Efficacy of intervertebral disc regeneration with stem cells — A systematic review and meta-analysis of animal controlled trials

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1. Introduction

Low back and neck pain have a point prevalence of 19% of the world’s population, a three-month prevalence of 31% in the United States (Strine and Hootman, 2007; Hoy et al., 2012, 2014). They are ranked the first and fourth most common causes for disability in the United States (Murray et al., 2013), and are associated with a tremendous expenditure of hundreds of billions ($80.1 billion to $91.8 billion) of US dollars annually (Martin et al., 2008). Intervertebral disc (IVD) degeneration is ubiquitous and increases with age, with a prevalence of over 70% in the age group of 50 years or younger, and over 90% in those older than 50 (Teraguchi et al., 2014). As an aging population becomes more active, disc degeneration becomes a larger issue. Disc degeneration is a degenerative process that occurs with age and following injuries (Heron and Duranceau, 2000). If the disc is impinged, it becomes painful, often termed discogenic pain. Discogenic pain accounts for 25% to 80% of all low back and neck pain (Rogers, 2003; Manchikanti et al., 2009; Gilbert et al., 2013; Strine and Hootman, 2007; Hoy et al., 2012, 2014). Management of intervertebral disc (IVD) degenerative disease is challenging, as it is accompanied by irreversible loss of IVD cells. Stem cell transplantation to the disc has shown promise in decelerating or arresting the degenerative process. Multiple pre-clinical animal trials have been conducted, but with conflicting outcomes. To assess the effect of stem cell transplantation, a systematic review and meta-analysis was performed. A comprehensive literature search was conducted through Week 3, 2015. Inclusion criteria consisted of controlled animal trials. Two reviewers screened abstracts and full texts. Disagreements were resolved by a third reviewer. Random effects models were constructed to pool standardized mean difference (SMD). Twenty two studies were included; nine of which were randomized. Statistically significant differences were found with the stem cell group exhibiting increased disc height index (SMD = 3.64, 95% confidence interval (CI): 2.49, 4.78; p < 0.001), increased MRI T2 signal intensity (SMD = 2.28, 95% CI: 1.48, 3.08; p < 0.001), increased Type II collagen mRNA expression (SMD = 3.68, 95% CI: 1.66, 5.70; p < 0.001), and decreased histologic disc degeneration grade (SMD = −2.97, 95% CI: −3.97, −1.97; p < 0.001). There was statistical heterogeneity between studies that could not be explained with pre-planned subgroup analyses based on animal species, study designs, and transplanted cell types. Stem cells transplanted to the IVD in quadruped animals decelerate or arrest the IVD degenerative process. Further studies in human clinical trials will be needed to understand if such benefit can be translated to bipedal humans.

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The degenerative intervertebral disc disease is characterized by cell death and degeneration of extracellular matrix (Urban and Roberts, 2003). Cell death occurs through an apoptosis process associated with aging, genetic propensity, and spinal loading (Lotz and Chin, 2000; Hunter et al., 2003; Livshits et al., 2011; Hirata et al., 2014; Yurube et al., 2014). The decrease of extracellular matrix synthesis and increase of extracellular matrix degeneration are associated with loss of cells and phenotype changes in the surviving cells secondary to local inflammatory responses (Trout et al., 1982; Urban and Roberts, 2003). As a result, the condition presents with dehydration of the nucleus pulposus, fissures of the annulus fibrosus, extrusion of the NP, and a cascade of inflammatory responses that perpetuate the cycle of loss of appropriate matrix (Urban and Roberts, 2003; Gilbert et al., 2013). Micro-environmental changes including neovascularization and nerve growth lead to clinical presentations of pain and altered biomechanical function (Adams et al., 1996; Freemont et al., 1997; Johnson et al., 2012; Richardson et al., 2008; Henriksson et al., 2009; Benneker et al., 2014).

The treatment of discogenic pain has been particularly challenging due to the irreversible loss of intervertebral disc cells. Current treatment modalities include pain medication (Koes et al., 1997; Van Tulder et al., 2000; Roelofs et al., 2002), therapies (Van Middelkoop et al., 2011; Jang and Lee, 2012), injections (Staal et al., 2009; Lu et al., 2014), nucleoplasty (Welch and Gerszten, 2002; Mirzai et al., 2007; Adam et al., 2013) and surgical discectomy (McCulloch, 1996; Soliman et al., 2014). None addresses the IVD degeneration. Because the extracellular matrix is synthesized and modulated by IVD cells, there has been significant interest in researching cell therapy utilizing stem cells and meniscocymal stem cells for the regeneration of the IVD (Trout et al., 1982; Kalsoen et al., 2008; Richardson et al., 2008; Henriksson et al., 2009; Benneker et al., 2014). Multiple pre-clinical randomized controlled animal trials have been performed, but often suffered with small sample size, heterogeneous designs, and conflicting outcomes. Since a consensus on the effect of stem cell transplantation in animals is needed to justify human clinical trials, we conducted a systematic review and a meta-analysis. Specifically, the objective of this study was to evaluate intervertebral disc regeneration due to stem cell transplantation in controlled animal trials. Objective outcomes of disc regeneration included: changes in disc height, nucleus pulposus rehydration on T2 weighted MRI images, histologic disc degeneration grade, and expression of type II collagen regeneration.

2. Methods

The study protocol was finalized in advance of any data collection, which defined objectives, search strategy, inclusion/exclusion criteria, data extraction, outcomes of interest, and analytical approaches. The reporting of this systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

2.1. Search strategy

We conducted a comprehensive search of seven databases, including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus, from each database’s inception to Week 3, 2015. Controlled vocabulary supplemented with keywords was used to search for studies of intervertebral disc height after stem cell transplantation. Search terms were broad and without language or country restrictions. The detailed strategy is available in Appendix 1.

2.2. Inclusion and exclusion criteria

We included pre-clinical controlled trials (randomized controlled trials (RCTs), and non-randomized controlled trials (N-RCTs)) that evaluated stem cell transplantation on experimental regeneration of the intervertebral disc in animals. We focused on the outcomes that were pertinent to the effect and mechanism in IVD regeneration (disc height index, MRI T2 signal intensity, Type II collagen expression, and histologic disc degeneration grade). Animals with any type of model in IVD degeneration secondary to IVD trauma by changing mechanical loading, puncture incision or gamma irradiation, or chemical assault with chemonucleolysis by chondroitinase ABC, chymopapain or fibronectin fragments were included regardless of species/breeds of animal. We did not restrict the type of intervention in control groups. Studies were excluded if they combined multiple treatments (e.g., stem cells and Rho-GTPase inhibitory agents) or if models of nontraumatic spinal cord injury were used. We also excluded studies without original data (e.g., clinical reviews, editorials, letters, or erratum) or without the outcomes of interest.

2.3. Data extraction

Two independent reviewers reviewed the abstracts and full texts of potentially relevant studies. Discrepancies between the reviewers were resolved through discussion and consensus. The same two reviewers extracted study details from the full text studies using a standardized pilot-tested form. The following data were extracted: the author, year of publication, animal species, disc degeneration model (traumatic or chemical), cell type, interventions in control groups, and outcomes of interest. When outcomes of interest were assessed serially, we extracted data for the final time point. Where multiple arms were included in the study, the control group and the stem cell transplantation group were selected.

2.4. Quality assessment

We applied the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) checklist to assess the methodological quality of the included studies (Sena et al., 2007). A 9-point-item check list was used to assess the risk for bias, including: (1) published in a peer-reviewed journal; (2) control of animals’ temperature; (3) randomized treatment allocation; (4) treatment allocation concealment; (5) blinded assessment of outcome; (6) use of anesthetics other than ketamine; (7) reporting of a sample size calculation; (8) statement of compliance with regulatory requirements; and (9) statement of potential conflict of interest.

2.5. Statistical analysis

We calculated standardized mean difference (SMD) and related 95% confidence interval (CI) for each study using Cohen’s d method to normalize for the different animal species. We then combined outcomes of interest across the included studies using the DerSimonian and Laird random effect methods. The heterogeneity was estimated using the Mantel–Haenszel model. We conducted subgroup analyses based on animal species (rabbit, dog, rat, pig, and sheep), study designs, and cell types (bone marrow stromal cells (BMSCs), and adipose-derived stem cells (ADMSCs)) to investigate potential sources of heterogeneity and the robustness of our findings. Heterogeneity across individual studies was assessed using the $I^2$ index and Cochran’s $Q$ statistical test, where $I^2 > 50\%$ and/or $p < 0.10$ suggest high heterogeneity. All meta-analyses were conducted using STATA version 13.1 (StataCorp, College Station, TX).
3. Results

3.1. Study characteristics

We identified 642 unique citations, of which 566 were excluded by title/abstract screening (Fig. 1). 22 studies were included in this review, including 9 (40.91%) RCTs and 13 (59.09%) N-RCTs. Animals used for studies included rabbits in 11 studies (50.00%), rats/mice in 6 (27.27%), dogs in 3 (13.64%), pigs in 1 (4.55%), and sheep in 1 (4.55%) (Table 1). Overall, 626 discs were studied, of which 313 were transplanted with stem cells and 313 were controls. The types of transplanted cell used in the studies included 18 BMSCs (81.82%), and 4 ADMSCs (18.18%). Mean maximal follow-up time was 16.79 weeks after transplantation (range: 5–56 weeks).

3.2. Risk of bias

Risk of bias of the included studies was high to moderate (Fig. 2). Most of the included studies did not report sufficient information to assess overall quality. Though all studies were peer-reviewed, 13 studies did not use randomization and no study reported methods of treatment concealment. Of the included studies, 44.44% reported compliance with regulatory requirements and 36.11% provided a statement on conflict of interest. Assessment of publication bias was not conducted due to the limited number of studies included in analysis and high heterogeneity ($I^2 > 50\%$) in all analyses (Serigano et al., 2010).

3.3. Outcomes

We identified 13 studies for the meta-analysis on disc height index (Fig. 3). We found that disc height index in the stem cell transplantation group was significantly higher than the control group (SMD = 3.64, 95% CI: 2.49, 4.78, $p < 0.001$, $I^2 = 91.3\%$). There were 14 studies that reported MRI T2 signal intensity outcomes (Table 2). A significant increase of MRI T2 signal intensity was found in the stem cell transplantation group compared with the control (SMD = 2.28, 95% CI: 1.48, 3.08, $p < 0.001$, $I^2 = 88.5\%$). 11 studies of stem cell transplantation were also found to significantly reduce histologic disc degeneration grade compared to the control group (SMD = −2.97, 95% CI: −3.97, −1.97, $p < 0.001$, $I^2 = 80.1\%$). Moreover, increased expression of type II collagen was identified in 9 studies (SMD = 3.68, 95% CI: 1.66, 5.70, $p < 0.001$, $I^2 = 95.8\%$).

3.4. Subgroup analysis

We conducted subgroup analyses based on animal species, cell types, and study design. We found no significant changes between subgroups and our main analysis in all, except one, of the subgroup analyses.

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Fig. 1. Flow diagram sketches the current system review identified, screened, included and excluded in meta-analysis.
One study reported disc height index in sheep and found a significant reduction of disc height index in the treated group (SMD = −2.75, 95% CI: −4.40, −1.09) (Ghosh et al., 2012). However, other studies reported significant increases in disc space height in dog, pig, rabbit, and rat models.

4. Discussion

We conducted a systematic review and meta-analysis to evaluate intervertebral disc regeneration with stem cells in animal controlled trials. Twenty two studies were included in the analysis. Stem cell transplantation was associated with significantly increased disc height index, T2 weighted MRI signal intensity, type II collagen expression, and significantly reduced histologic disc degenerative grade.

The degenerative IVD is the result of a series of changes in metabolism, biomechanics and morphology. The degeneration processes are closely related to cell loss, extracellular matrix (ECM) breakdown with collagen fiber denaturation and degradation, decreased disc osmotic pressure with dehydration and cleft formation, anabolic and catabolic unbalance with increased inflammatory cytokines and infiltrated immune cells, and neovascularization and nociceptive nerve ingrowth (Trout et al., 1982; Adams et al., 1996; Urban and Roberts, 2003; Zhang et al., 2005; Hughes et al., 2012; Gilbert et al., 2013). Since Pittenger et al. first demonstrated that the MSCs isolated from bone marrow possessed the potential of the multi-lineage differentiation (Pittenger et al., 1999), stem cells have been successfully distinguished and derived from many adult tissues, such as adipose, muscle, dermis, synovial membrane, synovial fluid, and cartilage (Barry and Murphy, 2004; Richardson et al., 2010). In this meta-analysis, the studies explored the strategy of cell-based IVD regeneration by means of stem cell transplantation in different animal models. It is noteworthy that these regeneration processes after stem cell transplantation seem to

(Tables 3, 4, 5). One study reported disc height index in sheep and found a significant reduction of disc height index in the treated group (SMD = −2.75, 95% CI: −4.40, −1.09) (Ghosh et al., 2012). However, other studies reported significant increases in disc space height in dog, pig, rabbit, and rat models.

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Note: BMSC, bone marrow stromal cell; ADMSC, adipose-derived mesenchymal stem cell; RCT, randomized controlled trial; N-RCT, non-randomized controlled trial.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Animal</th>
<th>Disc degeneration model</th>
<th>Study design</th>
<th>Types of cell</th>
<th>Follow-up (weeks)</th>
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<tr>
<td>Allon et al.</td>
<td>2010</td>
<td>USA</td>
<td>Rat</td>
<td>Partial nucleotomy</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>5</td>
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<tr>
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<td>2012</td>
<td>China</td>
<td>Rabbit</td>
<td>Needle puncture</td>
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<td>ADMSC</td>
<td>2</td>
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<td>Liang et al.</td>
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<td>Rat</td>
<td>Needle puncture</td>
<td>RCT</td>
<td>ADMSC</td>
<td>24</td>
</tr>
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<td>Rabbit</td>
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<td>RCT</td>
<td>BMSC</td>
<td>10</td>
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<td>2009</td>
<td>China</td>
<td>Mouse</td>
<td>Needle puncture</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>24</td>
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<tr>
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<td>Rabbit</td>
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<td>BMSC</td>
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<td>RCT</td>
<td>BMSC</td>
<td>24</td>
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<td>China</td>
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<td>Needle puncture</td>
<td>RCT</td>
<td>BMSC</td>
<td>12</td>
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<td>Nucleus pulposus aspiration</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>16</td>
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<tr>
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<td>Dog</td>
<td>Partial nucleotomy</td>
<td>RCT</td>
<td>ADMSC</td>
<td>48</td>
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<td>Sheep</td>
<td>Chondroitinase induction</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>24</td>
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<td>Hiyama et al.</td>
<td>2008</td>
<td>Japan</td>
<td>Dog</td>
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<td>N-RCT</td>
<td>BMSC</td>
<td>8</td>
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<tr>
<td>Ho et al.</td>
<td>2008</td>
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<td>Rabbit</td>
<td>Needle puncture</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>28</td>
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<td>Korea</td>
<td>Rat</td>
<td>Blade injury</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>8</td>
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<td>Needle puncture</td>
<td>N-RCT</td>
<td>ADMSC</td>
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<td>China</td>
<td>Rabbit</td>
<td>Needle puncture</td>
<td>N-RCT</td>
<td>ADMSC</td>
<td>8</td>
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<td>2006</td>
<td>Japan</td>
<td>Rabbit</td>
<td>Nucleus pulposus aspiration</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>24</td>
</tr>
<tr>
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<td>2010</td>
<td>Japan</td>
<td>Dog</td>
<td>Nucleus pulposus aspiration</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>12</td>
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<tr>
<td>Wu et al.</td>
<td>2007</td>
<td>China</td>
<td>Rat</td>
<td>Chondroitinase induction</td>
<td>N-RCT</td>
<td>BMSC</td>
<td>2</td>
</tr>
<tr>
<td>Yang et al.</td>
<td>2010</td>
<td>USA</td>
<td>Rabbit</td>
<td>Nucleus pulposus aspiration</td>
<td>RCT</td>
<td>BMSC</td>
<td>12</td>
</tr>
<tr>
<td>Subhan et al.</td>
<td>2014</td>
<td>Malaysia</td>
<td>Rabbit</td>
<td>Needle puncture</td>
<td>RCT</td>
<td>BMSC</td>
<td>16</td>
</tr>
<tr>
<td>Cai et al.</td>
<td>2015</td>
<td>China</td>
<td>Rabbit</td>
<td>Needle puncture</td>
<td>RCT</td>
<td>BMSC</td>
<td>10</td>
</tr>
</tbody>
</table>

Fig. 2. Risk of bias of the included studies.
be closely connected to a cascade of changes and can be expressed as follows: enhanced intra-discal cell phenotype induction (Pittenger et al., 1999; Zhang et al., 2007; Richardson et al., 2008; Gilbert et al., 2013; Hirata et al., 2014; Yurube et al., 2014), increased gene and protein expression of type II collagen (Zhang et al., 2005, 2007; Sakai et al., 2006; Yang et al., 2010; Feng et al., 2011a), restored intra-discal hydration (Zhao et al., 2008; Jeong et al., 2009, 2010; Feng et al., 2011a; Jiang et al., 2011; Wu et al., 2011; Liang et al., 2013), ameliorated ongoing disc degeneration processes (Sakai et al., 2006; Ho et al., 2008; Jeong et al., 2009; Yang et al., 2009; Allon et al., 2010; Feng et al., 2011a; Liang et al., 2013), and prevention of loss of disc height (Sakai et al., 2006; Wu et al., 2007, 2011; Yang et al., 2009, 2010; Liang et al., 2013).

Moreover, our study also sheds light on the mechanism of disc regeneration with stem cell transplantation. Stem cells have been known to maintain a regenerative capacity and have the ability to decelerate or arrest the degenerative processes by means of differentiating towards NP-like cells. It is hypothesized that the regeneration effect are the results of processes involving the production of intra-discal matrix by induced stem cells in vivo, stimulation of the progenitor cells of the disc by the trophic factors released by the stem cells, and decreased inflammatory response as a response to immunomodulating cytokines released by stem cells (Barry and Murphy, 2004; Richardson et al., 2010; Schmitt et al., 2012; Gilbert et al., 2013).

4.1. Clinical implications

The meta-analysis suggests that stem cells halt the degeneration processes in IVD and promote IVD regeneration in animal studies. It was hypothesized that those changes are attributed to the trophic, immunomodulating, and matrix producing the ability of the stem cells induced by the local environment after transplantation. Those findings provide a foundation for testing the effect of stem cells in human studies. Currently, a few closed or active clinical trials are listed in ClinicalTrials.gov. Three currently active trials are open label trials. One closed phase 2 clinical trial has not been reported in literature yet. There are more trials being planned for treatment of degenerative disc conditions with stem cells. Whether or not the benefit observed in animal studies could be translated to humans would depend on the outcomes of future trials.

4.2. Future works

Despite the encouraging results of this meta-analysis on the use of stem cells in IVD degeneration, for cell-based regenerative medicine to play a critical role in clinical treatment of discogenic pain, further research is required. Important research includes identification of appropriate transcriptional factors for induction of the MSCs towards nucleus pulposus-like cells, genome modification of the MSCs for

Table 2
The effects of stem cell transplantation on intervertebral disc degeneration.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of studies</th>
<th>SMD</th>
<th>95% CI</th>
<th>p value</th>
<th>I²</th>
<th>Heterogeneity p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc height Index</td>
<td>13</td>
<td>3.64</td>
<td>2.49, 4.78</td>
<td>&lt;0.001</td>
<td>91.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRI T2 signal</td>
<td>14</td>
<td>2.28</td>
<td>1.48, 3.08</td>
<td>&lt;0.001</td>
<td>88.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Histologic disc degenerative grade</td>
<td>11</td>
<td>−2.97</td>
<td>−3.97, −1.97</td>
<td>&lt;0.001</td>
<td>80.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type II collagen expression</td>
<td>9</td>
<td>3.68</td>
<td>1.66, 5.70</td>
<td>&lt;0.001</td>
<td>95.8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: SMD, standardized mean difference; 95% CI, 95% confidence interval.
potentiating matrix and trophic factor productions, and stimulation of the MSCs for enhanced immunomodulation activities. This requires better understanding of the genome composition and phenotypical expression of MSCs as well as the nucleus pulposus-like cells. In addition, human clinical trials will be needed to understand if the benefit identified in animal models can be translated to bipedal humans.

4.3. Limitations

Our study suffers several important limitations. First, all of the included studies were quadrupedal animal studies in which the largely non-weight-bearing spine may provide a more forgiving environment for the stem cells to survive and function. Second, substantial heterogeneity was observed across the studies in all of the outcomes ($I^2 > 50\%$). We were unable to evaluate potential publication bias due to high heterogeneity and the limited number of studies included. Publication bias is quite likely in animal studies.

Nevertheless, our study has several strengths. We conducted a comprehensive search of multiple databases, selected and appraised studies by independent pairs of reviewers, and followed a priori planned protocol that included several hypotheses for subgroup analysis. Almost all of the included studies show significant benefits across different animal species, cell types and study designs. Therefore, our results provide justification for further evaluation of stem cell transplantation in human trials.

5. Conclusion

Stem cells transplanted to the IVD in animals decelerate and arrest the IVD degenerative process. Further studies in human clinical trials will be needed to advance our knowledge of the benefit.

Competing interests

The authors have declared that no competing interest exists.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.gene.2015.03.022.

References


