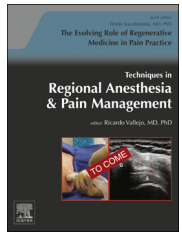
Techniques in Regional Anesthesia and Pain Management ▮ (2016) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/trap



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

Christine L. Hunt, DO, MS[a], *Stephanie Shen, MD*[b], *Ahmad Nassr, MD*[c], *Andre J. van Wijnen, PhD*[c], *A. Noelle Larson, MD*[c], *Jason S. Eldrige, MD*[d], *William D. Mauck, MD*[d], *Mathew J. Pingree, MD*[a,d], *Patricia J. Erwin, MLS*[e], *Mohamad Bydon, MD*[f], *Wenchun Qu, MD, MS, PhD*[a,d,g,*]

[a]*Department of Physical Medicine and Rehabilitation, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905*
[b]*Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota*
[c]*Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota*
[d]*Department of Anesthesiology, Pain Division, Mayo Clinic, Rochester, Minnesota*
[e]*Mayo Clinic Libraries, Mayo Clinic, Rochester, Minnesota*
[f]*Department of Neurologic Surgery, Mayo Clinic, Rochester, Minnesota*
[g]*Spine Center, Mayo Clinic, Rochester, Minnesota*

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.

*Corresponding author at: Department of Physical Medicine and Rehabilitation, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.
E-mail address: qu.wenchun@mayo.edu (W. Qu).

http://dx.doi.org/10.1053/j.trap.2016.09.006
1084-208X/

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