, and if the positive heterogeneity held, subgroup analysis was performed to determine its source. Random effects model was fitted for cases of unidentified heterogeneity source. Subgroup analysis was carried out based on animal gender, recipient species (mice, rat, and so), injury model (contusion, compression, hemisection, transection), location (cervical, thoracic, lumbar), and severity (moderate, severe), stem cell origin (brain, spine, other), intervention phase (acute, sub-acute, chronic), delivery route (intra spinal and so), graft type (allogeneic, xenogeneic), stem cell type (wild type NSPC; induced pluripotent stem cell-derived NSPC), number of transplanted cells, donor species (mice, rat, human, other), and age range (fetal, newborn, adult), co-treatment use, antibiotic, or immunosuppressive agents, observer neutrality, and follow-up period (less than 8 weeks, equal to, or more than 8 weeks). Eight weeks follow up was set based on the functional recovery duration in which plateau is being reached. It is worth mentioning that meta-analyses were carried out only if the data were reported by at least three studies.

RESULTS

Characteristics of the included studies

Search in electronic sources yielded 10,153 non-duplicated studies. Screening through titles and abstracts found 298 articles, 81 of which met the inclusion criteria. A total of 74 studies were included in the meta-analysis at last (Teng et al., 2002; Cummings et al., 2005; Hofstetter et al., 2005; Iwanami et al., 2005; Okada et al., 2005; Pallini et al., 2005; Karimi-Abdolrezaee et al., 2006, 2010; Macias et al., 2006; Ziv et al., 2006; Guo et al., 2007, 2012; Parr et al., 2007, 2008a,b; Tarasenko et al., 2007; Zhang et al., 2007; Bottai et al., 2008; Lowry et al., 2008; Pan et al., 2008; Hooshmand et al., 2009; Kumagai et al., 2009; Lee et al., 2009; Abematsu et al., 2010; Chen et al., 2010; Hu et al., 2010; Johnson et al., 2010; Salazar et al., 2010; Tsuji et al., 2010; Yamane et al., 2010; Du et al., 2011; Kim et al., 2011, 2012; Nori et al., 2011; Wang et al., 2011, 2014; Xu et al., 2011; Yasuda et al., 2011; Cheng et al., 2012; Cusimano et al., 2012; Fujimoto et al., 2012; Gu et al., 2012; Kobayashi et al., 2012; Lu et al., 2012, 2014; Amemori et al., 2013, 2015; He et al., 2013; Kumamaru et al., 2013; Luo et al., 2013; Nishimura et al., 2013; Nutt et al., 2013; Park et al., 2013; Piltti et al., 2013a,b; Sontag et al., 2013; van Gorp et al., 2013; Xia et al., 2013; Yang et al., 2013; Hong et al., 2014; Hwang et al., 2014; Iwasaki et al., 2014; Nemati et al., 2014; Ormond et al., 2014;

Sharp et al., 2014; Yuan et al., 2014; Iwai et al., 2015; Liu et al., 2015; Pomeshchik et al., 2015; Romanyuk et al., 2015; Salewski et al., 2015a,b; Yao et al., 2015; Yokota et al., 2015). Search flowchart and selection methods are presented in Fig. 1. These studies comprised 125 separate experiments whose data were included in the final analysis. In 60 studies, subject motor function was only evaluated (Cummings et al., 2005; Iwanami et al., 2005; Okada et al., 2005; Pallini et al., 2005; Ziv et al., 2006; Guo et al., 2007, 2012; Parr et al., 2007, 2008a,b; Tarasenko et al., 2007; Zhang et al., 2007; Bottai et al., 2008; Lowry et al., 2008; Pan et al., 2008; Hooshmand et al., 2009; Kumagai et al., 2009; Lee et al., 2009; Abematsu et al., 2010; Chen et al., 2010; Johnson et al., 2010; Tsuji et al., 2010; Yamane et al., 2010; Du et al., 2011; Kim et al., 2011, 2012; Nori et al., 2011; Wang et al., 2011, 2014; Xu et al., 2011; Yasuda et al., 2011; Cheng et al., 2012; Cusimano et al., 2012; Fujimoto et al., 2012; Gu et al., 2012; Kobayashi et al., 2012; Lu et al., 2012, 2014; Amemori et al., 2013, 2015; He et al., 2013; Kumamaru et al., 2013; Nishimura et al., 2013; Nutt et al., 2013; Park et al., 2013; Xia et al., 2013; Yang et al., 2013; Hong et al., 2014; Hwang et al., 2014; Iwasaki et al., 2014; Nemati et al., 2014; Ormond et al., 2014; Sharp et al., 2014; Yuan et al., 2014; Iwai et al., 2015; Liu et al., 2015; Pomeshchik et al., 2015; Romanyuk et al., 2015; Yokota et al., 2015; Salewski et al., 2015a) and in five just sensory status was assessed (Hu et al., 2010; Luo et al., 2013; Piltti et al., 2013a,b; Yao et al., 2015). These elements were both simultaneously assessed in 10 surveys (Teng et al., 2002; Hofstetter et al., 2005; Karimi-Abdolrezaee et al., 2006, 2010; Macias et al., 2006; Salazar et al., 2010; Sontag et al., 2013; van Gorp et al., 2013; Amemori et al., 2015; Salewski et al., 2015b). Characteristics of the included studies are presented in Table 1.

Gathered data from 2537 animals (1204 in control group and 1333 in the treatment group) were pooled and analyzed together. Evaluation was conducted on 101 female and 24 male experimental animals. Contusion model was the most commonly used SCI induction model performed on 68 experiments, followed by 24 transection, 15 clip compression, 14 hemisection, and four balloon compression experiments. Experiment-induced injuries were severe in half and moderate in the other half. Mean time interval between injury and treatment was 9.3 ± 11.3 days (ranged from 1 to 56 days). In 40 experiments transplantation was performed right after injury induction (acute phase), in 74 procedures were 3–10 days apart (sub-acute phase), and in 11 this gap was equal to or more than two weeks (chronic phase). Intra-spinal transplantation was carried out in 114 experiments. Graft type was allogeneic in 77 experiments. The number of transplanted cells ranged from 1×10^5 to 4×10^7 cells per kilograms of the animals' body weight. Quality assessment of the included studies is presented in Table 2.

Meta-analysis

Efficacy of neural stem cell transplantation on functional recovery. In literature review, 69 studies including

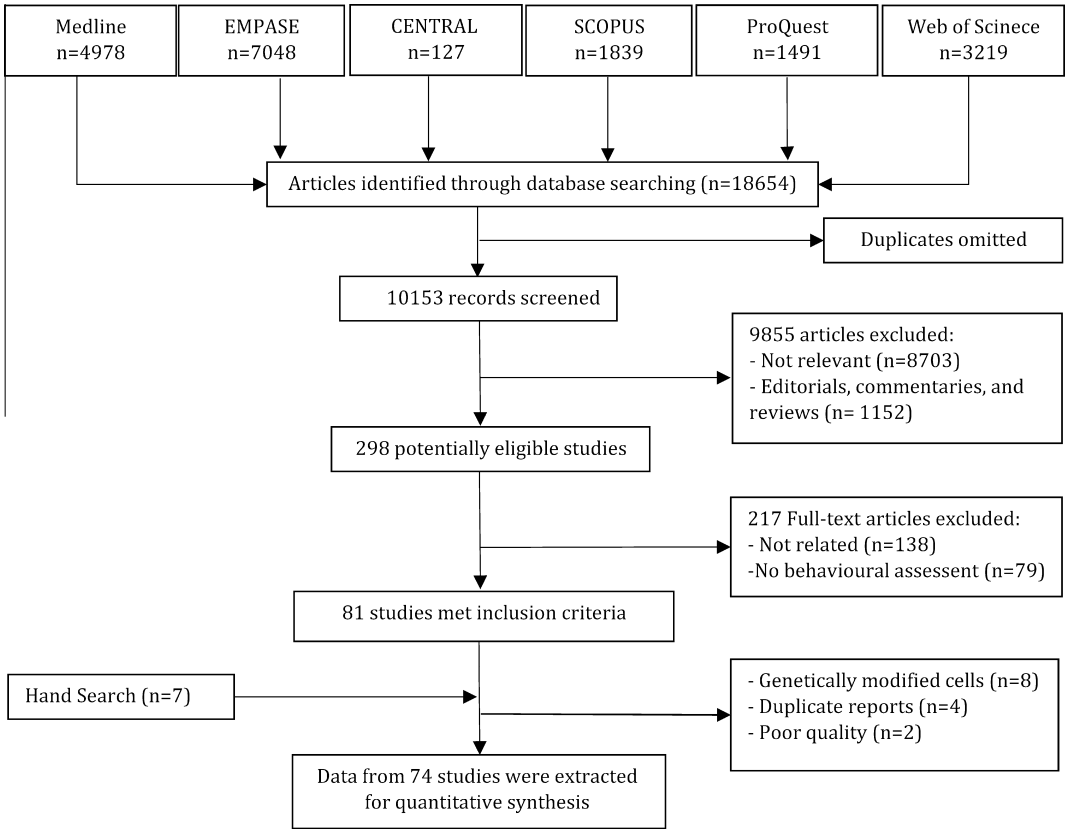

Fig. 1. Flowchart of including studies in the meta-analysis.

Table 1. Characteristics of included studies

Author, Year	Gender/Species/Weight (gr)	Model/Location of injury/Severity	Cell source/Donor/Graft/Dose/Type/Intervention time (day)	Immunosuppressive/ Antibiotic/Blinding	Follow up (week)
Abematsu et al., 2010	Male/Mice/37–45	Contusion/T9–T10/Severe	Brain/Fetus/Mice/IS/1 × 106/Allogeneic/7	Yes/Yes/Yes	8
Amemori et al., 2013	Male/Rat/270–300	Balloon compression/T8–T9/ Moderate	Spine/Fetus/Human/IS/5 × 105/Xenogeneic/7	Yes/Yes/Yes	8
Amemori et al., 2015	Male/Rat/270–300	Balloon compression/T8/Moderate	Lung/Fetus/Human/IS and IT/5 × 105/Xenogeneic/7	Yes/Yes/Yes	8
Bottai et al., 2008	Male/Mice/29–30	Contusion/T8/Moderate	Brain/Adult/Mice/IS/1 × 106/Allogeneic/1	No/No/Yes	8
Chen et al., 2010	Female/Rat/250–300	Hemisection/T9/Severe	Spine/Fetus/Rat/IS/2 × 105/Allogeneic/1	No/No/Yes	24
Cheng et al., 2012	Female/Rat/200–350	Contusion/T10/Moderate	Brain/Fetus/Human/IT/5 × 105/Xenogeneic/1	No/Yes/Yes	7
Cummings et al., 2005	Female/Mice/18–22	Contusion/T8/Moderate	Brain/Fetus/Human/IS/7.5 × 104/Xenogeneic/9	No/No/Yes	16
Cusimano et al., 2012	Male/Mice/20–22	Contusion/T11/Severe	Brain/Adult/Mice/IS/7.5 × 104 or 1.5 × 105/Allogeneic/7 or 21	No/Yes/Yes	8
Du et al., 2011	Female/Rat/220–250	Transection/T10/Severe	Brain/Newborn/Rat/IS/1.5 × 105/Allogeneic/1	No/Yes/Yes	8
Fujimoto et al., 2012	Female/Mice/18–20	Contusion/T10/Moderate	Skin fibroblast/Adult/Human/IS/5 × 105/Xenogeneic/7	No/Yes/Yes	9
Gu et al., 2012	Male/Rat/200–250	Transection/T10/Severe	Brain/Fetus/Mice/IS/2 × 104/Xenogeneic/1	No/No/No	4
Guo et al., 2007	Female/Rat/200–220	Transection/T9–T10/Severe	Brain/Newborn/Rat/IS/4 × 106/Allogeneic/1	No/Yes/No	8
Guo et al., 2012	Female/Rat/200–300	Transection/T8/Severe	Brain/Adult/Rat/IS/1.5 × 106/Allogeneic/1	Yes/Yes/Yes	12
He et al., 2013	Male/Rat/200–250	Transection/T10/Severe	Brain/Fetus/Mice/IS/3 × 105/Xenogeneic/1	No/No/Yes	4
Hofstetter et al., 2005	Female/Rat/250	Contusion/T8–T9/Moderate	Brain/Adult/Rat/IS/1 × 105/Allogeneic/7	No/No/Yes	9
Hong et al., 2014	Female/rat/230–250	Contusion/T8–T9/Moderate	Embryonic fibroblasts/Fetus/Mice/IS/1 × 106/ Xenogeneic/9	Yes/No/Yes	12
Hooshmand et al., 2009	Female/Mice/17–20	Contusion/T8/Moderate	Brain/Fetus/Human/IS/7.5 × 104/Xenogeneic/9	Yes/No/Yes	16
Hu et al., 2010	Female/Mice/20–22	Contusion/T8/Moderate	Whisker follicle/Adult/Mice/IS/1.4 × 105/Allogeneic/1	No/No/No	4
Hwang et al., 2014	Male/Rat/250–300	Contusion/T9/Severe	Spine/Fetus/Rat/IS/1 × 105/Allogeneic/7	No/No/Yes	7
Iwai et al., 2015	Female/Marmoset/300–350	Contusion/C5/Severe	Brain/Fetus/Marmoset/IS/1 × 106/Allogeneic/14	Yes/Yes/No	12
Iwanami et al., 2005	Female/Marmoset/280–350	Contusion/C5/Severe	Brain/Fetus/Human/IS/1 × 106/Xenogeneic/9	Yes/Yes/No	8
Iwasaki et al., 2014	Female/Rat/250	Compression/C6–C7/Moderate	Brain/Adult/Mice/IS/4 × 105/Xenogeneic/14	Yes/Yes/Yes	10
Johnson et al., 2010	Female/Rat/250–275	Hemisection/T9/Severe	Brain/Fetus/Mice/IS/1 × 105/Xenogeneic/14	Yes/Yes/Yes	8
Karimi-Abdolrezaee et al., 2010	Female/Rat/250	Compression/T7/Moderate	Brain/Adult/Mice/IS/4 × 105/Xenogeneic/49	Yes/Yes/Yes	9
Karimi-Abdolrezaee et al., 2006	Female/Rat/250	Compression/T6–T8/Moderate	Brain/Adult/Mice/IS/3–4 × 105/Xenogeneic/14	Yes/No/Yes	6
Kim et al., 2011	Female/Rat/250–300	Transection/T8/Severe	Brain/Adult/Rat/IS/2.5 × 105/Allogeneic/1	Yes/No/Yes	6
Kim et al., 2012	Male/Rat/250	Compression/T9/Moderate	Brain/Fetus/Mice/IS/3 × 105/Xenogeneic/1	Yes/No/Yes	6
Kobayashi et al., 2012	Female/Marmoset/300	Contusion/C5/Severe	Skin fibroblast/Adult/Human/IS/1 × 106/Xenogeneic/9	Yes/Yes/Yes	11
Kumagai et al., 2009	Female/Mice/20–22	Contusion/T10/Moderate	Brain/Fetus/Mice/IS/5 × 105/Allogeneic/9	No/No/Yes	6
Kumamaru et al., 2013	Female/Mice/20–30	Contusion/T10/Moderate	Spine/Fetus/Mice/IS/5 × 105/Allogeneic/1 or 7 or 13	No/No/Yes	6
Lee et al., 2009	/ dogs/25,000–32,000	Hemisection/L2/Severe	Brain/Fetus/Human/IS/1 × 107/Xenogeneic/1	No/Yes/Yes	12
Liu et al., 2015	Female/Rat/220–250	Transection/T10/Severe	Embryonic fibroblast/ Fetus/Mice/IS/1 × 106/ Xenogeneic/1	Yes/Yes/Yes	10
Lowry et al., 2008	Female/Mice/10_12	Hemisection/T8–T9/Severe	Spine/Fetus/Mice/IS/1 × 105/Allogeneic/1	No/No/Yes	4
Lu et al., 2012	Female/Rat/160–200	Transection/T3/Severe	Spine/Fetus/Rat and Human/IS/1.4 × 106/Xenogeneic/7 and 14	No/No/Yes	6
Lu et al., 2014	Female/Rat/160–200	Hemisection/C5/Severe	Skin/Adult/Human/IS/1.4 × 106/Xenogeneic/14	No/No/Yes	12
Luo et al., 2013	Female/Rat/180–250	Transection/T7–T9/Severe	Brain/Adult/Rat/IS/3 × 105/Allogeneic/1	Yes/Yes/Yes	4

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Table 1 (*continued*)

Author, Year	Gender/Species/Weight (gr)	Model/Location of injury/Severity	Cell source/Donor/Graft/Dose/Type/Intervention time (day)	Immunosuppressive/ Antibiotic/Blinding	Follow up (week)
Macias et al., 2006	Female/Rat/200–250	Contusion/T8/Moderate	Brain/Newborn/Mice/IS/1 × 105/Xenogeneic/8	Yes/Yes/Yes	4
Nemati et al., 2014	Male/monkeys/3000–6000	Contusion/T9–T10/Moderate	Brain/Adult/Monkey/IS/3–6 × 106/Allogeneic/10	Yes/Yes/Yes	26
Nishimura et al., 2013	Female/Mice/18–22	Contusion/T10/Moderate	Brain/Fetus/Mice/IS/5 × 105/Allogeneic/9 or 42	No/No/Yes	6
Nori et al., 2011	Female/mice/20–22	Contusion/T10/Moderate	Skin fibroblast/Adult/Human/IS/5 × 105/Xenogeneic/9	No/No/Yes	7
Nutt et al., 2013	Female/Rat/180–230	Contusion/C4/Moderate	Lung/Adult/Human/IS/2 × 105/Xenogeneic/28	Yes/No/Yes	8
Okada et al., 2005	Female/Mice/20–22	Contusion/T10/Moderate	Brain/Fetus/Mice/IS/5 × 105/Allogeneic/1 or 7	No/No/No	6
Ormond et al., 2014	Female/Rat/200–250	Contusion/T9–T10/Moderate or Severe	Brain/Adult/Rat/IS/1 × 106/Allogeneic/7	No/No/Yes	5
Pallini et al., 2005	Female/Mice/27–30	Transection/T7–T8/Severe	Brain/Fetus/Mice/IS/1 × 105/Allogeneic/1	No/No/No	12
Pan et al., 2008	Female/Rat/250–300	Transection/T8–T9/Severe	Brain/Fetus/Rat/IS/5 × 106/Allogeneic/1	No/Yes/Yes	12
Park et al., 2013	Female/Rat/250–300	Contusion/T10/Moderate	Brain/Fetus/Human/IS/5 × 105/Xenogeneic/7	No/No/Yes	6
Parr et al., 2008a	Female/Rat/250–300	Compression/T8–T9/Moderate	Brain/Adult/Rat/IS/2 × 105 or 1.25 × 105/Allogeneic/9	Yes/No/Yes	14
Parr et al., 2008b	Female/Rat/250–300	Compression/T8–T9/Moderate	Brain/Adult/Rat/IS/2 × 105 or 1.25 × 105/Allogeneic/9	Yes/No/Yes	12
Parr et al., 2007	Female/Rat/250–300	Compression/T8–T9/Moderate	Spine/Adult/Rat/IS/1 × 105/Allogeneic/1	Yes/No/Yes	16
Piltti et al., 2013a	Female/Rat/180–200	Contusion/T9/Severe	Brain/Fetus/Human/IS/2 × 105/Xenogeneic/9	Yes/Yes/Yes	13
Piltti et al., 2013b	Female/Rat/180–200	Contusion/T9/Severe	Brain/Fetus/Human/IS/2 × 105/Xenogeneic/9	Yes/Yes/Yes	13
Pomeshchik et al., 2015	Female/Mice/18–23	Contusion/T10/Moderate	Skin/Adult/Human/IS/4 × 105/Xenogeneic/7	Yes/No/Yes	5
Romanyuk et al., 2015	Male/Rat/270–300	Balloon compression/T8–T9/ Moderate	Lung/Fetus/Human/IS/5 × 105/Xenogeneic/7	Yes/Yes/Yes	8
Salazar et al., 2010	Female/Mice/15–20	Contusion/T9/Moderate	Brain/Fetus/Human/IS/7.5 × 104/Xenogeneic/30	No/Yes/Yes	16
Salewski et al., 2015a	Female/Mice/15–20	Compression/T6–T8/Moderate	Brain/Fetus/Human/IS/2 × 105/Allogeneic/7	Yes/No/Yes	8
Salewski et al., 2015b	Female/Mice/15–20	Compression/T6–T8/Moderate	Embryonic fibroblast/Fetus/Human/IS/2 × 105/ Allogeneic/7	Yes/No/Yes	8
Sharp et al., 2014	Female/Rat/145–160	Transection/T3/Severe	Brain/Fetus/Rat/IS/1.5 × 106/Allogeneic/14	No/Yes/Yes	7
Sontag et al., 2013	Female/m/20–25	Contusion/T9/Moderate	Brain/Fetus/Human/IS/7.5 × 105/Xenogeneic/9	Yes/No/Yes	10
Tarasenko et al., 2007	Male/Rat/230–340	Contusion/T10/Moderate	Brain/Fetus/Human/IS/1 × 105/Xenogeneic/9	Yes/Yes/Yes	12
Teng et al., 2002	Female/Rat/280–330	Hemisection/T9–T10/Severe	Brain/Newborn/Murine/IS/1 × 105/Xenogeneic/1	No/No/Yes	10
Tsuji et al., 2010	Female/Mice/20–22	Contusion/T10/Moderate	Embryonic stem cell/Fetus/Mice/IS/5 × 105/Allogeneic/9	No/No/Yes	5
van Gorp et al., 2013	Female/Rat/200–250	Compression/L3/Moderate	Spine/Fetus/Human/IS/1.2 × 105/Xenogeneic/3	Yes/Yes/Yes	8
Wang et al., 2014	Female/Rat/220–250	Transection/T10/Severe	Brain/Fetus/Rat/IS/1 × 106/Allogeneic/1	No/Yes/Yes	4
Wang et al., 2011	Female/Rat/220–250	Transection/T10/Severe	Brain/newborn/Rat/IS/1 × 106/Allogeneic/1	No/Yes/Yes	8
Xia et al., 2013	Female/Rat/200–300	Hemisection/T8/Severe	Spine/Fetus/Rat/IS/5 × 105/Allogeneic/1	No/Yes/Yes	24
Xu et al., 2011	Female/Rat/200	Contusion/T9/Moderate	Brain/Fetus/Rat/IS/5 × 105/Allogeneic/56	No/Yes/Yes	8
Yamane et al., 2010	Female/Marmoset/280–350	Contusion/C5/Moderate	Brain/Fetus/Human/IS/1 × 106/Xenogeneic/9	Yes/Yes/Yes	12
Yang et al., 2013	Male/Rat/300–350	Contusion/T9–T10/Moderate	Brain/Fetus/Porcine/IS/1 × 105/Xenogeneic/7	No/No/No	24
Yao et al., 2015	Male/Rat/200–220	Transection/T10/Severe	Brain/Fetus/Mice/IS/3 × 106/Xenogeneic/1	No/Yes/No	5
Yasuda et al., 2011	Female/Mice/20–22	Contusion/T10/Moderate	Brain/Fetus/Mice/IS/5 × 105/Allogeneic/9	No/No/Yes	6
Yokota et al., 2015	Female/Mice/20–22	Contusion/T8/Moderate or Severe	Brain/Fetus/Mice/IS/5 × 105/Allogeneic/9	No/No/No	6
Yuan et al., 2014	Female/Rat/250–300	Hemisection/T9–T10/Severe	Brain/Newborn/Mice/IS/1 × 107/Allogeneic/1	No/No/No	4
Zhang et al., 2007	Female/Rat/200–250	Transection/T10/Severe	Brain/Newborn/Rat/IS/1 × 106/Allogeneic/1	No/Yes/No	8
Ziv et al., 2006	Female/Mice/20–22	Contusion/T12/Severe	Brain/Fetus/Mice/ICV/5 × 105/Allogeneic/7	No/No/Yes	4

IS: intra-spinal; IT: intrathecal; ICV: intra cerebroventricular; T: thoracic level of spinal cord; C: cervical level spinal cord; L: lumbar level of spinal cord.

118 experiments had evaluated the efficacy of NSPC transplantation on functional recovery of subjects after SCI (Cummings et al., 2005; Iwanami et al., 2005; Okada et al., 2005; Pallini et al., 2005; Ziv et al., 2006; Guo et al., 2007, 2012; Parr et al., 2007, 2008a,b; Tarasenko et al., 2007; Zhang et al., 2007; Bottai et al., 2008; Lowry et al., 2008; Pan et al., 2008; Hooshmand et al., 2009; Kumagai et al., 2009; Lee et al., 2009; Abematsu et al., 2010; Chen et al., 2010; Johnson et al., 2010; Tsuji et al., 2010; Yamane et al., 2010; Du et al., 2011; Kim et al., 2011, 2012; Nori et al., 2011; Wang et al., 2011, 2014; Xu et al., 2011; Yasuda et al., 2011; Cheng et al., 2012; Cusimano et al., 2012; Fujimoto et al., 2012; Gu et al., 2012; Kobayashi et al., 2012; Lu et al., 2012, 2014; Amemori et al., 2013, 2015; He et al., 2013; Kumamaru et al., 2013; Nishimura et al., 2013; Nutt et al., 2013; Park et al., 2013; Xia et al., 2013; Yang et al., 2013; Hong et al., 2014; Hwang et al., 2014; Iwasaki et al., 2014; Nemati et al., 2014; Ormond et al., 2014; Sharp et al., 2014; Yuan et al., 2014; Iwai et al., 2015; Liu et al., 2015; Pomeshchik et al., 2015; Romanyuk et al., 2015; Yokota et al., 2015; Salewski et al., 2015a). Findings of this section are presented in Fig. 2. Transplantation of these cells significantly improved restoration of motor function in the subjects (Pooled SMD = 1.45; 95% CI: 1.23–1.67; $p < 0.001$; $I^2 = 81.0\%$). Publication bias was not observed in this part of the study (Coefficient = 1.30; 95% CI: −0.49 to 3.09; $p = 0.15$). Due to a considerable heterogeneity ($I^2 = 81.1\%$; $p < 0.001$), subgroup analysis was performed. According to the findings presented in Table 3, injury model, intervention phase, transplanted cells numbers, and immunosuppressive administration were found to be the main sources of heterogeneity. Cell efficacy considerably dropped (SMD = 0.58; 95% CI: 0.16–0.99) when cells were used in clip compression induced SCIs model compared to transection (SMD = 2.18; 95% CI: 1.45–2.93) model. Moreover, this treatment improved motor function recovery to a greater extent when cells were transplanted in acute (SMD = 1.80; 95% CI: 1.36–2.24) or sub-acute (SMD = 1.38; 95% CI: 1.08–1.67) phases compared to the chronic phase (SMD = 1.04; 95% CI: 0.47–1.60) ($p = 0.03$). Findings also showed better functional recovery where more than 3×10^6 cell dose/kg was transplanted (SMD = 1.74; 95% CI: 1.43–2.05) compared lower doses injection (SMD = 0.94; 95% CI: 0.67–1.22). Immunosuppressive administration provoked significantly lower efficacies (SMD = 0.87; 95% CI: 0.57–1.17).

In addition, co-treatment with growth factors (SMD = 0.93; 95% CI: −0.22 to 2.08) and Schwann cells or bone marrow-derived mesenchymal cells (SMD = 1.21; 95% CI: −0.24 to 2.65) hindered neural stem cells effects, while scaffold application (SMD = 2.19; 95% CI: 1.30–2.07) improved cells efficacy. Motor function recovery was also found to be lower when cells were transplanted in cervical injuries (SMD = 0.54; 95% CI: 0.05–1.03) compared to thoracic injuries (SMD = 1.52; 95% CI: 1.28–1.75). Finally, wild-type NSPC transplantation (SMD = 1.41; 95% CI: 1.18–1.64) and induced pluripotent stem cell-derived (iPSc-derived) NSPC (SMD = 1.64; 95% CI: 0.83–2.45) had similar effects on motor function recovery.

Efficacy of neural stem cell transplantation on sensory status. Allodynia. Nine studies (Hofstetter et al., 2005; Macias et al., 2006; Hu et al., 2010; Karimi-Abdolrezaee et al., 2010; Salazar et al., 2010; Piltti et al., 2013a,b; Sontag et al., 2013; Salewski et al., 2015b) including 11 experiments evaluated NSPCs efficacy on allodynia among the subjects (Fig. 3). NSPC transplantation had no significant effect on allodynia (Pooled SMD = 0.08; 95% CI: −0.33 to 0.49; $p = 0.69$; $I^2 = 58.4\%$). Study heterogeneity persuaded us to conduct subgroup analysis in this section as well. Since in all these surveys female mice were also included and intrathoracic spinal transplantation was performed, these factors were excluded from the subgroup analyses. As presented in Table 4, none of the evaluated factors significantly influenced NSPCs efficacy on allodynia.

Hyperalgesia. Eleven surveys (Teng et al., 2002; Hofstetter et al., 2005; Macias et al., 2006; Karimi-Abdolrezaee et al., 2010; Luo et al., 2013; Piltti et al., 2013a,b; van Gorp et al., 2013; Amemori et al., 2015; Salewski et al., 2015b; Yao et al., 2015) including 16 experiments examined NSPC efficacy of on hyperalgesia (Fig. 3). Pooled analysis demonstrated that NSPC transplantation had no significant effect on hyperalgesia (Pooled SMD = 0.25; 95% CI: −0.10 to 0.60; $p = 0.16$; $I^2 = 64.4\%$). However, subgroup analysis showed improved hyperalgesia to some extent when NSPCs were extracted from mice (SMD = 0.33; 95% CI: 0.02–0.67) rather than rats (SMD = −0.18; 95% CI: −0.56 to 0.21) or human (SMD = 0.37; 95% CI: −0.48 to 1.17). Transplantation of more than 3×10^6 cell dose/kg (SMD = 0.37; 95% CI: −0.02 to 0.77) in the first day after injury induction (SMD = 0.33; 95% CI: −0.02 to 0.24) slightly improved hyperalgesia as well. Findings are presented in Table 5.

DISCUSSION

The present study, for the first time, designed to review the data gathered from animal models evaluating of NSPC transplantation efficacy on functional recovery and neuropathic pain relief in SCI through a quantitative approach. Findings confirmed that NSPC transplantation could significantly improve motor function recovery in the studied animals. NSPC efficacy was affected by the injury model (compression, contusion, hemisection, and transection), intervention phase, transplanted cell number, and immunosuppressive administration. Scaffold use with transplanted NSPCs could also boost transplantation efficacy. In addition, mice-derived NSPCs were found to be considerably more effective for hyperalgesia alleviation than rat or human origin cells. Transplanted cell numbers and intervention phase were also reported to affect hyperalgesia improvement. Allodynia, on the other hand, was not affected by NSPC transplantation.

Reviews, on the other hand, have been reported improvement in NSPC implantation efficacy on motor

Table 2. Quality assessment of included studies

Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Abematsu et al., 2010	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Amemori et al., 2013	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Amemori et al., 2015	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Bottai et al., 2008	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	
Chen et al., 2010	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Cheng et al., 2012	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	
Cummings et al., 2005			✓	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓		
Cusimano et al., 2012	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	
Du et al., 2011	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Fujimoto et al., 2012	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Gu et al., 2012	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓		✓	
Guo et al., 2007	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓		✓	
Guo et al., 2012	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
He et al., 2013	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	
Hofstetter et al., 2005	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓			✓	✓	✓	✓
Hong et al., 2014	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	
Hooshmand et al., 2009	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hu et al., 2010	✓		✓	✓	✓	✓			✓	✓			✓			✓		✓	✓
Hwang et al., 2014			✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Iwai et al., 2015	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓		✓	✓
Iwanami et al., 2005	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓		✓	
Iwasaki et al., 2014	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Johnson et al., 2010	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	
Karimi-Abdolrezaee et al., 2010	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Karimi-Abdolrezaee et al., 2006	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Kim et al., 2011	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓		✓	✓
Kim et al., 2012	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓
Kobayashi, 2012	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓		✓	✓
Kumagai et al., 2009	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓
Kumamaru et al., 2013	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓
Lee et al., 2009	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓		✓	
Liu et al., 2015	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Lowry et al., 2008	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓
Lu et al., 2012	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓
Lu et al., 2014	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓
Luo et al., 2013	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Macias et al., 2006	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Nemati et al., 2014	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Nishimura et al., 2013	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓
Nori et al., 2011	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓		✓	✓	✓	✓	✓
Nutt et al., 2013	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	
Okada et al., 2005	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓		✓	
Ormond et al., 2014	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Pallini et al., 2005	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓		✓	
Pan et al., 2008	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	
Park et al., 2013	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓	
Parr et al., 2008a	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓		✓	✓	✓	✓	
Parr et al., 2008b	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	
Parr et al., 2007	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	
Piltti et al., 2013a	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Piltti et al., 2013b	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pomeshchik et al., 2015	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Romanyuk et al., 2015	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Salazar et al., 2010	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Salewski et al., 2015a	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Salewski et al., 2015b	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓			✓	✓	✓	✓
Sharp et al., 2014	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Sontag et al., 2013	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Tarasenko et al., 2007	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Teng et al., 2002	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Tsuji et al., 2010	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓		✓	✓
van Gorp et al., 2013	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Wang et al., 2014	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓

Table 2 (*continued*)

Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Wang et al., 2011	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Xia et al., 2013	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Xu et al., 2011	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Yamane et al., 2010	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓		✓	
Yang et al., 2013	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Yao et al., 2015	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Yasuda, 2011	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Yokota et al., 2015	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓		✓	✓
Yuan et al., 2014	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓		✓	✓
Zhang et al., 2007	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓		✓	
Ziv et al., 2006	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓			✓	✓	✓	✓

1. Compliance with animal welfare regulations; 2. Statement describing control of temperature; 3. Publication in a peer-reviewed journal; 4. Description of anima; species; 5. Designation of strain; 6. Number of animals per group; 7. Sample size calculation; 8. Present of animals' age/weight; 9. Description of level of Injury; 10. Severity of Injury 11. Randomly assigning animals to a specific group; 12. Allocation concealment 13. Description of the control groups; 14. Bladder expression; 15. Description of the reasons to exclude animals from the experiment during the study (attrition); 16. Use of appropriate tests to prove hypothesis; 17. Blindness of assessor; 18. Description of statistical analysis; 19. Statement of any potential conflict of interest.

function recovery too. For instance, Tetzlaff et al. also reported that most surveys have verified the positive effects of NSPC transplantation on motor function outcomes of the evaluated animals. However, they did not find the optimal source of NSPCs for this purpose (Tetzlaff et al., 2011). In this regard, we performed subgroup analysis based on donor species and NSPC embryonic or adult source. No significant differences were observed between embryonic and adult NSPC effects on motor function recovery, or neuropathic pain relief. Mothe and Tator found relative improvements of motor function recovery in response to NSPC transplantation (Mothe and Tator, 2013).

Although, NSPCs are suitable sources for SCI alleviation, ethical issues on fetal human origin tissues and lack of autologous cell sources have limited their uses (Mothe and Tator, 2013). Therefore, adult tissue-derived NSPCs may be used for SCI treatment. In recent years, alternative sources were introduced for NSPC derivation. IPSC-derived NSPCs originated from reprogramed somatic cells provide an autologous source for NSPCs without ethical concerns. In spite of experimental studies with improved motor function recovery post iPSC-derived NSPC transplantation in SCI cases, some studies depicted no significant effect. The present meta-analysis showed that both wild-type and iPSC-derived NSPCs could drastically improve motor function recovery. Previous studies demonstrated that iPSC-derived NSPCs provide therapeutic benefits via the same mechanisms as wild-type or embryonic stem cell-derived NPSCs (Lu et al., 2012). Transplantation of iPSC-derived NSPCs could improve myelin repair, axon regeneration, and neurotropic factors secretion while reduced secondary inflammatory responses, (Nori et al., 2011; Fujimoto et al., 2012; Nutt et al., 2013; Romanyuk et al., 2015). Therefore, similar efficacy of the two mentioned sources of stem cells in motor function recovery was not unexpected. Including seven studies in their systematic review, Lee-Kubli and Lu demonstrated promising survival, differentiation and therapeutic effect of iPSC-derived NSPC transplantation after SCI. However, they stated that ideal iPSC reprograming and differentiation remain unclear and need further investigation (Lee-Kubli and Lu, 2015). Our results have reached to the conclusion as Lee-Kubli and Lu study.

We included 12 studies in which iPSC-derived NSPCs provoked a great efficacy differences in motor function recovery (Tsuji et al., 2010; Nori et al., 2011; Fujimoto et al., 2012; Nutt et al., 2013; Hong et al., 2014; Lu et al., 2014; Amemori et al., 2015; Liu et al., 2015; Pomeshchik et al., 2015; Romanyuk et al., 2015; Salewski et al., 2015b). One plausible reason for such heterogeneity may be rooted in the age of somatic cell donor (embryonic or adult). Therefore, we performed more specific analyses, based on the iPSC embryonic or adult somatic source. In this context, results showed that efficacy of embryonic-derived iPSCs (SMD = 1.89; 95% CI: 0.93–2.84) was considerably higher than those with adult somatic source (SMD = 0.79; 95% CI: 0.32–1.25). The difference may be due to adult somatic tissue-derived iPSCs characteristics i.e., the cells displayed significant resistance to differentiation (Tsuji et al., 2011). Mothe and Tator, stated that adult human NSPCs were difficult to expand for sufficient cell transplantation. They also added that iPSCs could trigger T-cell induced immune response in syngeneic recipients (Mothe and Tator, 2013). Moreover, adult tissue-derived iPSCs were not as safe as embryonic-derived clones which, could form teratoma in SCI implantation (Tsuji et al., 2011). However, our current knowledge regarding iPSC-derived NSPC tumorigenicity, safety, and alternative reprograming is still insufficient.

Motor function recovery post NSPC transplantation is generally affected by intervention phase. Findings revealed that a shorter time gap between injury induction and transplantation could improve the efficiency of the treatment. Accordingly, transplantation during acute and sub-acute phases is associated with better results compared to chronic phase. This might be due to the partial irreversible nature of the injuries in chronic phase (Oyinbo, 2011). Similar efficacy of the acute and sub-acute phases has been the notable finding among the studies. This is incongruent with the current assumption, since acute phase inflammatory responses

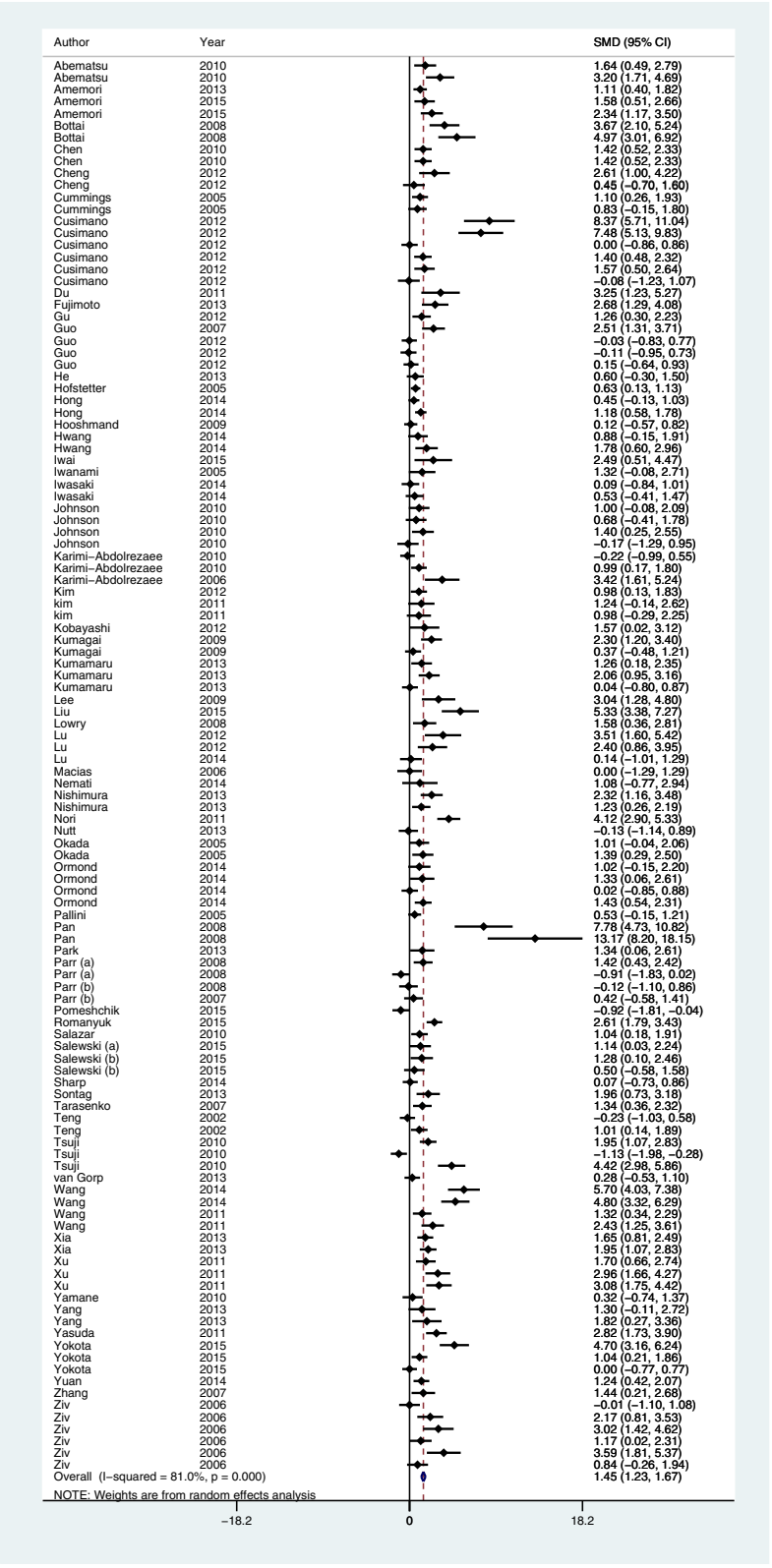

Fig. 2. Efficacy of neural stem/progenitor cells transplantation on motor function recovery after spinal cord injury. This method significantly improved functional recovery.

creates a cytotoxic environment, which is incompatible with the NSPC survival and differentiation and focuses on better results of the cell therapy in sub-acute phase than acute and chronic phases (Mothe and Tator, 2013). The present study showed that treatment in the acute phase had even slightly higher efficacy than sub-

Table 3. Subgroup analyses of the effect of neural stem/progenitor cells on functional recovery

Characteristic	*P* for bias[a]	Model	*P* (I^2)[b]	Effect size [c] (95% CI)	*P*
Gender					
Male	0.93	REM	< 0.001 (80.3%)	1.91 (1.37–2.45)	< 0.001
Female	0.43	REM	< 0.001 (80.9%)	1.35 (1.10–1.56)	< 0.001
			Overall significance test among subgroups		0.14
Recipient species					
Mice	0.05	REM	< 0.001 (85.1%)	1.68 (1.27–2.09)	< 0.001
Rat	0.17	REM	< 0.001 (78.9%)	1.30 (1.03–1.58)	< 0.001
Other	0.45	FEM	0.12 (42.3%)	1.48 (0.64–2.31)	< 0.001
			Overall significance test among subgroups		0.42
Injury model					
Contusion	0.92	REM	< 0.001 (81.7%)	1.54 (1.23–1.86)	< 0.001
Clip compression	0.44	REM	0.001 (61.4%)	0.58 (0.16–0.99)	0.007
Balloon compression	0.31	REM	0.04 (63.9%)	1.88 (1.11–2.64)	< 0.001
Hemisection	0.49	REM	0.004 (57.4%)	1.10 (0.69–1.51)	< 0.001
Transection	0.44	REM	< 0.001 (88.1%)	2.18 (1.45–2.93)	< 0.001
			Overall significance test among subgroups		**0.045**
Location of injury					
Cervical	0.13	FEM	0.20 (28.3%)	0.54 (0.05–1.03)	0.03
Thoracic	0.52	REM	< 0.001 (81.9%)	1.52 (1.28–1.75)	< 0.001
Lumbar	NA	NA	NA	NA	NA
			Overall significance test among subgroups		**0.054**
Severity of injury					
Mild	NA	NA	NA	NA	NA
Moderate	0.61	REM	< 0.001 (80.0%)	1.28 (0.99–1.57)	< 0.001
Severe	0.59	REM	< 0.001 (82.5%)	1.70 (1.33–2.06)	< 0.001
			Overall significance test among subgroups		0.17
Stem cells derivation origin					
Brain	0.65	REM	< 0.001 (81.7%)	1.50 (1.24–1.77)	< 0.001
Spine	0.06	REM	< 0.001 (71.1%)	1.51 (1.03–1.98)	< 0.001
Other	0.81	REM	< 0.001 (89.6%)	1.64 (0.83–2.45)	< 0.001
			Overall significance test among subgroups		0.39
Cell type					
wt-NSPCs	0.74	REM	< 0.001 (78.5%)	1.41 (1.18–1.64)	< 0.001
iPSC-NSPCs	0.81	REM	< 0.001 (89.6%)	1.64 (0.83–2.45)	< 0.001
			Overall significance test among subgroups		0.75
Intervention phase[d]					
Acute	0.20	REM	< 0.001 (82.8%)	1.80 (1.36–2.24)	< 0.001
Subacute	0.79	REM	< 0.001 (83.2%)	1.38 (1.08–1.67)	< 0.001
Chronic	0.90	REM	< 0.001 (75.1%)	1.04 (0.47–1.60)	< 0.001
			Overall significance test among subgroups		**0.044**
Delivery route					
Intra spinal	0.65	REM	< 0.001 (81.5%)	1.42 (1.19–1.66)	< 0.001
Other	0.92	REM	< 0.001 (74.9%)	1.88 (1.04–2.71)	< 0.001
			Overall significance test among subgroups		0.43
Graft type					
Allogeneic	0.35	REM	< 0.001 (83.3%)	1.66 (1.35–1.97)	< 0.001
Xenogeneic	0.02	REM	< 0.001 (75.1%)	1.13 (0.81–1.44)	< 0.001
			Overall significance test among subgroups		0.10
Number of transplanted cells					
$< 3 \times 10^6$ cell dose/kg	0.92	REM	< 0.001 (64.5%)	0.94 (0.67–1.22)	< 0.001
$\geqslant 3 \times 10^6$ cell dose/kg	0.13	REM	< 0.001 (84.3%)	1.74 (1.43–2.05)	< 0.001
		‘	*Overall significance test among subgroups*		**0.02**
Donor species					
Mice	0.54	REM	< 0.001 (83.1%)	1.48 (1.13–1.83)	< 0.001
Rat	0.06	REM	< 0.001 (83.3%)	1.53 (1.10–1.97)	< 0.001
Human	0.39	REM	< 0.001 (76.5%)	1.33 (0.89–1.76)	< 0.001
Other	0.73	FEM	0.72 (0.0%)	1.61 (0.79–2.44)	< 0.001
			Overall significance test among subgroups		0.82

(*continued on next page*)

Table 3 (*continued*)

Characteristic	*P* for bias[a]	Model	*P* (I^2)[b]	Effect size [c] (95% CI)	*P*
Donor age					
Fetal	0.37	REM	< 0.001 (78.7%)	1.60 (1.33–1.87)	< 0.001
Newborn	> 0.99	REM	< 0.001 (71.8%)	1.32 (0.64–2.00)	< 0.001
Adult	0.90	REM	< 0.001 (84.3%)	1.14 (0.69–1.59)	< 0.001
			Overall significance test among subgroups		0.20
Use of co-treatment					
No	0.99	REM	< 0.001 (81.2%)	1.36 (1.10–1.62)	< 0.001
Scaffold	0.84	REM	< 0.001 (82.2%)	2.19 (1.30–2.07)	< 0.001
SC cells or BMMSC	0.60	REM	< 0.001 (88.9%)	1.21 (−0.24 to 2.65)	0.10
Growth factors	0.12	REM	< 0.001 (85.6%)	0.93 (−0.22 to 2.08)	0.11
Other	0.002	REM	< 0.001 (78.9%)	1.79 (1.16–2.41)	< 0.001
			Overall significance test among subgroups		0.72
Use of antibiotic					
No	0.17	REM	< 0.001 (77.9%)	1.24 (0.98–1.51)	< 0.001
Yes	0.56	REM	< 0.001 (84.0%)	1.77 (1.37–2.16)	< 0.001
			Overall significance test among subgroups		0.11
Use of immunosuppressive agents					
No	0.94	REM	< 0.001 (82.7%)	1.80 (1.49–2.10)	< 0.001
Yes	0.49	REM	< 0.001 (72.4%)	0.87 (0.57–1.17)	< 0.001
			Overall significance test among subgroups		**0.003**
Blinding of observer					
No	0.74	REM	< 0.001 (67.7%)	1.34 (0.85–1.84)	< 0.001
Yes	0.85	REM	< 0.001 (82.3%)	1.48 (1.23–1.73)	< 0.001
			Overall significance test among subgroups		0.82
Follow up period					
< 8 weeks	0.003	REM	< 0.001 (81.6%)	1.49 (1.14–1.84)	< 0.001
⩾ 8 weeks	0.69	REM	< 0.001 (80.9%)	1.42 (1.21–1.72)	< 0.001
			Overall significance test among subgroups		0.96

Subacut: 3–10 days after injury; Chronic: equal or more than 14 days. REM: random effect model; FEM: fixed effect, CI: confidence interval; NA: not applicable because of low number of included studies; wt-NSPCS: wild type neural stem/progenitor cells; iPSC-NSPCs: induced pluripotent stem cell-derived neural stem cells.

[a] Publication bias based on Begg's and Egger's test.

[b] Heterogeneity among studies.

[c] Standardized mean difference.

[d] Acute: immediately after injury.

acute phase. It seems that the early presence of neural stem cells at the lesion site post injury can slow down inflammatory processes and decrease neural deaths. Various studies have shown neural stem cell modulatory effects on inflammatory/immune responses (Lee et al., 2008a,b; Bacigaluppi et al., 2009; Ottoboni et al., 2015). This is also rather compatible with our previous meta-analysis in which we showed higher efficiencies of bone marrow derived mesenchymal cell transplantation in neuropathic pain relief after SCI if the procedure carries out during the first 4 days of injury (Hosseini et al., 2015).

In the present meta-analysis, we found that the NSPC transplantation efficacy varied based on the injury induction model i.e. clip compression efficacy has found to be lower than the transection model. Different inflammatory processes seem to be the plausible explanation for this observation. In the transection model, the inflammatory processes are not activated in the first 12 h post injury and the nervous tissue is still viable at the edges of the cut point (Kao and chang, 1977) and NSPC transplantation can suspend inflammatory activation at the time. Yet, cell seeding has also been done using a scaffold in most of these surveys. In the compression model however, the inflammatory processes are activated from the first or second hour post-injury and the function and survival of the transplanted cells should be affected accordingly. Despite rare complete transection injuries in human, compression and contusion injuries are more prevalent (Bunge et al., 1993). Therefore, caution should be taken if clinical trials with NSPCs are designed.

Due to major discrepancies, the optimum number of transplanted cells is still a matter of debate. Median number of the cells per kilograms of animal's body weight was 4.3×10^6 (interquartile range = 1.1×10^6–2×10^7). In the present study, the 3×10^6 cell dose/kg cut-off point was chosen based on some clinical situations (Hosseini et al., 2015). Higher doses have shown to provoke better functional recovery (Hosseini et al., 2015). This could be due to NSPC survival chance at higher doses efficient connections in the injured tissue.

Surprisingly, immunosuppressive administration has shown to decrease the efficacy in transplanted NSPC functional recovery after SCI (SMD = 0.79 vs.

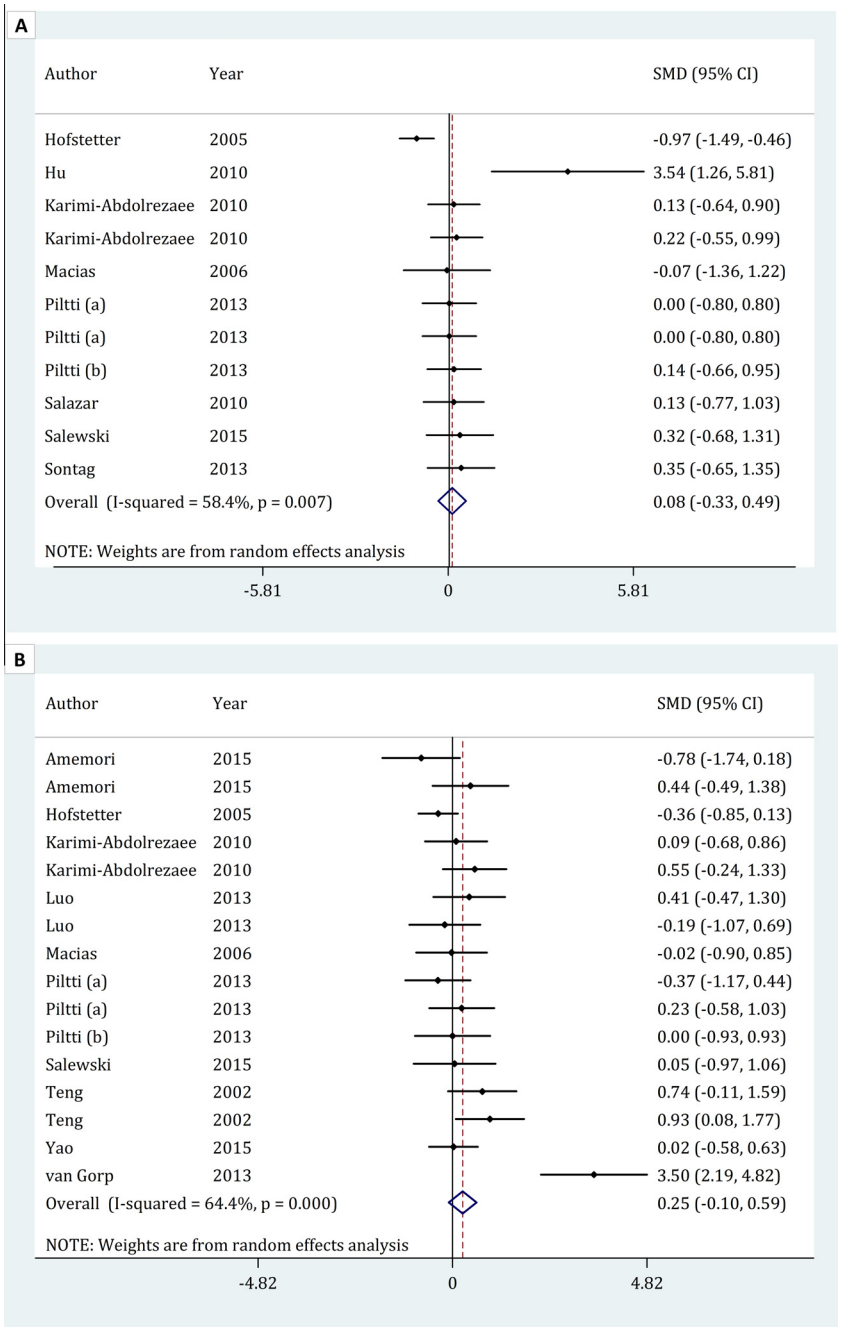

Fig. 3. Efficacy of neural stem/progenitor cells transplantation on allodynia (A) and hyperalgesia (B) after spinal cord injury. Neural stem/progenitor cells transplantation had no significant effect on allodynia and hyperalgesia.

SMD = 1.91). This is extremely difficult to rationalize. Most *in vivo* and *in vitro* studies have shown inhibitory effects of immunosuppressive medications on transplantation rejection and its facilitative influence on cell survival. Moreover, these agents can decrease inflammatory responses activated by traumatic spinal injury and increases growth and axon branching speed at the lesion site (Madsen et al., 1998; Xu et al., 1998). Immunosuppressive drug inhibitory effects on functional recovery might be due to their negative effects on wound and spinal cord healing (Park et al., 2013). However, we did not observe significant association between immunosuppressive use and efficacy of bone marrow derived stem cell transplantation with neuropathic pain relief after SCI (Hosseini et al., 2015). These findings are indicative of the need for further investigations on this matter.

The role of NSPC transplantation in neuropathic pain relief was another subject of this study. Analyses showed that NSPC transplantation could relieve hyperalgesia without any effect on allodynia. Eaton in his study showed that neural cell lines could alleviate neuropathic pains (Eaton, 2004). He only included those surveys with genetically engineered cell lines capable of

Table 4. Subgroup analyses of the effect of neural stem/progenitor cells on allodynia

Characteristic	*P* for bias[a]	Model	*P* (I^2)[b]	Effect Size [c] (95% CI)	*P*
Recipient species					
Mice	0.50	FEM	0.07 (48.6%)	0.65 (−0.27 to 1.57)	0.16
Rat	0.55	FEM	0.05 (60.9%)	−0.13 (−0.54 to 0.28)	0.53
			Overall significance test among subgroups		0.18
Injury model					
Contusion	0.91	REM	0.003 (68.1%)	0.08 (−0.49 to 0.64)	0.80
Compression	0.12	FEM	0.96 (0.0%)	−0.27 (−0.21 ti 0.69)	0.39
			Overall significance test among subgroups		0.55
Severity of injury					
Moderate	0.46	REM	0.001 (70.2%)	0.16 (−0.43 to 0.76)	0.60
Severe	0.30	FEM	0.96 (0.0%)	0.05 (−0.41 to 0.51)	0.84
			Overall significance test among subgroups		0.96
Stem cells derivation origin					
Brain	0.72	FEM	0.12 (36.5%)	−0.13 (−0.38 to 0.12)	0.31
Other	NA	NA	NA	NA	NA
			Overall significance test among subgroups		NA
Intervention phase[d]					
Acute	0.11	REM	< 0.001 (93.1%)	1.14 (−3.27 to 5.55)	0.62
Subacute	0.37	FEM	0.99 (0.0%)	0.12 (−0.25 to 0.49)	0.49
Chronic	0.60	FEM	0.98 (0.0%)	0.16 (−0.30 to 0.63)	0.54
			Overall significance test among subgroups		0.44
Graft type					
Allogeneic	0.60	REM	< 0.001 (88.8%)	0.62 (−1.22 to 2.45)	0.51
Xenogeneic	0.54	FEM	0.99 (0.0%)	0.12 (−0.18 to 0.42)	0.44
			Overall significance test among subgroups		0.46
Number of transplanted cells					
$< 3 \times 10^6$ cell dose/kg	0.55	REM	0.07 (48.6%)	−0.13 (−0.54 to 0.28)	0.53
$\geqslant 3 \times 10^6$ cell dose/kg	0.50	REM	0.05 (60.9%)	0.65 (−0.27 to 1.57)	0.17
			Overall significance test among subgroups		0.18
Donor species					
Mice	0.49	REM	0.01 (64.0%)	0.51 (−0.40 to 1.43)	0.27
Rat	NA	NA	NA	NA	NA
Human	0.38	FEM	0.99 (0.0%)	0.13 (−0.22 to 0.49)	0.46
			Overall significance test among subgroups		0.79
Donor age					
Fetal	0.009	FEM	0.99 (0.0%)	0.13 (−0.22 to 0.49)	0.46
Newborn	NA	NA	NA	NA	NA
Adult	0.49	REM	< 0.001 (85.3%)	−0.29 (−0.82 to 1.40)	0.69
			Overall significance test among subgroups		0.38
Use of co-treatment					
No	0.46	REM	0.003 (88.0%)	0.09 (−0.42 to 0.60)	0.73
Yes	NA	NA	NA	NA	NA
			Overall significance test among subgroups		0.79
Use of antibiotic					
No	0.50	REM	< 0.001 (85.3%)	0.46 (−0.85 to 1.76)	0.49
Yes	0.55	FEM	0.99 (0.0%)	0.10 (−0.22 to 0.41)	0.56
			Overall significance test among subgroups		0.22
Use of immunosuppressive agents					
No	0.81	REM	< 0.001 (88.4%)	0.50 (−1.20 to 2.2)	0.56
Yes	0.34	FEM	0.99 (0.0%)	0.08 (−0.33 to 0.49)	0.38
			Overall significance test among subgroups		0.32
Blinding of observer					
No	NA	NA	NA	NA	NA
Yes	0.81	FEM	0.12 (36.5%)	−0.05 (−0.38 to 0.28)	0.78
			Overall significance test among subgroups		NA

Table 4 (*continued*)

Characteristic	*P* for bias[a]	Model	*P* (I^2)[b]	Effect Size [c] (95% CI)	*P*
Follow up period					
< 8 weeks	0.50	REM	0.047 (62.4%)	0.56 (−0.28 to 1.39)	0.19
⩾ 8 weeks	0.55	REM	0.08 (47.3%)	−0.14 (−0.57 to 0.29)	0.53
			Overall significance test among subgroups		0.21

Subacut: 3–10 days after injury; Chronic: equal or more than 14 days; REM: random effect model; FEM: fixed effect, CI: confidence interval; NA: not applicable because of low number of included studies.

[a] Publication bias based on Begg's and Egger's test.

[b] Heterogeneity among studies.

[c] Standardized mean difference.

[d] Acute: immediately after injury.

Table 5. Subgroup analyses of the effect of neural stem/progenitor cells on hyperalgesia

Characteristic	*P* for bias[a]	Model	*P* (I^2)[b]	Effect Size [c] (95% CI)	*P*
Gender					
Male	0.30	FEM	0.19 (39.8%)	−0.05 (−0.50 to 0.40)	0.81
Female	0.84	REM	< 0.001 (68.2%)	0.34 (−0.07 to 0.75)	0.94
			Overall significance test among subgroups		0.44
Recipient species					
Rat	0.14	REM	< 0.001 (66.7%)	0.26 (−0.10 to 0.63)	0.16
Other	NA	NA	NA	NA	NA
			Overall significance test among subgroups		NA
Injury model					
Contusion	0.33	FEM	0.74 (0.0%)	−0.18 (−0.50 to 0.14)	0.29
Clip compression	0.17	REM	< 0.001 (86.1%)	0.96 (−0.29 to 2.22)	0.13
Balloon compression	NA	NA	NA	NA	NA
Hemisection	NA	NA	NA	NA	NA
Transection	0.60	REM	< 0.001 (65.8%)	0.06 (−0.37 to 0.50)	0.77
			Overall significance test among subgroups		0.64
Location of injury					
Thoracic	0.44	FEM	0.28 (15.3%)	0.07 (−0.13 to 0.27)	0.50
Lumbar	NA	NA	NA	NA	NA
			Overall significance test among subgroups		NA
Severity of injury					
Moderate	0.18	REM	< 0.001 (83.5%)	0.34 (−0.32 to 0.99)	0.31
Severe	0.80	FEM	0.34 (9.6%)	0.20 (−0.10 to 0.50)	0.19
			Overall significance test among subgroups		0.84
Stem cells derivation origin					
Brain	0.54	FEM	0.38 (6.9%)	0.10 (−0.12 to 0.32)	0.12
Spine	NA	NA	NA	NA	NA
Lung	NA	NA	NA	NA	NA
			Overall significance test among subgroups		NA
Cell type					
wt-NSPCs	0.58	REM	< 0.001 (65.8%)	0.30 (−0.07 to 0.67)	0.11
iPSC-NSPCs	NA	NA	NA	NA	NA
			Overall significance test among subgroups		NA
Intervention phase[d]					
Acute	0.99	FEM	0.27 (22.6%)	0.33 (−0.02 to 0.24)	**0.07**
Subacute	0.99	REM	< 0.001 (76.3%)	0.20 (−0.38 to 0.79)	0.38
Chronic	NA	NA	NA	NA	NA
			Overall significance test among subgroups		0.89
Delivery route					
Intra spinal	0.32	REM	< 0.001 (66.4%)	0.24 (−0.12 to 0.61)	0.20
Other	NA	NA	NA	NA	NA
			Overall significance test among subgroups		NA

(*continued on next page*)

Table 5 (*continued*)

Characteristic	*P* for bias[a]	Model	*P* (I^2)[b]	Effect Size [c] (95% CI)	*P*
Graft type					
Allogeneic	0.25	FEM	0.50 (0.0%)	−0.15 (−0.51 to 0.21)	0.43
Xenogeneic	0.73	REM	< 0.001 (69.3%)	0.37 (−0.08 to 0.81)	0.10
			Overall significance test among subgroups		0.40
Number of transplanted cells					
$< 3 \times 10^6$ cell dose/kg	0.73	REM	< 0.001 (69.7%)	0.20 (−0.24 to 0.64)	0.37
$\geqslant 3 \times 10^6$ cell dose/kg	0.16	FEM	0.26 (25.5%)	0.37 (−0.02 to 0.77)	**0.06**
			Overall significance test among subgroups		0.65
Donor species					
Mice	0.33	FEM	0.40 (1.8%)	0.33 (0.02–0.65)	**0.04**
Rat	0.53	FEM	0.33 (9.9%)	−0.18 (−0.56 to 0.21)	0.36
Human	0.99	REM	< 0.001 (80.4%)	0.37 (−0.48 to 1.17)	0.28
			Overall significance test among subgroups		0.47
Donor age					
Fetal	0.33	REM	< 0.001 (81.3%)	0.47 (−0.35 to 1.29)	0.26
Newborn	0.19	FEM	0.27 (22.9%)	0.56 (0.07–1.05)	**0.03**
Adult	0.30	FEM	0.22 (27.5%)	−0.04 (−0.33 to 0.25)	0.78
			Overall significance test among subgroups		0.43
Use of co-treatment					
No	0.21	REM	< 0.001 (74.0%)	0.25 (−0.20 to 0.70)	0.28
Yes	0.73	FEM	0.41 (0.0%)	0.30 (−0.10 to 0.71)	0.15
			Overall significance test among subgroups		0.90
Use of antibiotic					
No	0.42	REM	0.03 (67.3%)	0.29 (−0.38 to 0.97)	0.40
Yes	0.16	REM	0.001 (66.5%)	0.25 (−0.19 to 0.67)	0.27
			Overall significance test among subgroups		0.72
Use of immunosuppressive agents					
No	0.53	REM	0.03 (67.5%)	0.25 (−0.34 to 0.85)	0.40
Yes	0.21	REM	0.001 (66.3%)	0.25 (−0.18 to 0.70)	0.27
			Overall significance test among subgroups		0.97
Blinding of observer					
No	NA	NA	NA	NA	NA
Yes	0.54	REM	< 0.001 (66.6%)	0.27 (−0.10 to 0.65)	0.94
			Overall significance test among subgroups		NA
Follow up period					
> 8 weeks	0.14	FEM	0.72 (0.0%)	0.16 (−0.18 to 0.51)	0.36
$\geqslant$ 8 weeks	0.62	REM	< 0.001 (75.0%)	0.32 (−0.20 to 0.83)	0.23
			Overall significance test among subgroups		0.30

Subacut: 3–10 days after injury; Chronic: equal or more than 14 days. REM: random effect model; FEM: fixed effect, CI: confidence interval; NA: not applicable because of low number of included studies; wt-NSPCS: wild type neural stem/progenitor cells; iPSC-NSPCs: induced pluripotent stem cell-derived neural stem cells.

[a] Publication bias based on Begg's and Egger's test.

[b] Heterogeneity among studies.

[c] Standardized mean difference.

[d] Acute: immediately after injury.

secreting potentially anti-nociceptive mediators, and immortalized cell lines used for neuropathic pain relief, rather than neural stem cells. Secretion of anti-nociceptive mediators such as met-enkephalin, gamma-aminobutyric acid (GABA), and opioids can attenuate neuropathic pain symptoms. That would be the reason for the discrepant results of the two studies Furthermore, Franchi et al. in their narrative review referred to the neural stem cells as the suitable sources for neural regeneration and neuropathic pain relief (Franchi et al., 2014). In spite of our study that addresses central models, Franchi et al mainly focuses the chronic construction of the sciatic nerve model with a peripheral aspect suitable for neural injuries induction. Referring to the different mechanisms of peripheral and central pain models (Burnett and Zager, 2004; Scholz and Woolf, 2007; Oyinbo, 2011), this controversy is predictable.

According to Li and Lepski neural stem cell transplantation has no significant effect on sensory status after SCIs (Li and Lepski, 2013). This might be due to the neural stem cell high tendency for glial cell differentiation. Some studies have a differentiation rate of 40% to glial cells post transplantation compared with much less rate for neuronal differentiation (Tarasenko

et al., 2007). These changes might exacerbate secondary injuries developed within the first hours post SCI and can persist through months or sometimes years after the insult (Rowland et al., 2008).

In our previous meta-analysis (Hosseini et al., 2015), we showed that bone marrow-derived mesenchymal stem cell implantation could improve allodynia with no significant effects on hyperalgesia unless it was implanted during the acute phase of injury. Mesenchymal stem cells could attenuate most unfavorable acute and chronic damages in the injured spinal cord (Wright et al., 2007; Teixeira et al., 2013). Implanted cells have a neuroprotective role (Uccelli et al., 2008) and can reduce pro-inflammatory cytokines, reactive oxygen species, and asteriogliosis (Abrams et al., 2009). These cells can also enhance host neural stem cell to oligodendrocytes differentiation and stimulate re-myelination (Rivera et al., 2006). However, NSPCs have less immunomodulatory properties and are apt to differentiate into astrocytes. Since NSPCs can develop some degree of allodynia and hyperalgesia in SCI animals (Hofstetter et al., 2005; Macias et al., 2006), their transplantation cannot significantly improve allodynia and hyperalgesia in the SCI animal models. According to Mothe and Tator, only pre-differentiated NSPCs grafts in astrocytes can improve allodynia (Mothe and Tator, 2013).

Finally, subgroup analysis showed more improvements in hyperalgesia when NSPCs were extracted from mice rather than rats or human. Several reasons are required to explain this phenomenon. According to Mothe and Tator human derived NSPCs were either unavailable or difficult to grow (Mothe and Tator, 2013). In addition, Drukker and Benvenisty showed that human-derived NSPCs rejection imposed a great threat to their clinical use in regenerative medicine (Drukker and Benvenisty, 2004). In contrast, mouse NSPCs are a non-immunogenic immune-privileged tissue, and can be transplanted into allogeneic recipients without immunosuppressive regimens side effects (Hori et al., 2003).

STRENGTHS AND LIMITATIONS

In the present study, extended electronic search, authors contact, and manual webpage search were used to include maximum number of articles and gray literature. This method provided us with 74 studies and 125 experiments in the meta-analysis. Accordingly, data from 2382 animal subjects were pooled together and then analyzed. Absence of publication bias was one of the strengths of this survey. Heterogeneity in analyses was one of the study limitations, which was overcome through subgroup analysis. Lack of observers blinded to some included studies was another limitation. However, since in subgroup analysis neutrality is irrelevant to NSPCs transplantation efficacy on functional recovery and sensory condition, bias would accordingly be at its minimum levels.

CONCLUSION

Findings of the present meta-analysis showed that the efficacy of NSPC transplantation depends on the injury model, intervention phase, number of transplanted cells, immunosuppressive medications, and probably the cell source. The efficacy of this treatment method is higher in transection and contusion injury models than compression one. The shorter the interval between injury and treatment, led to the better the functional recovery and sensory condition. The best treatment dose was also found to be higher than 3×10^6 cell dose/kg. Immunosuppressive drug administration was found to negatively affect motor function recovery. Scaffold use could also boost NSPC efficacy on motor function recovery.

AUTHOR CONTRIBUTIONS

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

CONFLICT OF INTEREST

There are no conflicts of interest to report.

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REFERENCES

Abematsu M, Tsujimura K, Yamano M, Saito M, Kohno K, Kohyama J, Namihira M, Komiya S, Nakashima K (2010) Neurons derived from transplanted neural stem cells restore disrupted neuronal circuitry in a mouse model of spinal cord injury. J Clin Investig 120:3255–3266.

Abrams MB, Dominguez C, Pernold K, Reger R, Wiesenfeld-Hallin Z, Olson L, Prockop D (2009) Multipotent mesenchymal stromal cells attenuate chronic inflammation and injury-induced sensitivity to mechanical stimuli in experimental spinal cord injury. Restorat Neurol Neurosci 27:307–321.

Amemori T, Romanyuk N, Jendelova P, Herynek V, Turnovcova K, Prochazka P, Kapcalova M, Cocks G, Price J, Sykova E (2013) Human conditionally immortalized neural stem cells improve locomotor function after spinal cord injury in the rat. Stem Cell Res Ther 4:68.

Amemori T, Ruzicka J, Romanyuk N, Jhanwar-Uniyal M, Sykova E, Jendelova P (2015) Comparison of intraspinal and intrathecal implantation of induced pluripotent stem cell-derived neural precursors for the treatment of spinal cord injury in rats. Stem Cell Res Ther 6:257.

Antonic A, Sena ES, Lees JS, Wills TE, Skeers P, Batchelor PE, Macleod MR, Howells DW (2013) Stem cell transplantation in traumatic spinal cord injury: a systematic review and meta-analysis of animal studies. PLoS Biol 11 e1001738.

Bacigaluppi M, Pluchino S, Jametti LP, Kilic E, Kilic Ü, Salani G, Brambilla E, West MJ, Comi G, Martino G (2009) Delayed post-ischaemic neuroprotection following systemic neural stem cell transplantation involves multiple mechanisms. Brain:awp174.

Backonja MM, Irving GA, Argoff C (2006) Rational multidrug therapy in the treatment of neuropathic pain. Curr Pain Headache Rep 10:34–38.

Bottai D, Madaschi L, Di Giulio AM, Gorio A (2008) Viability-dependent promoting action of adult neural precursors in spinal cord injury. Mol Med (Cambridge, Mass) 14:634–644.

Bunge RP, Puckett WR, Becerra JL, Marcillo A, Quencer RM (1993) Observations on the pathology of human spinal cord injury. A review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination. Adv Neurol 59:75–89.

Burnett MG, Zager EL (2004) Pathophysiology of peripheral nerve injury: a brief review. Neurosurg Focus 16:1–7.

Chen G, Hu YR, Wan H, Xia L, Li JH, Yang F, Qu X, Wang SG, Wang ZC (2010) Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells and Schwann cells. Chin Med J 123:2424–2431.

Cheng I, Mayle RE, Cox CA, Park DY, Smith RL, Corcoran-Schwartz I, Ponnusamy KE, Oshtory R, Smuck MW, Mitra R, Kharazi AI, Carragee EJ (2012) Functional assessment of the acute local and distal transplantation of human neural stem cells after spinal cord injury. Spine J 12:1040–1044.

Cummings BJ, Uchida N, Tamaki SJ, Salazar DL, Hooshmand M, Summers R, Gage FH, Anderson AJ (2005) Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. Proc Natl Acad Sci USA 102:14069–14074.

Cusimano M, Biziato D, Brambilla E, Doneg M, Alfaro-Cervello C, Snider S, Salani G, Pucci F, Comi G, Garcia-Verdugo JM, De Palma M, Martino G, Pluchino S (2012) Transplanted neural stem/precursor cells instruct phagocytes and reduce secondary tissue damage in the injured spinal cord. Brain 135:447–460.

Drukker M, Benvenisty N (2004) The immunogenicity of human embryonic stem-derived cells. Trends Biotechnol 22:136–141.

Du BL, Xiong Y, Zeng CG, He LM, Zhang W, Quan DP, Wu JL, Li Y, Zeng YS (2011) Transplantation of artificial neural construct partly improved spinal tissue repair and functional recovery in rats with spinal cord transection. Brain Res 1400:87–98.

Eaton M (2004) Cell therapy for neuropathic pain in spinal cord injuries. Exp Opin Biol Ther 4:1861–1869.

Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634.

Finnerup NB (2013) Pain in patients with spinal cord injury. Pain 154: S71–S76.

Finnerup NB, Otto M, McQuay HJ (2005) Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 118:289–305.

Franchi S, Castelli M, Amodeo G, Niada S, Ferrari D, Vescovi A, Brini AT, Panerai AE, Sacerdote P (2014) Adult stem cell as new advanced therapy for experimental neuropathic pain treatment. BioMed Res Int 2014:470983.

Fujimoto Y, Abematsu M, Falk A, Tsujimura K, Sanosaka T, Juliandi B, Semi K, Namihira M, Komiya S, Smith A, Nakashima K (2012) Treatment of a mouse model of spinal cord injury by transplantation of human induced pluripotent stem cell-derived long-term self-renewing neuroepithelial-like stem cells. Stem Cells (Dayton, Ohio) 30:1163–1173.

Gu YL, Yin LW, Zhang Z, Liu J, Liu SJ, Zhang LF, Wang TH (2012) Neurotrophin expression in neural stem cells grafted acutely to transected spinal cord of adult rats linked to functional improvement. Cell Mol Neurobiol 32:1089–1097.

Guenot M, Lee JW, Nasirinezhad F, Sagen J (2007) Deafferentation pain resulting from cervical posterior rhizotomy is alleviated by chromaffin cell transplants into the rat spinal subarachnoid space. Neurosurgery 60:919–925 (discussion 919–925).

Guo JS, Zeng YS, Li HB, Huang WL, Liu RY, Li XB, Ding Y, Wu LZ, Cai DZ (2007) Cotransplant of neural stem cells and NT-3 gene modified Schwann cells promote the recovery of transected spinal cord injury. Spinal Cord 45:15–24.

Guo X, Zahir T, Mothe A, Shoichet MS, Morshead CM, Katayama Y, Tator CH (2012) The effect of growth factors and soluble Nogo-66 receptor protein on transplanted neural stem/progenitor survival and axonal regeneration after complete transection of rat spinal cord. Cell Transplant 21:1177–1197.

Hama A, Sagen J (2007) Behavioral characterization and effect of clinical drugs in a rat model of pain following spinal cord compression. Brain Res 1185:117–128.

Hassannejad Z, Sharif-Alhoseini M, Shakouri-Motlagh A, Vahedi F, Zadegan SA, Mokhatab M, Rezvan M, Saadat S, Shokraneh F, Rahimi-Movaghar V (2015) Potential variables affecting the quality of animal studies regarding pathophysiology of traumatic spinal cord injuries. Spinal Cord.

He BL, Ba YC, Wang XY, Liu SJ, Liu GD, Ou S, Gu YL, Pan XH, Wang TH (2013) BDNF expression with functional improvement in transected spinal cord treated with neural stem cells in adult rats. Neuropeptides 47:1–7.

Hofstetter CP, Holmstrom NA, Lilja JA, Schweinhardt P, Hao J, Spenger C, Wiesenfeld-Hallin Z, Kurpad SN, Frisen J, Olson L (2005) Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome. Nat Neurosci 8:346–353.

Hong JY, Lee SH, Lee SC, Kim JW, Kim KP, Kim SM, Tapia N, Lim KT, Kim J, Ahn HS, Ko K, Shin CY, Lee HT, Scholer HR, Hyun JK, Han DW (2014) Therapeutic potential of induced neural stem cells for spinal cord injury. J Biol Chem 289:32512–32525.

Hooshmand MJ, Sontag CJ, Uchida N, Tamaki S, Anderson AJ, Cummings BJ (2009) Analysis of host-mediated repair mechanisms after human CNS-stem cell transplantation for spinal cord injury: Correlation of engraftment with recovery. PLoS One 4.

Hori J, Ng TF, Shatos M, Klassen H, Streilein JW, Young MJ (2003) Neural progenitor cells lack immunogenicity and resist destruction as allografts. Stem Cells (Dayton, Ohio) 21:405–416.

Hosseini M, Karami Z, Janzadenh A, Jameie SB, Haji Mashhadi Z, Yousefifard M, Nasirinezhad F (2014) The effect of intrathecal administration of muscimol on modulation of neuropathic pain symptoms resulting from spinal cord injury; an experimental study. Emergency (Tehran, Iran) 2:151–157.

Hosseini M, Yousefifard M, Aziznejad H, Nasirinezhad F (2015) The effect of bone marrow-derived mesenchymal stem cell transplantation on allodynia and hyperalgesia in neuropathic animals: a systematic review with meta-analysis. Biol. Blood Marrow Transpl 21:1537–1544.

Hu YF, Gourab K, Wells C, Clewes O, Schmit BD, Sieber-Blum M (2010) Epidermal neural crest stem cell (EPI-NCSC)-mediated recovery of sensory function in a mouse model of spinal cord injury. Stem Cell Rev Rep 6:186–198.

Hwang DH, Shin HY, Kwon MJ, Choi JY, Ryu BY, Kim BG (2014) Survival of neural stem cell grafts in the lesioned spinal cord is enhanced by a combination of treadmill locomotor training via insulin-like growth factor-1 signaling. J Neurosci 34:12788–12800.

Iwai H, Shimada H, Nishimura S, Kobayashi Y, Itakura G, Hori K, Hikishima K, Ebise H, Negishi N, Shibata S, Habu S, Toyama Y, Nakamura M, Okano H (2015) Allogeneic neural stem/progenitor cells derived from embryonic stem cells promote functional recovery after transplantation into injured spinal cord of nonhuman primates. Stem Cells Transl Med 4:708–719.

Iwanami A, Kaneko S, Nakamura M, Kanemura Y, Mori H, Kobayashi S, Yamasaki M, Momoshima S, Ishii H, Ando K, Tanioka Y, Tamaoki N, Nomura T, Toyama Y, Okano H (2005) Transplantation of human neural stem cells for spinal cord injury in primates. J Neurosci Res 80:182–190.

Iwasaki M, Wilcox JT, Nishimura Y, Zweckberger K, Suzuki H, Wang J, Liu Y, Karadimas SK, Fehlings MG (2014) Synergistic effects of self-assembling peptide and neural stem/progenitor cells to promote tissue repair and forelimb functional recovery in cervical spinal cord injury. Biomaterials 35:2617–2629.

Johnson PJ, Tatara A, McCreedy DA, Shiu A, Sakiyama-Elbert SE (2010) Tissue-engineered fibrin scaffolds containing neural progenitors enhance functional recovery in a subacute model of SCI. Soft Matter 6:5127–5137.

Kao T, Chang LW (1977) The mechanism of spinal cord cavitation following spinal cord transection. J Neurosurg 46:197–209.

Karimi-Abdolrezaee S, Eftekharpour E, Wang J, Morshead CM, Fehlings MG (2006) Delayed transplantation of adult neural precursor cells promotes remyelination and functional neurological recovery after spinal cord injury. J Neurosci 26:3377–3389.

Karimi-Abdolrezaee S, Eftekharpour E, Wang J, Schut D, Fehlings MG (2010) Synergistic effects of transplanted adult neural stem/

progenitor cells, chondroitinase, and growth factors promote functional repair and plasticity of the chronically injured spinal cord. J Neurosci 30:1657–1676.
Kim H, Zahir T, Tator CH, Shoichet MS (2011) Effects of dibutyryl cyclic-AMP on survival and neuronal differentiation of neural stem/progenitor cells transplanted into spinal cord injured rats. PLoS One 6 e21744.
Kim HJ, Oh JS, An SS, Pennant WA, Gwak SJ, Kim AN, Han PK, Yoon DH, Kim KN, Ha Y (2012) Hypoxia-specific GM-CSF-overexpressing neural stem cells improve graft survival and functional recovery in spinal cord injury. Gene Ther 19:513–521.
Kobayashi Y, Okada Y, Itakura G, Iwai H, Nishimura S, Yasuda A, Nori S, Hikishima K, Konomi T, Fujiyoshi K, Tsuji O, Toyama Y, Yamanaka S, Nakamura M, Okano H (2012) Pre-evaluated safe human iPSC-derived neural stem cells promote functional recovery after spinal cord injury in common marmoset without tumorigenicity. PLoS One 7 e52787.
Kumagai G, Okada Y, Yamane J, Nagoshi N, Kitamura K, Mukaino M, Tsuji O, Fujiyoshi K, Katoh H, Okada S, Shibata S, Matsuzaki Y, Toh S, Toyama Y, Nakamura M, Okano H (2009) Roles of ES cell-derived gliogenic neural stem/progenitor cells in functional recovery after spinal cord injury. PLoS One 4 e7706.
Kumamaru H, Saiwai H, Kubota K, Kobayakawa K, Yokota K, Ohkawa Y, Shiba K, Iwamoto Y, Okada S (2013) Therapeutic activities of engrafted neural stem/precursor cells are not dormant in the chronically injured spinal cord. Stem Cells (Dayton, Ohio) 31:1535–1547.
Kumru H, Soler D, Vidal J, Navarro X, Tormos J, Pascual-Leone A, Valls-Sole J (2013) The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: an evoked potentials and quantitative thermal testing study. Eur. J. Pain 17:55–66.
Lee-Kubli CA, Lu P (2015) Induced pluripotent stem cell-derived neural stem cell therapies for spinal cord injury. Neural Regenerat Res 10:10–16.
Lee S-T, Chu K, Jung K-H, Kim S-J, Kim D-H, Kang K-M, Hong NH, Kim J-H, Ban J-J, Park H-K (2008a) Anti-inflammatory mechanism of intravascular neural stem cell transplantation in haemorrhagic stroke. Brain 131:616–629.
Lee S-T, Chu K, Park H-K, Jung K-H, Kim M, Lee SK, Roh J-K (2008b) New concept of neural stem cell transplantation: anti-inflammatory role. International Journal of Stem Cells 1:36–42.
Lee SH, Chung YN, Kim YH, Kim YJ, Park JP, Kwon DK, Kwon OS, Heo JH, Kim YH, Ryu S, Kang HJ, Paek SH, Wang KC, Kim SU, Yoon BW (2009) Effects of human neural stem cell transplantation in canine spinal cord hemisection. Neurol Res 31:996–1002.
Li J, Lepski G (2013) Cell transplantation for spinal cord injury: a systematic review. BioMed Res Int 2013.
Liu C, Huang Y, Pang M, Yang Y, Li S, Liu L, Shu T, Zhou W, Wang X, Rong L, Liu B (2015) Tissue-engineered regeneration of completely transected spinal cord using induced neural stem cells and gelatin-electrospun poly (lactide-co-glycolide)/polyethylene glycol scaffolds. PLoS One 10.
Lowry N, Goderie SK, Adamo M, Lederman P, Charniga C, Gill J, Silver J, Temple S (2008) Multipotent embryonic spinal cord stem cells expanded by endothelial factors and Shh/RA promote functional recovery after spinal cord injury. Exp Neurol 209:510–522.
Lu P, Wang Y, Graham L, McHale K, Gao M, Wu D, Brock J, Blesch A, Rosenzweig ES, Havton LA, Zheng B, Conner JM, Marsala M, Tuszynski MH (2012) Long-distance growth and connectivity of neural stem cells after severe spinal cord injury. Cell 150:1264–1273.
Lu P, Woodruff G, Wang Y, Graham L, Hunt M, Wu D, Boehle E, Ahmad R, Poplawski G, Brock J, Goldstein LS, Tuszynski MH (2014) Long-distance axonal growth from human induced pluripotent stem cells after spinal cord injury. Neuron 83:789–796.
Luo Y, Zou Y, Yang L, Liu J, Liu S, Liu J, Zhou X, Zhang W, Wang T (2013) Transplantation of NSCs with OECs alleviates neuropathic pain associated with NGF downregulation in rats following spinal cord injury. Neurosci Lett 549:103–108.
Macias MY, Syring MB, Pizzi MA, Crowe MJ, Alexanian AR, Kurpad SN (2006) Pain with no gain: allodynia following neural stem cell transplantation in spinal cord injury. Exp Neurol 201: 335–348.
Madsen JR, MacDonald P, Irwin N, Goldberg DE, Yao G-L, Meiri KF, Rimm IJ, Stieg PE, Benowitz LI (1998) Tacrolimus (FK506) increases neuronal expression of GAP-43 and improves functional recovery after spinal cord injury in rats. Exp Neurol 154:673–683.
Mann R, Schaefer C, Sadosky A, Bergstrom F, Baik R, Parsons B, Nalamachu S, Stacey BR, Tuchman M, Anschel A, Nieshoff EC (2013) Burden of spinal cord injury-related neuropathic pain in the United States: retrospective chart review and cross-sectional survey. Spinal Cord 51:564–570.
Marineo G, Iorno V, Gandini C, Moschini V, Smith TJ (2012) Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: results of a pilot, randomized, controlled trial. J Pain Symptom Manage 43:87–95.
Mark Richardson R, Broaddus WC, Holloway KL, Fillmore HL (2005) Grafts of adult subependymal zone neuronal progenitor cells rescue hemiparkinsonian behavioral decline. Brain Res 1032:11–22.
Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151:264–269.
Mothe AJ, Tator CH (2013) Review of transplantation of neural stem/progenitor cells for spinal cord injury. Int J Dev Neurosci 31:701–713.
Nasirinezhad F, Hosseini M, Karami Z, Yousefifard M, Janzadeh A (2015a) Spinal 5-HT3 receptor mediates nociceptive effect on central neuropathic pain; possible therapeutic role for tropisetron. J Spinal Cord Med.
Nasirinezhad F, Hosseini M, Salari S (2015b) Anti-allodynic efficacy of NMDA antagonist peptide and noradrenaline alone and in combination in rodent neuropathic pain model. Korean J Pain 28:96–104.
Nemati S, Jabbari R, Hajinasrollah M, Mehrjerdi NZ, Azizi H, Hemmesi K, Moghiminasr R, Azhdari Z, Talebi A, Mohitmafi S, Dizaj AVT, Sharifi G, Baharvand H, Rezaee O, Kiani S (2014) Transplantation of adult monkey neural stem cells into a contusion spinal cord injury model in rhesus macaque monkeys. Cell J 16:117–130.
Nishimura S, Yasuda A, Iwai H, Takano M, Kobayashi Y, Nori S, Tsuji O, Fujiyoshi K, Ebise H, Toyama Y, Okano H, Nakamura M (2013) Time-dependent changes in the microenvironment of injured spinal cord affects the therapeutic potential of neural stem cell transplantation for spinal cord injury. Mol Brain 6:3.
Nori S, Okada Y, Yasuda A, Tsuji O, Takahashi Y, Kobayashi Y, Fujiyoshi K, Koike M, Uchiyama Y, Ikeda E, Toyama Y, Yamanaka S, Nakamura M, Okano H (2011) Grafted human-induced pluripotent stem-cell-derived neurospheres promote motor functional recovery after spinal cord injury in mice. Proc Natl Acad Sci USA 108:16825–16830.
Nutt SE, Chang EA, Suhr ST, Schlosser LO, Mondello SE, Moritz CT, Cibelli JB, Horner PJ (2013) Caudalized human iPSC-derived neural progenitor cells produce neurons and glia but fail to restore function in an early chronic spinal cord injury model. Exp Neurol 248:491–503.
Okada S, Ishii K, Yamane J, Iwanami A, Ikegami T, Katoh H, Iwamoto Y, Nakamura M, Miyoshi H, Okano HJ, Contag CH, Toyama Y, Okano H (2005) In vivo imaging of engrafted neural stem cells: its application in evaluating the optimal timing of transplantation for spinal cord injury. FASEB J 19:1839–1841.
Ormond DR, Shannon C, Oppenheim J, Zeman R, Das K, Murali R, Jhanwar-Uniyal M (2014) Stem cell therapy and curcumin synergistically enhance recovery from spinal cord injury. PLoS One 9 e88916.
Ottoboni L, De Feo D, Merlini A, Martino G (2015) Commonalities in immune modulation between mesenchymal stem cells (MSCs) and neural stem/precursor cells (NPCs). Immunol Lett.

Oyinbo CA (2011) Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this multiply cascade. Acta Neurobiol Exp 71:281–299.
Pallini R, Vitiani LR, Bez A, Casalbore P, Facchiano F, Di Giorgi Gerevini V, Falchetti ML, Fernandez E, Maira G, Peschle C, Parati E (2005) Homologous transplantation of neural stem cells to the injured spinal cord of mice. Neurosurgery 57:1014–1024.
Pan HC, Cheng FC, Lai SZ, Yang DY, Wang YC, Lee MS (2008) Enhanced regeneration in spinal cord injury by concomitant treatment with granulocyte colony-stimulating factor and neuronal stem cells. J Clin Neurosci 15:656–664.
Park DY, Mayle RE, Smith RL, Corcoran-Schwartz I, Kharazi AI, Cheng I (2013) Combined transplantation of human neuronal and mesenchymal stem cells following spinal cord injury. Global Spine J 3:1–6.
Parr AM, Kulbatski I, Tator CH (2007) Transplantation of adult rat spinal cord stem/progenitor cells for spinal cord injury. J Neurotrauma 24:835–845.
Parr AM, Kulbatski I, Wang XH, Keating A, Tator CH (2008a) Fate of transplanted adult neural stem/progenitor cells and bone marrow-derived mesenchymal stromal cells in the injured adult rat spinal cord and impact on functional recovery. Surg Neurol 70:600–607.
Parr AM, Kulbatski I, Zahir T, Wang X, Yue C, Keating A, Tator CH (2008b) Transplanted adult spinal cord-derived neural stem/progenitor cells promote early functional recovery after rat spinal cord injury. Neuroscience 155:760–770.
Piltti KM, Salazar DL, Uchida N, Cummings BJ, Anderson AJ (2013a) Safety of epicenter versus intact parenchyma as a transplantation site for human neural stem cells for spinal cord injury therapy. Stem Cells Transl Med 2:204–216.
Piltti KM, Salazar DL, Uchida N, Cummings BJ, Anderson AJ (2013b) Safety of human neural stem cell transplantation in chronic spinal cord injury. Stem Cells Transl Med 2:961–974.
Pomeshchik Y, Puttonen KA, Kidin I, Ruponen M, Lehtonen S, Malm T, Akesson E, Hovatta O, Koistinaho J (2015) Transplanted human induced pluripotent stem cell-derived neural progenitor cells do not promote functional recovery of pharmacologically immunosuppressed mice with contusion spinal cord injury. Cell Transplant 24:1799–1812.
Rivera FJ, Couillard-Despres S, Pedre X, Ploetz S, Caioni M, Lois C, Bogdahn U, Aigner L (2006) Mesenchymal stem cells instruct oligodendrogenic fate decision on adult neural stem cells. Stem Cells (Dayton, Ohio) 24:2209–2219.
Romanyuk N, Amemori T, Turnovcova K, Prochazka P, Onteniente B, Sykova E, Jendelova P (2015) Beneficial effect of human induced pluripotent stem cell-derived neural precursors in spinal cord injury repair. Cell Transplant 24:1781–1797.
Rowland JW, Hawryluk GWJ, Kwon B, Fehlings MG (2008) Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. Neurosurg Focus 25.
Salazar DL, Uchida N, Hamers FP, Cummings BJ, Anderson AJ (2010) Human neural stem cells differentiate and promote locomotor recovery in an early chronic spinal cord injury NOD-scid mouse model. PLoS One 5 e12272.
Salewski RP, Mitchell RA, Li L, Shen C, Milekovskaia M, Nagy A, Fehlings MG (2015a) Transplantation of induced pluripotent stem cell-derived neural stem cells mediate functional recovery following thoracic spinal cord injury through remyelination of axons. Stem Cells Transl Med 4:743–754.
Salewski RP, Mitchell RA, Shen C, Fehlings MG (2015b) Transplantation of neural stem cells clonally derived from embryonic stem cells promotes recovery after murine spinal cord injury. Stem Cells Dev 24:36–50.
Scholz J, Woolf CJ (2007) The neuropathic pain triad: neurons, immune cells and glia. Nat Neurosci 10:1361–1368.
Sharp K, Boroujerdi A, Steward O, Luo ZD (2012) A rat chronic pain model of spinal cord contusion injury. Methods Mol Biol 851:195–203.
Sharp KG, Yee KM, Steward O (2014) A re-assessment of long distance growth and connectivity of neural stem cells after severe spinal cord injury. Exp Neurol 257:186–204.
Sistrom CL, Mergo PJ (2000) A simple method for obtaining original data from published graphs and plots. Am J Roentgenol 174:1241–1244.
Sontag CJ, Nguyen HX, Kamei N, Uchida N, Anderson AJ, Cummings BJ (2013) Immunosuppressants affect human neural stem cells in vitro but not in an in vivo model of spinal cord injury. Stem Cells Transl Med 2:731–744.
Sun D, Gugliotta M, Rolfe A, Reid W, McQuiston AR, Hu W, Young H (2011) Sustained survival and maturation of adult neural stem/progenitor cells after transplantation into the injured brain. J Neurotrauma 28:961–972.
Tarasenko YI, Gao J, Nie L, Johnson KM, Grady JJ, Hulsebosch CE, McAdoo DJ, Wu P (2007) Human fetal neural stem cells grafted into contusion-injured rat spinal cords improve behavior. J Neurosci Res 85:47–57.
Teixeira FG, Carvalho MM, Sousa N, Salgado AJ (2013) Mesenchymal stem cells secretome: a new paradigm for central nervous system regeneration? Cell Mol Life Sci 70:3871–3882.
Teng YD, Lavik EB, Qu X, Park KI, Ourednik J, Zurakowski D, Langer R, Snyder EY (2002) Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. Proc Natl Acad Sci USA 99:3024–3029.
Tetzlaff W, Okon EB, Karimi-Abdolrezaee S, Hill CE, Sparling JS, Plemel JR, Plunet WT, Tsai EC, Baptiste D, Smithson LJ, Kawaja MD, Fehlings MG, Kwon BK (2011) A systematic review of cellular transplantation therapies for spinal cord injury. J Neurotrauma 28:1611–1682.
Tsuji O, Miura K, Fujiyoshi K, Momoshima S, Nakamura M, Okano H (2011) Cell therapy for spinal cord injury by neural stem/progenitor cells derived from iPS/ES cells. Neurotherapeutics: the journal of the American Society for Experimental. Neurotherapeutics 8:668–676.
Tsuji O, Miura K, Okada Y, Fujiyoshi K, Mukaino M, Nagoshi N, Kitamura K, Kumagai G, Nishino M, Tomisato S, Higashi H, Nagai T, Katoh H, Kohda K, Matsuzaki Y, Yuzaki M, Ikeda E, Toyama Y, Nakamura M, Yamanaka S, Okano H (2010) Therapeutic potential of appropriately evaluated safe-induced pluripotent stem cells for spinal cord injury. Proc Natl Acad Sci USA 107:12704–12709.
Uccelli A, Moretta L, Pistoia V (2008) Mesenchymal stem cells in health and disease. Nat Rev Immunol 8:726–736.
van Gorp S, Leerink M, Kakinohana O, Platoshyn O, Santucci C, Galik J, Joosten EA, Hruska-Plochan M, Goldberg D, Marsala S, Johe K, Ciacci JD, Marsala M (2013) Amelioration of motor/sensory dysfunction and spasticity in a rat model of acute lumbar spinal cord injury by human neural stem cell transplantation. Stem Cell Res Ther 4:57.
Wang JM, Zeng YS, Wu JL, Li Y, Teng YD (2011) Cograft of neural stem cells and schwann cells overexpressing TrkC and neurotrophin-3 respectively after rat spinal cord transection. Biomaterials 32:7454–7468.
Wang L, Wei FX, Cen JS, Ping SN, Li ZQ, Chen NN, Cui SB, Wan Y, Liu SY (2014) Early administration of tumor necrosis factor-alpha antagonist promotes survival of transplanted neural stem cells and axon myelination after spinal cord injury in rats. Brain Res 1575:87–100.
Wright KT, El Masri W, Osman A, Roberts S, Chamberlain G, Ashton BA, Johnson WE (2007) Bone marrow stromal cells stimulate neurite outgrowth over neural proteoglycans (CSPG), myelin associated glycoprotein and Nogo-A. Biochem Biophys Res Commun 354:559–566.
Xia L, Wan H, Hao SY, Li DZ, Chen G, Gao CC, Li JH, Yang F, Wang SG, Liu S (2013) Co-transplantation of neural stem cells and Schwann cells within poly (L-lactic-co-glycolic acid) scaffolds facilitates axonal regeneration in hemisected rat spinal cord. Chin Med J 126:909–917.
Xu CJ, Xu L, Huang LD, Li Y, Yu PP, Hang Q, Xu XM, Lu PH (2011) Combined NgR vaccination and neural stem cell transplantation promote functional recovery after spinal cord injury in adult rats. Neuropathol Appl Neurobiol 37:135–155.

Xu J, Fan G, Chen S, Wu Y, Xu XM, Hsu CY (1998) Methylprednisolone inhibition of TNF-α expression and NF-kB activation after spinal cord injury in rats. Mol Brain Res 59:135–142.

Yamane J, Nakamura M, Iwanami A, Sakaguchi M, Katoh H, Yamada M, Momoshima S, Miyao S, Ishii K, Tamaoki N, Nomura T, Okano HJ, Kanemura Y, Toyama Y, Okano H (2010) Transplantation of galectin-1-expressing human neural stem cells into the injured spinal cord of adult common marmosets. J Neurosci Res 88:1394–1405.

Yang JR, Liao CH, Pang CY, Huang LLH, Chen YL, Shiue YL, Chen LR (2013) Transplantation of porcine embryonic stem cells and their derived neuronal progenitors in a spinal cord injury rat model. Cytotherapy 15:201–208.

Yao ZG, Sun XL, Li P, Liu HL, Wu HL, Xi ZQ, Zheng ZH (2015) Neural stem cells transplantation alleviate the hyperalgesia of spinal cord injured (SCI) associated with down-regulation of BDNF. Int J Clin Exp Med 8:404–412.

Yasuda A, Tsuji O, Shibata S, Nori S, Takano M, Kobayashi Y, Takahashi Y, Fujiyoshi K, Hara CM, Miyawaki A, Okano HJ, Toyama Y, Nakamura M, Okano H (2011) Significance of remyelination by neural stem/progenitor cells transplanted into the injured spinal cord. Stem Cells (Dayton, Ohio) 29:1983–1994.

Yokota K, Kobayakawa K, Kubota K, Miyawaki A, Okano H, Ohkawa Y, Iwamoto Y, Okada S (2015) Engrafted neural stem/progenitor cells promote functional recovery through synapse reorganization with spared host neurons after spinal cord injury. Stem Cell Rep 5:264–277.

Yuan N, Tian W, Sun L, Yuan R, Tao J, Chen D (2014) Neural stem cell transplantation in a double-layer collagen membrane with unequal pore sizes for spinal cord injury repair. Neural Regenerat Res 9:1014–1019.

Zhang X, Zeng Y, Zhang W, Wang J, Wu J, Li J (2007) Co-transplantation of neural stem cells and NT-3-overexpressing Schwann cells in transected spinal cord. J Neurotrauma 24:1863–1877.

Ziv Y, Avidan H, Pluchino S, Martino G, Schwartz M (2006) Synergy between immune cells and adult neural stem/progenitor cells promotes functional recovery from spinal cord injury. Proc Natl Acad Sci USA 103:13174–13179.

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