SPINE An International Journal for the study of the spine Publish Ahead of Print

DOI : 10.1097/BRS.0000000000001549

Cell-Based Therapies for lumbar discogenic low back pain - Systematic Review and Single Arm Meta-Analysis

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Acknowledgement: November 9, 2015

1st Revise: December 27, 2015

2nd Revise: January 22, 2016

Accept: February 1, 2016

The manuscript submitted does not contain information about medical device(s)/drug(s).

No funds were received in support of this work.

No relevant financial activities outside the submitted work.

Study Design A systematic review and single arm meta-analysis of clinical trials.

Objective To assess the efficacy of mesenchymal stem cells (MSC) or chondrocyte in patients with discogenic low back pain.

Summary of Background Data There is no previous review evaluated the efficacy of MSC or chondrocyte therapy in adults with discogenic low back pain.

Methods: A comprehensive literature search was conducted from database on PubMed, Ovid MEDLINE, Ovid EMBASE, EBSCO and Web of Science from database inception through on September 10th, 2015. We included clinical trials that evaluated stem cells or chondrocyte-based therapy in patients with disc-genic back pain. The primary outcomes of interest were pain score and Oswestry Disability Index (ODI). We performed random effects model meta-analyses to assess net changes in the same outcome variables. Heterogeneity between studies was estimated by I^2 statistic.

Results The initial search identified 1393 articles, of which 6 studies were eligible for this review. The pooled mean difference in pain score from baseline to follow-up points was 44.2 points decreased (95%CI: -61.8 to −26.5, p<0.001, I^2=99.4%). Meanwhile, the pooled mean difference in ODI from baseline to follow-up points was 32.2 points decreased (95%CI: -41.6 to −22.9, p<0.001, I^2=99.5%). No related adverse effects were reported by the included studies.

Conclusion Cell-based therapy is for patients who have discogenic low back pain associated with improved pain relief and Oswestry Disability Index. More stringently designed randomized double-blind clinical trials with appropriately determined sample sizes will be needed to confirm its clinical efficacy and safety.

Key words: stem cell, chondrocyte, disc, pain, regeneration

Level of Evidence: 4

INTRODUCTION

Discogenic low back pain originating from intervertebral disc degeneration is considered to be one of the major causes of chronic low back pain (CLBP) [1]. Combined physical therapy such as activity modification, chiropractic care, exercise and medical therapies[2,3] are successful in relieving pain in approximately 90% of the patients. However, the remaining 10% become chronic and generate a serious public health problem as CLBP[4]. Surgical treatments for chronic, severe, discogenic back pain include spinal fusion or artificial disc replacement[5]. Patients with more than two abnormal discs typically have no surgical options based on a consensus against three-level or more fusion surgeries in the medical community. Recently, a prospective randomized studies comparing fusion versus non-surgical therapy in patients with moderate to severe low back pain and disability that had persisted for one year or more showed an average of 35.3 % improvement in the surgical group and a 20 % improvement in the non-surgical group[5].

The treatment of discogenic pain has been particularly challenging due to the irreversible loss of intervertebral disc (IVD) cells. Inter vertebral discs contain 3 distinct cell populations, annulus fibrosus cells, nucleus pulposus cells, and endplate chondrocytes. Because the extracellular matrix is synthesized and modulated by IVD cells, there has been significant interest in researching cell therapy utilizing chondrocyte cells or mesenchymal stem cells (MSCs) for the regeneration of the IVD[6]. Cell therapy approach may address underlying sources of disc degeneration by mitigating inflammation in the nucleus pulposus, rehydration of the nucleus by re-modelling of the tissue or recruiting peripheral cells, nutrients and/or by restoring the disc height to remove pressure from adjacent nerves[7, 8].

Multiple clinical case series trials have been performed, but often suffered with small sample size, heterogeneous designs, and conflicting outcomes. Meanwhile, the effects of these treatments are not yet fully understood and there is a lack of firm evidence on the efficacy and safety of stem cell therapy for those patients due to the absence of sufficiently powered randomized controlled trials. To better represent the currently available clinical evidence and provide a foundation for future research, we conducted this systematic review and single arm meta-analysis of the literature examining the efficacy of cell therapy in the treatment of patients with discogenic low back pain.

MATERIALS AND METHODS

Search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9]. The searches were performed on PubMed, Ovid MEDLINE, Ovid EMBASE, EBSCO and Web of Science from database inception through on September 10th, 2015. Key search terms were cell therapy and intervertebral disc. Each concept used a combination of controlled vocabulary (MeSH and EMTREE) combined with text words for each database which uses subject heading (PubMed, MEDLINE, EMBASE, EBSCO). Web of Science depended primarily on text words alone.

Inclusion and exclusion criteria

An inclusion criterion was any type of cell therapies for discogenic low back pain patients. We cannot restrict any type of cells either the number of patients. Outcomes of interest included changes of pain score and Oswestry Disability Index (ODI) after treatment. Exclusion criteria were unavailable or unclear data and duplicate reports.

Study selection

Once all relevant full-text papers had been gathered, the reference lists of each eligible paper were scrutinized by two reviewers (T.W., H.X.) for any omitted studies. Each search was imported into an EndNote (Thomson Reuters Research Soft), a bibliographic database manager, and duplicates removed. All conflicts were discussed and resolved with a third author (J.H.). The reference sections of all articles were used to identify additional relevant articles.

Data collection process and Outcome measures

Following selection of all relevant articles, two authors (T.W., H.X.) extracted all data into a pre-constructed data table. The following data was extracted: author, year published, population, age, sample size, cell type,

cell dose and deliver pathway, fellow up period, and main evaluation index. The outcome measures collected were changes of pain score and ODI after treatment.

Assessment of risk of bias

Quality assessment risk of bias was evaluated using the scale form "Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions"[10]. The checklist contains 9 questions that relate to the selection, performance, attrition, detection, and reporting bias. Risk of bias was independently assessed by two authors for each study. Disagreements were resolved by discussion between the two authors.

STATISTICAL ANALYSIS

We performed random effects model meta-analyses to assess net changes in the same outcome variables. Existence of heterogeneity among effect sizes of individual studies was assessed using the I^2 index and Q statistic. Heterogeneity was analyzed with the I^2 statistic, and heterogeneity was defined as low (25% to 50%), moderate (50% to 75%), or high (＞75%) [11]. Subgroup analyses were conducted based on follow-up periods (6 months *vs* 12 months or more), injected cell type (stem cell *vs* chondrocyte), and cell preprocessing condition (expanded *vs* non-expanded). We conducted meta-regression analysis to determine factors related to decrease in pain score after cell therapy. Data analyses were performed using Comprehensive Meta-analysis version 3.0 (Bio stat Inc., Englewood, NJ).

RESULTS

1. Study characteristics

The initial search identified 1393 articles, of which 6 studies[12,13,14,15,16,17] were eligible for this review (Figure1). Characteristics of 6 studies are described in Table 1. All studies were published from 2006 to 2015 and 74 patients were included. Three studies1[2,13,15] utilized stem cells and another three studies[14,16,17] utilized chondrocytes. Five studies used expanded cells[13,14,15,16,17] and one[12] utilized un-expanded cells. Cells were injected into lumbar disc with the range from one to 23 ± 5 million cell dose. Among the 6 trials the mean duration of follow-up was 22 months with a range of 12-36 months.

2. Clinical outcomes

1) Decreased pain score (Numerical Rating Scale, NRS & visual analog scale, VAS) after treatment

Five studies assessed pain score after treatment using VAS[12,13,15,16] (0-100) or NRS[14] (0-10). The pooled mean difference in pain score from baseline to follow-up points was 44.2 points decreased (95%CI: -61.8 to −26.5, p<0.001, I^2=99.4%, Figure 2)

2) Decreased Oswestry Disability Index (ODI) after treatment

Five studies assessed *Oswestry Disability Index (ODI,* 0-100) after treatment[12,13,14,15,16]. The ODI is an assessment tool that is used to measure a patient's impairment and quality of life (i.e., how badly the pain has affected their life). The test is the "gold standard" of low back functional outcome tools. The pooled mean difference in ODI from baseline to follow-up points was 32.2 points decreased (95%CI: -41.6 to −22.9, p<0.001, I^2=99.5%, Figure 3).

3) Subgroup and meta-regression analyses on the changes in pain score

We conducted subgroup analysis to explore the source of heterogeneity in pain score with respect to follow-up periods (6 months vs 12 months or more), injected cell type (stem cell vs chondrocyte), and cell preprocessing condition (expanded vs non-expanded). The analysis demonstrated that there was no difference of decreased pain score between these respects (table-2). We also conducted meta-regression analysis to determine factors related to decrease in pain score after stem cell therapy. The results showed that pain score decrease was related to cell type (stem cells vs chondrocytes). Stem cells were more effective than chondrocytes in decreased pain score (table-3).

4) MRI Evaluation

Four trails[14,15,16,17] performed morphologic grading of the MRI data after intervention. MRI showed improvements in some patients with improvements in disc contour or height[14]. The ratio of fluid content of the affected segments to healthy segments was low at the beginning of treatment. This value did not change significantly at 6 months but increased to at 12 months[15]. Autologous cultured disc-derived chondrocytes treated group showed a substantially higher normalization as 41% normal fluid content compared with only

25% normal content in the control group[16]. In Mochida's study[17], the degeneration at the IVD where the activated nucleus pulpous (NP) cells were transplanted was less than grade III (according to Pfirrmann's classification) on MRI at the beginning of the study. They found that there were no examples where degeneration of the transplanted IVD became worse up to the final follow-up at 3 years.

5) Other evaluation index

In Mochida's study[17], the clinical outcome using the Japanese Orthopedic Association (JOA) scoring system improved from 14.2 ± 4.8 points preoperatively to 27.2 ± 1.6 points at 3 years after transplantation of the activated NP cells. All of the patients who worked returned to their original job after an average of 5.8 weeks. In Coric's study, the mean SF-36 physical component summary (baseline 35.3, 12-month 46.9; p = 0.0002) scores improved significantly from baseline[14]. High-intensity zones (HIZs), consistent with posterior anular tears, were present at baseline and was either absent or improved (in 89% patient) by 6 months[14].

6) Safety

There were no related adverse events reported in all of the included studies. There was no tumor formation observed in any clinical cases in stem cell transplantation during fellow up period.

3. Risk of bias

Quality assessment risk of bias was evaluated using the scale which contains 9 questions that relate to the selection, performance, attrition, detection, and reporting bias. Risk of bias detail of each study was demonstrated in Table 4. The likelihood of publication bias has been tested by using funnel plot and Egger regression for pain score. Funnel plot was roughly symmetric shape and the Egger regression analysis was not significant (p=0.896), suggesting less susceptibility to publication bias.

DISCUSSION

Degenerative disc disease (DDD) is an age-related debilitating orthopedic pathology with a prevalence of over 90 % in people older than 50 years of age[18]. DDD results from a combined effect of adverse loading, dehydration, cellular apoptosis, and an imbalance in tissue anabolism and catabolism. The normal disc is a

relatively acellular tissue with the average cell density of 5.8×10^3 cells/mm^3 that decreases significantly with age, but plays a paramount role in matrix synthesis and maintenance of a healthy tissue[19]. There is an increased expression of pro-inflammatory cytokines and proteolytic enzymes with a concomitant reduction in matrix anabolism[20]. Disc degeneration commonly involves changes in disc morphology and composition of the extracellular matrix as well as loss of NP cells. So a potential therapeutic strategy would be the augmentation of the NP cell population to restore normal biologic function and matrix insufficiencies.

In recent years, research activities have intensified in tissue engineering and regenerative medicine, and pre-clinical studies have demonstrated encouraging results[21]. In pre-clinical research, one of three biological approaches is typically used to address the degenerative process: stimulating anabolic processes; modulating catabolic processes; and providing new cells[22]. Tissue-engineered cellular therapy has focused on chondrocyte[23] or stem cell replacement therapy[24]. Biologic approaches to treating discogenic pain are appealing due to their less invasive and financially costly nature compared to surgery.

Cell type: Several sources have been investigated in cell therapy research for DDD. Autologous or allogeneic chondrocytes appear safe and effective in initial clinical trials. Intervertebral disc chondrocytes, such as NP cells, have been successfully isolated from intervertebral disc tissue, culture expanded, and used as a means to treat disc degeneration. Although many studies focusing on the NP, consensus among the research community is lacking in defining the NP cell phenotype. A consensus agreement will allow easier distinguishing of NP cells from annulus fibrosus (AF) cells and endplate chondrocytes. Recently, Risbud et al[25] reported the NP phenotypic markers: stabilized expression of HIF-1α, GLUT-1, aggrecan/collagen II ratio >20, Shh, Brachyury, KRT18/19, CA12, and CD24. The largest clinical trial to date, the Euro DISC study demonstrated that clinical outcomes improved at 2 years[26]. But this treatment is limited to patients requiring disc surgery; otherwise patients not undergoing disc surgery would require harvesting of cells from an adjacent disc. The use of allogeneic chondrocytes either obtained from surgical or from cadaveric donors, would potentially overcome the hurdles associated with the use of autologous disc cells[14].

A high-quality disc matrix and maintenance of the number of disc cells are necessary for the restraint of intervertebral disc degeneration. However, the ability of disc cells to reproduce on their own is low. The

capability of NP cells isolated from a degenerated NP alone is not sufficient enough to slow further disc degeneration. It has been proved that the monoculture of NP cells can enhance the cell numbers, but the number was anticipated as insufficient in terms of quality and quantity for clinical applications[27]. Recently, Mochida et al reported that human NP cells with co-culture with MSCs will activated NP cell transplantation. In their study, one million activated NP cells were transplanted into the degenerated disc adjacent to the fused level at 7 d after the first fusion surgery and the findings suggest the minimal efficacy of this treatment to slow the further degeneration of human intervertebral discs.

Mesenchymal stem cells (MSCs) show exciting promise for disc repair and other tissue engineering strategies. MSCs can be isolated from numerous tissues including bone marrow, adipose tissue, and synovium[28]. MSCs possess the capacity for self-renewal, thus maintaining their undifferentiated phenotype in multiple subcultures, but when exposed to the appropriate stimuli they can undergo differentiation into cells of the mesenchymal lineage such as chondrocytes. Bone marrow derived MSCs (BMDSCs) were the most commonly used stem cell treatment. BMDSCs represent only a small percentage of the total number of cells in bone marrow, and the number of cells useful for regenerative medicine applications is extremely low[29] and MSCs from bone marrow also significantly decreases with donor age[30,31]. Ruan's study indicated that Human umbilical cord tissue-derived mesenchymal stem cells (HUCMSCs) could be induced to differentiate to NP-like cells by co-culturing with nucleus pulposus cells[32]. It suggested that HUC-MSCs could be differentiated into nucleus pulposus-like cells after being grafted into a degenerative disc, and thus could restore the extracellular matrix. Embryonic allograft cells are appealing for their regenerative capacity, but their safe use is of concern.

Cell amount: Cell number considerations were not, however, discussed in the majority of studies. Serigano[33] reported that the optimal dose of autologous MSCs in the canine model was 1×10^6 cells. In 2006, Scott M.W. et al[34] first reported living human studies of cell therapy for DDD. A total of 5 ml of bone marrow aspirate was obtained and then 1 ml of unexpanded HSCs was injected into each of the problematic discs. Patients then underwent a 2-week course of hyperbaric oxygen therapy to assist in oxygen delivery to the

discs, which are known for their poor blood flow. They found that hematopoietic stem cells (HSCs) injection did not correlate with reduced pain, and thus intradiscal HSC injection appears to be of little value.

As we know, 1ml of unexpanded HSCs represented only a small percentage of the total number of cells. Kenneth et al[12] also utilized unexpanded bone marrow concentrate. In their study, 55 ml bone marrow aspirate was collected and then was processed using the ART bone marrow concentration system to produce a bone marrow concentrated cell preparation (Average CD34+/lineage– cell concentration 1.66×10^6/ml, 2-3ml for injection). So the appropriate cell amount maybe the one of the key points to get better therapeutic effect for DDD.

Cell leakage: The issues of cell leakage need to be considered when calculating the ideal cell dose to administer. MSCs can migrate out of the nucleus and undesirable bone formation may occur. While cause cannot be inferred from this study, the presence of MSCs in the osteophytes suggests a potential side-effect with this approach. IVD regeneration strategies need to focus on cell carrier systems and annulus-sealing technologies to avoid pitfalls[35].

Interestingly, Yoshikawa et al[36] utilized pieces of collagen sponge as scaffold containing autologous MSCs to avoid cell leakage and grafted percutaneously to degenerated intervertebral discs. A cell carrier/scaffold is paramount to effectively deliver progenitor cells into the NP, protecting them from the harsh environment of the disc, preventing cell leakage by in situ polymerization properties and restoring mechanical properties while the regeneration process takes place[37]. Scaffolds have been used in many animal studies[38, 39] to enhance the regenerative properties of the transplanted cells. However, future research should continue the development of effective and safe cell-delivery systems.

Limitation

Our study has several limitations. Although we conducted a comprehensive search of five databases, only 6 studies were included in this systematic review. This small number of studies and included number of patients limited our confidence on the findings. A considerable degree of heterogeneity was still observed among the included trials. This might be due to differences in patients' characteristics, such as different

causes and severity at baseline and various treatment protocols, or otherwise unknown biases in those studies. In addition, the follow-up on average (24 months) is not long enough. Clinical benefits of cell therapy for patients with discogenic low back pain need further investigation and reevaluated in large group, multicenter and randomized controlled study.

CONCLUSION

In summary, the findings of this single arm meta-analysis suggest that MSC and chondrocyte therapy for discogenic low back pain associated with improved pain relief and Oswestry Disability Index. Although it seems to be a safe and effective treatment of discogenic low back pain, there are still many questions that future studies will hopefully answer. On the basis of the literature to date, the optimal cell therapy protocol remains unclear. At this time, cell therapy is not a standard treatment of for discogenic pain. However, in patients who have not adequately responded to traditional nonoperative treatments, cell therapy could be a treatment consideration. Meanwhile, according to the sample number is not large enough; clinical benefits of cell therapy for patients with discogenic low back pain need further investigation and reevaluation to test the clinical efficacy.

Acknowledgments

We would like to thank all authors who shared individual patient data.

hymal stem cells injection in degenerated
intervertebral disc: cell leakage may induce
osteophyte formation

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Figure 1 Flow of participants through trial

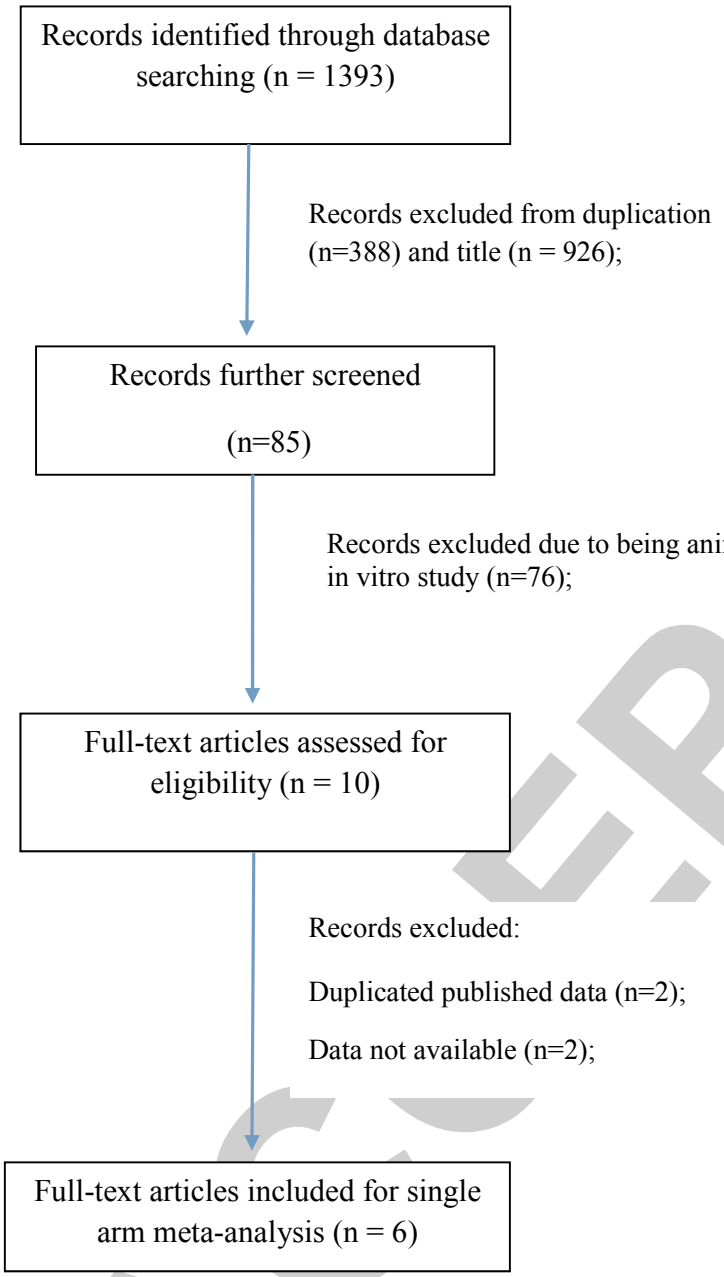

Figure 2 Decreased pain score (NRS & VAS, 0-100) after treatment

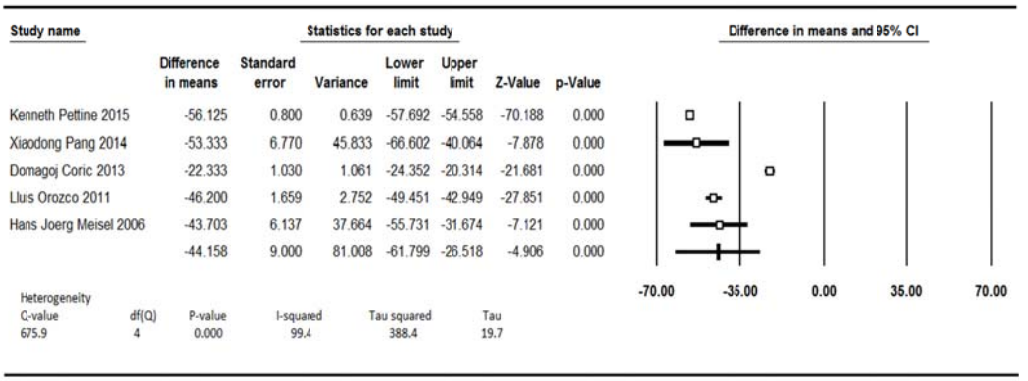

Figure 3 Decreased Oswestry Disability Index (ODI, 0-100) after treatment

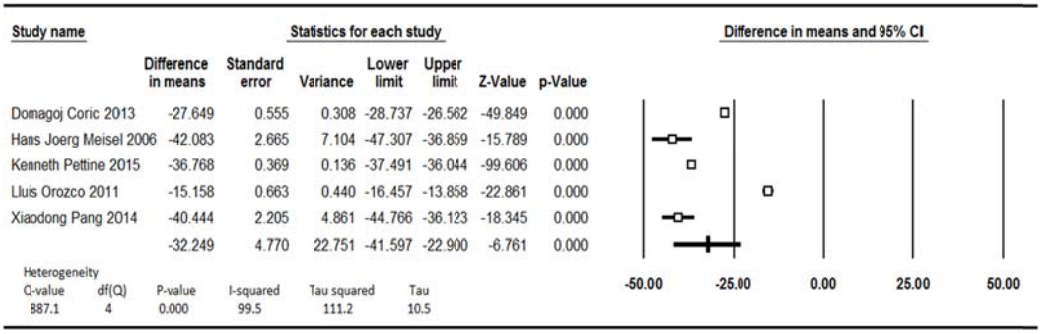

Table 1: The characteristics of the enrolled studies

Study	Sample size	Patients age (years)	Population	Cell type	Cell dose and deliver pathway	Fellow up (month)	Main evaluation index
Mochida[17]	9	20-29 years	Patients with Pfirrmann's grade III disc degeneration and posterior lumbar intervertebral fusion.	Autologous cultured nucleus pulposus chondrocytes that co-cultured with (MSCs)	One million activated autologous NP cells were injected into the degenerated disc 7 d after fusion surgery,	36 months	JOA and MRI
Kenneth Pettine 2015[12]	26	18-61 years (median 40)	Patients presented with symptomatic moderate to severe discogenic low back pain	Autologous bone marrow concentration (non-expanded)	2–3 ml of bone marrow concentrate was injected in lumbar disc (1.66×10^6/ml)	24 months	ODI, VAS and MRI
Xiao dong Pang 2014[13]	2	41.5 ± 3.5 (mean ± SD)	Patients with low back pain > 2 years without lower leg pain and provocative discography (+).	Cultured human umbilical cord tissue-derived mesenchymal stem cells	1-2ml of Cultured HUC-MSCs (1 × 10^7/ml) injected into lumbar disc immediately following discography	24 months	ODI and VAS scores
Domagoj Coric 2013[14]	15	19-47 years (median 40)	Patients with single-level, symptomatic lumbar DDD from L-3 to S-1 and medically	Expanded allogeneic juvenile chondrocyte cells	Mean 1.3 ml (1-2ml, 10^7/ml) cells solution was injected in the center of the disc space	12 months	ODI and NRS scores,36-Item Short Form Health

			refractory low back pain				Survey and MRI
Lluis Orozco 2011[15]	10	35± 7 (mean ± SD)	Patients with degenerative disc disease and persistent low-back pain (> 6 months; Decrease of disc height > 50 %;)	Autologous expanded bone marrow-derived mesenchymal stem cells	23 ± 5 * 10^6 autologous expanded BMSCs was injected into the nucleus pulposus area	12 months	ODI and VAS scores and MRI
Hans Joerg Meisel 2006[16]	12	18-75 years	Patients with discogenic pain after repeat discograms. Patients were treated cell therapy at least 3 months post the endoscopic.	Autologous cultured disc-derived chondrocytes (from surgical treatment of their disc prolapse)	Cells are injected into disc approximately 12 weeks following discectomy. The cell dose was not mentioned.	24 months	ODI, VAS scores and MRI

Table 2: Subgroup analysis to explore the source of heterogeneity on changes of pain score (VAS, 0-100).

Subgroup	Mean difference (95% CI)	I^2
Fellow up period		
6 months	-44.7 (-64.3 to - 24)	99.8
12 months or more	-45.6 (-60.1 to -31.1)	99.1
Cell type		
Stem cell	-52.5 (-61.1 to -43.8)	98.3
Chondrocyte	-32.5 (-54.7 to -10.3)	98.1
Expanded or non-expanded		
Expanded	-41.3(-58.5 to -24.2)	99.5
Non-expanded	-57.1 (-57.9 to -56.4)	0

Table 3: Meta-regression analyses to assess the relationship between the changes pain score (VAS) and study characteristics

Study characteristics	95% CI of Mean difference	Stand Error	P
6 months fellow-up *vs* 12 months or more	(-9.7 to 6.3)	4.1	0.68
Stem cell *vs* Chondrocyte	(-27.6 to -9.3)	4.6	0.001
Expanded *vs* Non-expanded	(-17.3 to 3.7)	5.3	0.21

Table 4 Checklist for quality assessment of the case series study

Risk of bias	Criterion	Mochida 2015	Kenneth Pettine 2015	Xiao dong Pang 2014	Domagoj Coric 2013	Lluis Orozco 2011	Hans Joerg Meisel 2006
Selection bias	Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?	Yes	Yes	Yes	Yes	Yes	Yes
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Yes	Yes	Yes	Yes	Yes	Yes
	Did the study maintain fidelity to the intervention protocol?	Yes	Yes	Yes	Yes	Yes	Yes
Attrition bias	If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?	Yes	Yes	Yes	Yes	Yes	NA
Detection bias	Were the outcome assessors blinded to the intervention or exposure status of participants?	NA	Yes	No	Yes	No	No

	Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
	Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
	Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?	No	No	No	No	No	Yes
Reporting bias	Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?	Yes	Yes	Yes	Yes	Yes	Yes

Spine

Cell-Based Therapies for lumbar discogenic low back pain - a Systematic Review and Single Arm Meta-Analysis

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Key Points

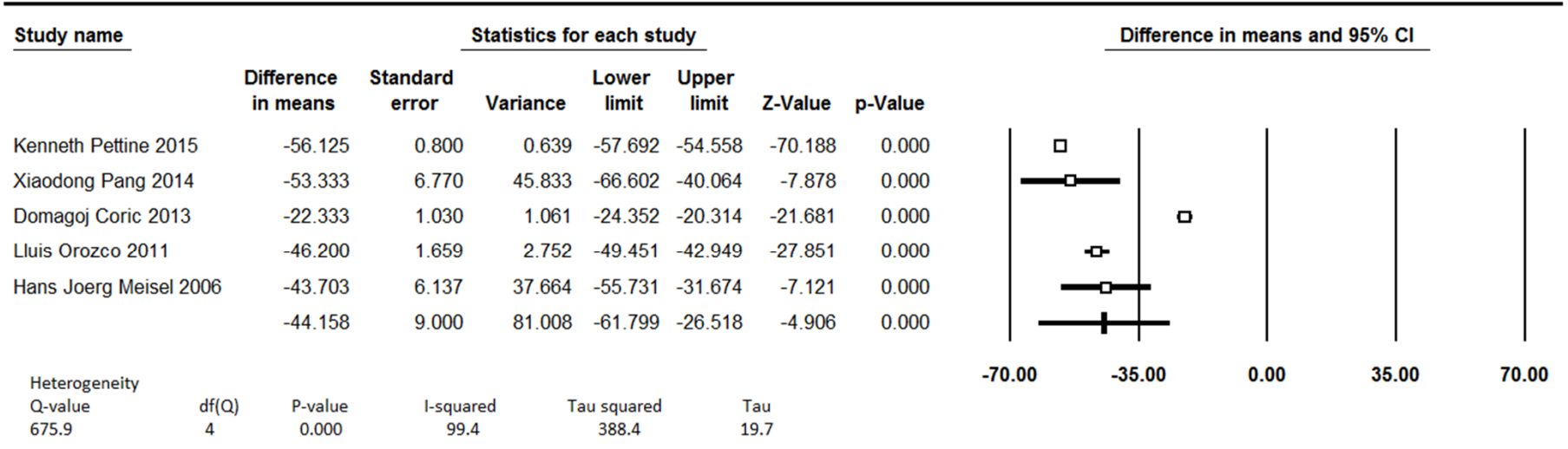
Cell-Based Transplantation Therapy (Mesenchymal stem cells or chondrocytes) for patients who have discogenic low back pain is associated with improved pain relief and Oswestry Disability Index.

The optimal cell therapy protocol for discogenic low back pain remains unclear.

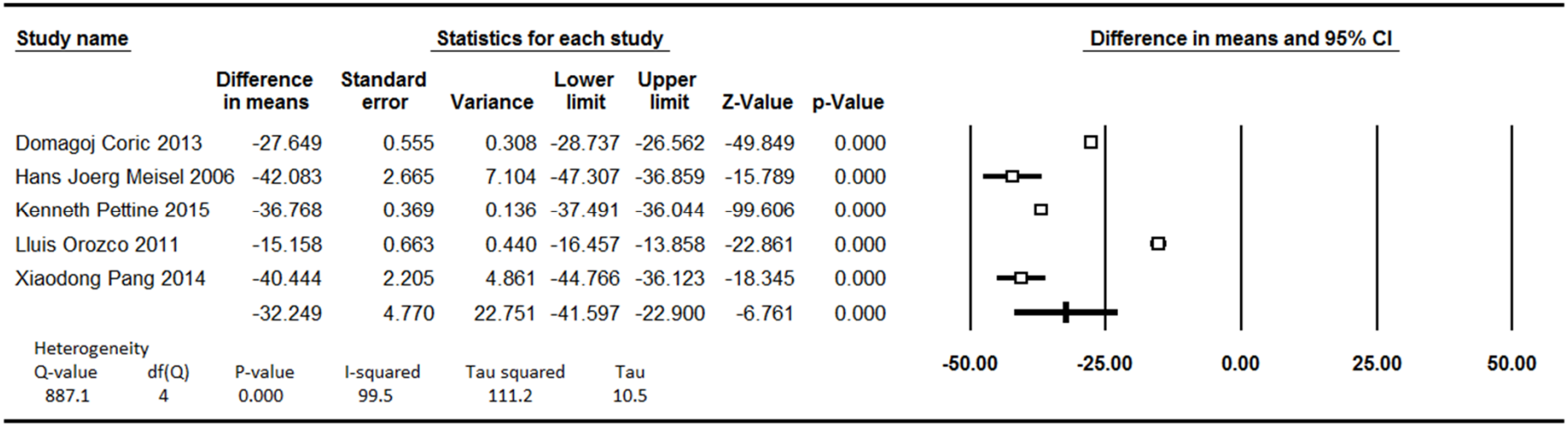
Clinical benefits of cell therapy for patients with disc-genic low back pain need further investigation and reevaluation to test the clinical efficacy.

The characteristics of the enrolled studies

Study	Sample size	Patients age (years)	Population	Cell type	Cell dose and deliver pathway	Fellow up (month)	Main evaluation index
Mochida	9	20-29 years	Patients with Pfirrmann's grade III disc degeneration and posterior lumbar intervertebral fusion.	Autologous cultured nucleus pulposus chondrocytes that co-cultured with (MSCs)	One million activated autologous NP cells were injected into the degenerated disc 7 d after fusion surgery,	36 months	JOA and MRI
Kenneth Pettine 2015	26	18-61 years (median 40)	Patients presented with symptomatic moderate to severe discogenic low back pain	Autologous bone marrow concentration (non-expanded)	2–3 ml of bone marrow concentrate was injected in lumbar disc (1.66×10^6/ml)	24 months	ODI, VAS and MRI
Xiao dong Pang 2014	2	41.5 ± 3.5 (mean ± SD)	Patients with low back pain > 2 years without lower leg pain and provocative discography (+).	Cultured human umbilical cord tissue-derived mesenchymal stem cells	1-2ml of Cultured HUC-MSCs (1 × 10^7/ml) injected into lumbar disc immediately following discography	24 months	ODI and VAS scores
Domagoj Coric 2013	15	19-47 years (median 40)	Patients with single-level, symptomatic lumbar DDD from L-3 to S-1 and medically refractory low back pain	Expanded allogeneic juvenile chondrocyte cells	Mean 1.3 ml (1-2ml, 10^7/ml) cells solution was injected in the center of the disc space	12 months	ODI and NRS scores,36-Item Short Form Health Survey and MRI
Lluis Orozco 2011	10	35± 7 (mean ± SD)	Patients with degenerative disc disease and persistent low-back pain (> 6 months; Decrease of disc height > 50 %;)	Autologous expanded bone marrow-derived mesenchymal stem cells	23 ± 5 * 10^6 autologous expanded BMSCs was injected into the nucleus pulposus area	12 months	ODI and VAS scores and MRI
Hans Joerg Meisel 2006	12	18-75 years	Patients with discogenic pain after repeat discograms. Patients were treated cell therapy at least 3 months post the endoscopic.	Autologous cultured disc-derived chondrocytes (from surgical treatment of their disc prolapse)	Cells are injected into disc approximately 12 weeks following discectomy. The cell dose was not mentioned.	24 months	ODI, VAS scores and MRI



Decreased pain score (NRS & VAS, 0-100) after treatment: The pooled mean difference in pain score from baseline to follow-up points was 44.2 points decreased (95%CI: -61.8 to −26.5, p<0.001, I^2=99.4%)



Decreased Oswestry Disability Index (ODI, 0-100) after treatment: The pooled mean difference in ODI from baseline to follow-up points was 32.2 points decreased (95%CI: -41.6 to −22.9, p<0.001, I^2=99.5%).