Techniques in Regional Anesthesia and Pain Management ▮ (2016) ▮▮▮–▮▮▮

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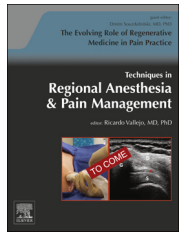

Current understanding of safety and efficacy of stem cell therapy for discogenic pain—A systematic review of human studies

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ARTICLE INFO

Keywords:
Stem cells
Disc degeneration
Regenerative medicine

ABSTRACT

This study is a systematic review of human clinical studies of stem cell therapy for discogenic pain. To summarize the current human trials and feasibility studies involving mesenchymal stem cell (MSC) therapy for treatment of discogenic pain. A search of Ovid databases and Clinicaltrials.gov was conducted from inception through July 2016. We included human clinical trials and case reports that evaluated treatment with injected MSCs for patients with discogenic back pain. The outcomes of interest for published studies included pain score, Oswestry Disability Index, and T2-weighted magnetic resonance imaging signal intensity indicative of water content of the nucleus pulposus. The initial search in Ovid databases using the selected search terms identified 408 results, of which 11 were included in this review based on selection criteria. This includes 6 completed studies and 5 ongoing clinical trials, 4 of which were confirmed active at the time of retrieval. In the 6 completed studies involving intradiscal stem cell injections, improvement in pain score, Oswestry Disability Index, and T2-weighted magnetic resonance imaging signal intensity of nucleus pulposus were reported. Currently active clinical trials focus on establishing safety, tolerability, and efficacy with respect to injected MSCs for discogenic pain. Although pain and functional benefit have been reported in association with stem cell therapy, longer-term safety studies and more randomized controlled trials are needed to examine the safety and efficacy of stem cell therapy for discogenic pain.

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http://dx.doi.org/10.1053/j.trap.2016.09.006
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Introduction

With almost one-third of the US population experiencing low back pain within a given 3-month period, it is the leading cause of disability in the developed world and places a heavy cost burden on health care.[1] In the United States alone, low back pain can carry a price tag in excess of $500 billion.[2] One of the leading causes of low back pain is intervertebral disk (IVD) degeneration, which itself has a prevalence of over 90% in populations older than 50 years of age.[3]

The IVD functions to facilitate flexibility and movement of the spinal column. It is composed of the nucleus pulposus (NP), a central gelatinous core, the annulus fibrosis, an outer ring of lamellated collagen fibers, and endplates. Disk degeneration has a multifactorial etiology including genetic, mechanical, and nutritional factors[4] and results in degeneration of the extracellular matrix and cell death.[5] Patients with degenerative disk disease (DDD) present with dehydration and extrusion of the NP, annulus fibrosus fissures, and inflammation leading to mechanical pain.[6]

Treatment of DDD traditionally begins with analgesics, physical therapies, and interventional management of pain. It may progress to surgical interventions such as lumbar fusion or disk arthroplasty.[7] Although these treatments can have short-term pain relief, they do not address the underlying etiology of irreversible IVD cell loss and extracellular matrix degradation. As the inner cells of the nucleus pulposes have chondrocytic morphology, research using mesenchymal stem cells (MSCs) for the regeneration of the IVD has attracted significant interest.[8]

Although the research focus on MSC therapy was primarily on preclinical studies, several case reports raised concerns involving serious adverse outcomes of stem cell therapy,[9-15] although prospective studies investigating the safety of MSC treatment have not identified any serious adverse events resulting directly from treatment.[14] Persistent concerns regarding safety include cell leakage leading to osteophyte formation[12] and using MSC populations with low immunogenicity.[16] Calls for careful assessment of the safety of MSCs rightfully continue,[17,18] but human clinical trials involving MSC treatment of DDD are thus far reassuring. Cells harvested from adipose tissue are well studied and of particular interest given their relative abundance, ease of harvest, and low immunogenicity.[19-22]

Previously, a systematic review and meta-analysis were conducted by the senior author to evaluate IVD regeneration due to stem cell transplantation in controlled animal trials and concluded that transplanted stem cells decelerated and arrested the IVD degenerative process.[23] Additional studies in human clinical trials have recently been published and larger randomized trials are ongoing. However, they are limited by small sample size, heterogeneous trial designs, and conflicting outcomes and as such, this systematic review was conducted with the aim to better synthesize current clinical evidence and provide a research base for future randomized controlled trials (RCTs) involving MSC transplantation in the treatment of patients with discogenic pain due to DDD.

Methods

The study protocol was discussed among the authors before data collection, including appropriate search terms, inclusion and exclusion criteria, and outcomes of interest. We have conducted our review in compliance with guidelines set forth by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[24]

Search strategy

Searches were performed on Ovid Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Ovid CENTRAL (Cochrane Central Register of Clinical Trials 1991 to present), and Ovid EMBASE 1988 to present. The results of each database search were downloaded into EndNote X7, a bibliographic database manager, and the duplicates were removed.

To retrieve all of the relevant articles, a combination of controlled vocabulary and text words were used. The initial search was performed in MEDLINE using the subject heading stem cell transplantation (expanded to include specific stem cell transplants, eg, mesenchymal) augmented by text words including bone marrow, precursor, chondrocyte, and allogeneic as well as acronyms such as MSC and BMCS within 3 words of transplant* (truncation to include other endings), implant* or inject*. The same process was used to describe IVD disease. Subject headings included back pain, IVD degeneration, and displacement and were augmented with text words such as discogenic pain. The search was then translated into the terms used in EMBASE.

The other source searched for current clinical trials was through the NIH database via Clinicaltrials.gov. Search terms used included stem cells, mesenchymal stem cells, DDD, and IVD, and the search included interventional studies only. A total of 16 trials were identified through this search and are included in the strategy as outlined in the Figure.

Eligibility criteria

Only clinical trials and case reports involving human studies receiving intradiscal stem cell injection therapy were considered for inclusion in this review. Given the small number of studies involving human subjects our inclusion criteria were broad. Controlled studies as well as single-arm studies are included. Studies published as abstracts and posters are included. Studies that involved surgical treatment as part of the study design were excluded. No limitations were placed on language or publication date, and our review included studies that spanned from 2008-2016.

Data collection

Two independent reviewers (C.H. and W.Q.) reviewed the abstracts and full texts of potentially relevant studies and considered appropriate studies for inclusion. Discrepancies were resolved through discussion and consensus between the 2 authors. The same 2 authors extracted data from the full-text articles. Data extracted include author, year, study

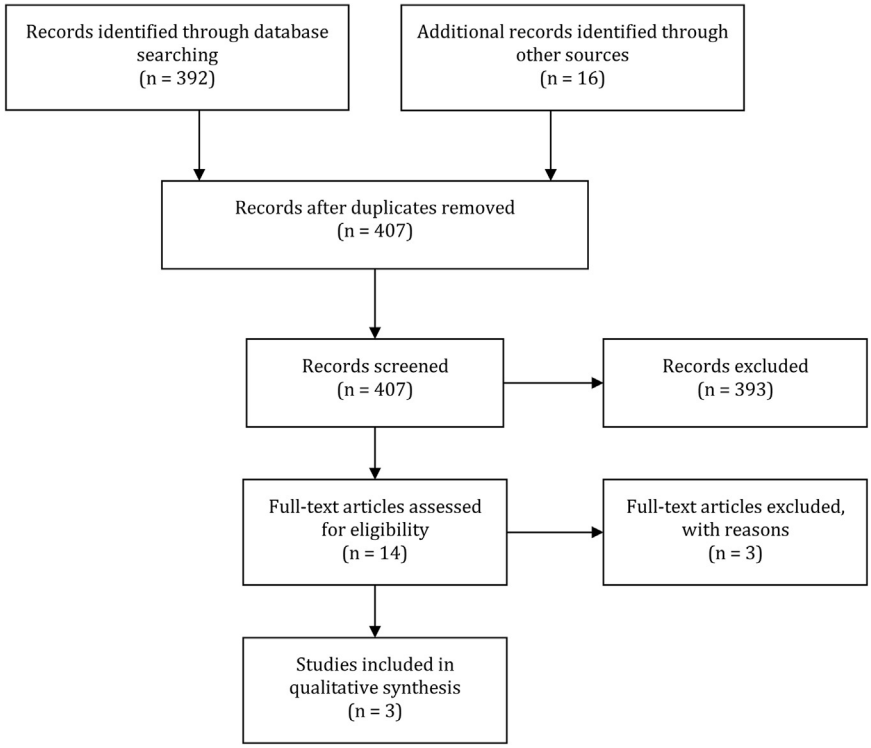

Fig – Search strategy including identified records, and number reviewed and exclude. Note that "other source" refers to searching of NIH database.

design, sample size, cell type, injected cell count, and outcome measures.

Assessment of bias

Human trials involving MSC treatment are still improving in their robustness. Of the 6 completed studies in our review, 4 were open label, the fifth is a report of two cases, and 1 is a RCT. Of the five ongoing trials, 3 are RCTs. Open-label non-randomized studies have a much higher degree of bias than blinded RCTs but can provide information regarding safety and tolerability of interventions, which can be helpful when designing more robust studies in the future. Their inclusion in this review is appropriate for a complete and relevant analysis of the current state of MSC injection for treatment of pain due to DDD.

Results

Study selection and characteristics

From the database search described above, 407 studies were screened after duplicate removal, and 393 records excluded after initial screening. Screening included review of full abstract where available. Records were excluded based on inclusion and exclusion criteria as described above. The 3 full-text records that were excluded included 3 clinical trials that included invasive surgery as part of the research design. Final studies included in our review included 6 completed trials and 5 ongoing trials.

Data extracted from the studies included author, publication year, number of study participants and study arms, study design, cell type, cell dosage, and outcome measures. Outcome measures included safety and tolerability, pain as assessed by the Visual Analog Scale or Numeric Rating Scale, Oswestry Disability Index, Short-Form Questionnaires, and disk fluid as measured by magnetic resonance imaging (MRI). When outcomes were measured across serial time points, only the final outcome measure was included for ease of comparison. Study citations are included in Tables 1 and 2.

Study results

None of the studies in Table 1 reported serious adverse events associated with MSC treatment. Bae et al did report incidence of back pain was 10% in their study cohort following treatment, which was not statistically significant among groups and thus not clearly attributable to the intervention, and indeed not unexpected in patients with history of discogenic pain. All of the completed studies reported statistically significant improvement in the treatment groups in pain and function as measured by the Visual Analog Scale or Numeric Rating Scale. Studies that compared MRI pretreatment and posttreatment reported that many patients realized improvement in water content of the treated disks, including 10 of the 13 patients at 6 months in the study by Coric et al, 8 out of 20 patients in the study by Pettine et al,[29] and 6 out of 10 patients in the study by Pettine and Coric.[30] Ratio of fluid content of affected disk segments to healthy segments increased from 0.62 $\pm$ 0.03 at baseline to 0.72 $\pm$ 0.03 at 12 months following MSC transplantation in the study by Orozco et al. In studies that assessed effect on overall quality of

Table 1 – Characteristics of completed studies.

Study	N	Design	Cell type	Dosage	Outcomes
Bae et al[25]	100	RCT, 3 arms	Allogeneic MPC, immunoselected	6 M 18 M + HA carrier	VAS, ODI, SF-36, WPAI
Coric et al[26]	15	Open label, single arm	Allogeneic chondrocytes, cultured	100–200 M with fibrin carrier	NRS, ODI, SF-36, MRI
Orozco et al[27]	10	Open label, single arm	Autologous BMSC, cultured	18–28 M	VAS, ODI, SF-36, MRI
Pang et al[28]	2	Case study	Allogeneic HUC-MSCs, cultured	100 M	VAS, ODI, MRI
Pettine et al[29]	26	Open label, 2 arms	Autologous BMSC	2–3 mL	VAS, ODI, MRI
Pettine and Coric[30]	14	Open label, single arm	Allogeneic chondrocytes	10 M with fibrinogen and thrombin carrier	NRS, ODI, SF-36, MRI

BMSC, bone marrow stem cells; HA, hyaluronic acid; HUC-MSCs, human umbilical cord mesenchymal stem cells; M, million; MPC, mesenchymal precursor cells; N, sample size; NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; VAS, Visual Analog Scale; WPAI, Work Productivity and Activity Impairment scale.

life as measured by the SF questionnaire, patients realized improvement in the physical component of the assessment. Follow-up in all completed studies was through 12-24 months.

Two of the ongoing clinical trials in Table 2 are RCTs. Most include as outcome measures change in disk water content as measured by MRI, pain, disability, and overall quality of life following MSC treatment for discogenic pain. All involve human subjects with low back pain and history of DDD with nonresponse to conservative treatment for 3-6 months. Totally, 3 trials use adipose derived stem cells as the interventional MSC treatment. Table 2 includes Phase III of a industry sponsored trial, the Phase II results of which were included in Table 1.[25] All trials are confirmed active with the exception of that sponsored by Biostar, which was last verified in March 2014.

Discussion

Summary of evidence

MSC transplantation is theorized to facilitate regeneration of the IVD by differentiation to an NP cell-like phenotype or through stimulation of endogenous NP cells in the IVD. Liu et al. recently demonstrated a biophysical interaction between transplanted MSCs and degenerated NP cells leading to improved expression of proteoglycan and type II collagen and the proliferation of degenerated NP cells.[36] Wang et al. previously summarized the proposed mechanisms of regeneration following MSC transplantation including enhanced IVD cell phenotype induction, increased expression of type II collagen, restoration of IVD hydration, and amelioration of disk degenerative processes and loss of disk height. Through differentiation into NP-like cell types, stem cells are hypothesized to enhance the production of disk matrix, release trophic factors that stimulate disk progenitor cells, and release cytokines that decrease the inflammatory response. The results of their meta-analysis of controlled trials involving animal models supported the theory that stem cells may arrest degeneration and promote regeneration within the IVD.[23] Although the current literature aims to link the proposed mechanisms behind MSC transplantation with improvement in back pain and function, there is a lack of sufficient high quality studies to demonstrate whether disk regeneration indeed results from MSC implantation.[37] The results of this systematic review suggest that human clinical

Table 2 – Characteristics of current, ongoing clinical trials.

Sponsor	N	Phase	Design	Cell type	Dosage	Outcomes
Red de Terapia Celular[31]	24	I-II	RCT, 2 arms	Allogeneic BMSC, cultured	25 M	VAS, ODI, SF-12, MRI, AEs
Mesoblast[32]	330	III	RCT, 3 arms	Allogeneic MPC	6 M 6 M + HA	VAS, ODI
Bioheart[33]	100	II	Open label, single arm	Autologous AMSC + PRP	Will vary	VAS, ODI
Biostar[34]	8	I-II	Open label, single arm	Autologous AMSC	40 M	VAS, MRI, AEs
Inbo Han, CHA University[35]	10	I	Open label, single arm	Autologous AMSC	20–40 M + HA	VAS, ODI, SF-36, MRI, DHI, AEs

AMSC, adipose derived mesenchymal stem cells; AEs, adverse events; ODI, Oswestry Disability Index; PRP, platelet-rich plasma; VAS, Visual Analog Scale.

trials may bear out what the research to date has proposed regarding the mechanisms of IVD regeneration via MSC transplantation, especially if outcomes that elucidate to what extent disk regeneration may have actually taken place can be measured.

Completed studies involving 167 human subjects examining the safety and efficacy of MSCs in the treatment of discogenic pain reported no adverse events related to MSCs. Improvement in pain, function, and water content in the NP was reported. This review suggests that intradiscal MSC injection holds promise to improve pain and function. This should encourage continued research efforts to undertake more high quality studies including RCTs with human subjects that include as outcome measures estimates of the regeneration of the IVD as well as pain and function. These should include subjective and objective outcome measures as well as careful documentation of methods, cell type and dosage, and any adverse outcomes.

Limitations

As discussed, a significant limitation with the current literature in this area is the paucity of RCTs.[38] Considerable bias exists in open-label studies, which as precursors to RCTs can nevertheless serve to examine the safety and tolerability of interventions prior to design of more high quality studies. In this review we attempted to limit publication bias by including unpublished clinical trials, but there is always a risk for incomplete retrieval of research especially with respect to unpublished studies.

Conclusions

Intradiscal MSC transplantation presents a novel way to address the underlying cause of disk pathology in DDD that traditional conservative, interventional, and surgical treatments fail to address.[39] Further research should focus on cell engineering, scaffold development,[40] and opportunities to design high-quality RCTs.

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