Effectiveness of autologous or biologic non-surgical interventions for discogenic pain and functional capacity compared to non-surgical and surgical interventions: A systematic review protocol

Authors

Anita Osuji[1] Jennifer Greenwood[1,2]

1. Rosalind Franklin University of Medicine and Science, North Chicago, Illinois
2. RFUMS Center for Interprofessional Evidence-Based Practice: A JBI Centre of Excellence

Abstract

Objective: The systematic review aims to assess the effectiveness of autologous or biologic non-surgical interventions compared to other types of non-surgical used for patients suffering from discogenic pain syndrome up to 36-months post-treatment.

Introduction: The intervertebral discs that cushion and support the vertebral column are subject to gradual breakdown. During this process, proteoglycans and proinflammatory mediators are released with subsequent sensitization of the nociceptors with pain transduction, transmission, perception and modulation (stimulatory or inhibitory). This perceived pain is referred to as discogenic pain syndrome (DPS), affecting primarily the lower vertebrae. Various therapies exist for the treatment of DPS such as conventional methods like acupuncture to surgeries like spinal fusion. Considering the potential risks of invasive surgery, assessing the effectiveness of autologous and biologic non-surgical interventions compared to other techniques is proposed to identify alternatives and compare outcomes related to quality of life and pain.

Inclusion criteria: Studies including patients over 18 years of age, anesthesia physical status ≤ 3, and treated for discogenic pain will be considered. Patients diagnosed with degenerative disc diseases and discogenic pain, different genders, ethnic groups, geographic locations, and socioeconomic status will be considered. Studies in English and other languages that are available in English will be included, with no time limit.

Methods: Six databases and two registers will be systematically searched: JBI, Cochrane CENTRAL register, PubMed, MEDLINE, Embase, CINAHL, and the WHO ICTRP and NIH Clinical Trials. Grey literature will also be identified if available. Two independent reviewers will conduct study selection and assessment of methodological quality using JBI critical appraisal tools. Data will be extracted for tabular and narrative synthesis. When possible, results will be pooled for meta-analysis using a random effects model. Heterogeneity will be assessed using standard X^2 and I^2 tests. To establish certainty in the evidence, the Grading of Recommendations, Assessment, Development and

Evaluation (GRADE) framework will be adopted to interpret the results and Summary of Findings tables will be created.

Systematic review registration number: PROSPERO CRD42024560127

Keywords: back pain; discogenic pain; autologous therapy; nonsurgery; surgery

Introduction

One of the most pervasive forms of chronic pain is attributed to damaged or degenerated intervertebral discs, leading to discogenic pain syndrome (DPS). According to a Global Burden of Disease Study done in 2017, the authors reported that low back pain was the leading global cause of years lived with disability (YLDs).[1] The incidence of individuals who have degenerative spine disease of the lumbar region and associated lower back pain is as high as 266 million individuals worldwide.[2] Europe was the leading continent with over 110 million cases, while Latin America/Caribbean had 48.8 million, and Sub-Saharan Africa had over 52 million prevalent cases.[1] The individual burden of discogenic disease is substantial due to direct medical costs, lost productivity, and disability.[3]

The intervertebral disc consists of a compressible nucleus pulposus, surrounded by a tough fibrocartilaginous annulus fibrosus, and functions as a shock absorber between the vertebrae.[4] Herniation, bulging, and annular tears are among the pathologies that may lead to alterations in the intervertebral disc. These pathologies often interact and can progress over time, potentially leading to chronic discogenic pain throughout adulthood. Discogenic pain arises from complex changes in late intervertebral disc (IVD) degeneration that affect the peripheral and central nervous systems.[5] It can result from biomechanical instability, endplate damage, nerve ingrowth and sensitization, and inflammation. The causes of discogenic pain and IVD degeneration include mechanical overloading, oxidative stress, metabolic disorders, and genetic factors.[5] The specific pain mechanisms can vary depending on the exact nature and location of the disc pathology, which is why a thorough diagnostic workup is crucial for effective treatment planning. Diagnostic confirmation of intervertebral disc herniation and its precise location is achieved through CT or MRI. Initial treatment for discogenic disease is usually conservative, involving rest, pain management, and possibly the administration of intradiscal injection modalities.[6] However, surgical decompression may be necessary if symptoms persist despite non-surgical management, or if there is significant motor impairment.[6]

Discogenic pain syndrome significantly impacts patients' quality of life and functional abilities. Effective management of this condition is critical, especially considering the varying accessibility to surgical interventions across different regions. Unfortunately, there are nearly 5 billion people who lack access to basic surgical care.[2] Given the inherent challenges and resource demands of surgical interventions for DPS, non-surgical alternatives present a compelling option.

Autologous treatments, such as stem cell therapy and platelet-rich plasma (PRP) injections, utilize the patient's own biological materials, mitigating the risks associated with immune rejection and compatibility.[7] In addition, these therapies are minimally invasive, have shorter recovery times, and are more cost-effective.[8] Therefore, understanding the efficacy of autologous treatments and biologic injectable interventions are essential to inform alternative treatment options in areas where barriers to surgical treatments exist. In addition, as a subset of non-surgical interventions for the management of DPS, cell-based autologous methods may be advantageous over traditional injection-based techniques with respect to recovery time, drug-related adverse reactions such as allergic hypersensitivities or anaphylaxis, and restoration of the disc's inherent strength and structure.[9] In addition, autologous techniques have relatively fewer costs when compared to other techniques. For example, the average cost of a single stem cell injection is approximately $4,000 (USD),[10] while the median cost for spinal fusion in 2019 was reported to be $21,784 (USD).[11] Autologous and biologic injections may be an ideal alternative for patients and geographical areas with limited financial and surgical resources.

Due to its prevalence, multiple non-surgical and surgical treatments are available for patients with DPS, ranging from minimally invasive techniques to surgical placement of implants in the spine. Interventions for DPS can be performed by various types of healthcare providers. Anesthesia providers, including both physicians and certified registered nurse anesthetists specialized in pain management, can also administer these autologous interventional procedures. By contrast, specialty trained surgeons often perform the more invasive procedures, such as spinal fusions and disc replacements. The use of various types of specialists in the treatment of DPS may improve access to care for some patients in resource limited environments.

Functional outcomes and disability, measured by tools like the Oswestry Disability Index (ODI)[12] and Roland-Morris Disability Questionnaire (RMDQ),[13] capture the extent to which discogenic pain affects patients' daily lives and activities. These measures provide a comprehensive view of the impact of living with discogenic pain, beyond traditional pain measures such as Numeric Rating Scales (NRS) and Visual Analog Scales (VAS), and opioid use. While NRS, VAS and medication refills quantify the intensity and management of pain, functional assessments reveal how pain interferes with physical and social functioning.

Given the potential of cell-based autologous and biologic interventions in managing DPS, it is critical to evaluate the effectiveness of these treatments compared to other non-surgical interventions to establish their comparative effectiveness. This evaluation will provide valuable insights for healthcare providers and policymakers, ensuring that patients receive the most appropriate and effective care based on their unique circumstances and the resources available. While numerous studies have evaluated these treatments individually, there is a lack of comprehensive, comparative analyses that assess their relative effectiveness in treating DPS of the lumbar spine over an extended follow-up period.

A preliminary search of the Cochrane Database of Systematic Reviews, CINAHL, MEDLINE, and JBI Evidence Synthesis was conducted in September 2024. A systematic review published in 2022 was found in which the authors investigated autologous treatments for lower back pain, however they did not provide outcome data related to the relative impact of the autologous treatments compared to other non-surgical interventions.[14] They reported on the outcomes of the autologous treatment groups only, limiting the readers' ability to determine the relative effectiveness of the treatment.[14] In addition, their search was conducted in 2020. Given the rapid pace of innovation in the field of regenerative medicine and biologic therapies, we anticipate that this proposed review will include several studies not cited by Schneider et al. The significant advancements in stem cell research, PRP applications, and other autologous treatments warrant a fresh evaluation of the current evidence. This ensures that all healthcare practitioners and stakeholders utilize the most up-to-date and accurate information when making clinical decisions to improve patient outcomes.

Review question

What is the effectiveness of autologous or biologic non-surgical interventions compared to other treatment techniques (e.g., therapeutic injections, and surgical techniques) for the treatment of discogenic pain syndrome in the lumbar spine among patients with degenerative disc diseases up to 36 months post-treatment?

Inclusion criteria

Participants

This review will include studies of patients over 18 years of age, anesthesia physical status $\leq$ 3 with a diagnosis of back pain, degenerative disc disease (DDD), or DPS. The relevant diagnosis will have been made by a provider qualified to diagnose DDD or DPS with follow-up times ranging from 6 to 36 months. Participants must have no cognitive deficits that might interfere with their ability to report symptoms. Discogenic pain will include diagnosis of intervertebral disc degeneration, radiculopathy, vertebrogenic dysfunction, radiculopathy and spinal stenosis related to disc herniation and chronic low back pain of unknown mechanism. Exclusion criteria include studies of pregnant patients, patients with spinal malignancy or infection, central neuro or motor deficits, local or systemic infection, animal studies, single-group studies without comparison groups, and studies lacking intervertebral disc focus. These conditions are excluded since they are expected to impact the patient's experiences of pain that are unrelated to the degenerative process.

Interventions

This systematic review will consider studies that examined cell-based autologous non-surgical interventional treatment techniques such as growth factor therapy, genetic therapy, platelet rich plasma, bone marrow concentrate, progenitor cells, autologous intervertebral disc (IVD) cells,

autologous chondrocytes, mesenchymal stem cells from bone marrow aspiration, embryonic stem cells, and pluripotent stem cells.

Comparators

Studies that report on patients that have undergone non-surgical interventional techniques such as disease-modifying antirheumatic drugs, intradiscal methylene blue injections, intradiscal epidural steroid injection, epidural steroid injections, pulsed radiofrequency, thermal annular procedures, kyphoplasty, facet injections, percutaneous adhesiolysis, spinal cord stimulation, medial branch nerve root block, intra-articular injection, and neurostimulation will be considered as comparison groups. Injections at any lumbar level will be considered for inclusion.

Outcomes

This review will consider studies that include the following primary outcomes: disability measured with ODI and/or the RMDQ, activity level evaluated with International Physical Activity ordinal scale or any other validated physical activity scales reported in the literature. Secondary outcomes will include quantitative measures of pain, such as a pain VAS or NRS, and opioid use as measured by frequency of filled prescriptions. Patients must be followed for features of discogenic pain for at least 12 months after treatment and up to 36 months for inclusion in this review.

Types of studies

This review will consider both experimental, quasi-experimental and observational study designs including randomized controlled trials, non-randomized controlled trials, pre and post studies with a comparison group. In addition, analytical observational studies including retrospective and prospective cohort studies and case-control studies will be considered for inclusion.

Methods

The proposed systematic review will be conducted in accordance with the JBI methodology for systematic reviews of effectiveness evidence.[15] This protocol has been registered with PROSPERO (CRD# 42024560127).

Search strategy

A three-step search strategy will be utilized to identify both published and unpublished studies that meet inclusion criteria. An initial limited search of Ovid MEDLINE, PubMed, and Cochrane Database of Systematic Reviews was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for PubMed (see Appendix 1). A search strategy, including all identified keywords and index terms, will be adapted for each included database and/or information

source. Finally, the reference list of all included studies selected for critical appraisal will be searched to determine their eligibility for inclusion.

Databases to be searched for relevant studies include: JBI Evidence Synthesis, Cochrane CENTRAL Register, Ovid MEDLINE, PubMed, Embase, CINAHL (EBSCO), and National Library of Science. No date limiter will be applied. In addition, two registers including the WHO ICTRP and NIH Clinical Trials will be searched. Sources of grey literature and unpublished studies will include MedNar, Global Index Medicus, and the NY Academy of Medicine Grey Literature report. Studies published in any language will be considered if a translation to English is available.

Study selection

Following the systematic search, all identified citations will be uploaded into Zotero (Zotero 6.0.36., Zotero Reference Management Software, Virginia Beach, VA, USA) and duplicates removed. Following a pilot test, titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Full text of potentially relevant studies will be retrieved, and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI, JBI, Adelaide, Australia).[16] The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of studies at the full text stage will be recorded and reported in an appendix. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with a third reviewer The results of the search and the study inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[17]

Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers for methodological quality using standardized critical appraisal instruments from JBI for experimental, quasi-experimental and observational studies.[18] Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative and tabular form. All studies, regardless of methodological quality, will undergo data extraction and synthesis.

Data extraction

Data will be extracted from all studies by a single reviewer and checked for accuracy by a second reviewer. The data extracted will include specific details about the study participants, study design, cell-based autologous non-surgical interventions (technique, frequency), other non-surgical interventional techniques, surgical techniques, and outcomes of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. In direct comparison studies, the relative measure of effect, p-

value, and 95% confidence interval will be extracted. Authors of papers will be contacted to request additional or missing data when necessary.

Data synthesis

Studies will, where possible, be pooled with statistical meta-analysis using JBI SUMARI.[19] Effect sizes will be expressed as standardized mean differences for continuous data and odds ratios for dichotomous data, and their corresponding 95% confidence intervals (CIs) will be calculated for analysis. Statistical heterogeneity will be assessed using the standard Chi-square (χ^2) and I-square (I^2) statistics. Statistical analyses will be performed using the random effects model. When appropriate, the fixed effects model will be used if fewer than 5 studies are included in the meta-analysis.[19] A sensitivity analysis will be conducted to determine the impact of the methodological quality or sample size. To investigate publication bias, a funnel plot using Egger test will be generated using IBM SPSS v.26 (Armonk, NY) if there are 10 or more studies in the meta-analysis.

Considering different therapies adopted by clinicians, subgroup analyses will be conducted to investigate the effectiveness of specific cell-based autologous non-surgical techniques compared to other non-surgical interventional techniques for discogenic treatment when possible. Studies will be organized by each cell-based autologous intervention versus non-surgical techniques, and cell-based autologous technique compared to surgical interventions in head-to-head comparisons in the same study. Subgroup analysis may be used to categorize the results based on the type of non-surgical or surgical intervention in the comparator group. Where statistical pooling is not possible, the findings will be presented in narrative form using figures and tables to aid in the data presentation.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a Summary of Findings (SoF) will be created using GRADEpro GDT 2000 (McMaster University, ON, Canada). This will be undertaken by two independent reviewers at the outcome level. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The table will include results for the direct comparisons of cell-based autologous interventional techniques compared to other non-surgical interventional techniques. The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. For comparison purposes, the cell-based autologous interventional techniques will be considered as the intervention group. The outcomes reported in the SoF will include disability scores (measured with ODI or RMQD), physical activity level, pain severity (NRS or VAS), and opioid use (frequency, number of prescription refills, hospitalization rates).

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Author contributions

AO: conceptualization, methodology, critical appraisal, data extraction, data synthesis, writing (original draft, review, editing); JG: conceptualization, methodology, critical appraisal, data extraction, data synthesis, supervision, writing (review and editing).

Conflicts of interest

There is no conflict of interest in this project.

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Appendices

Appendix I: Search strategy

PubMed

Search conducted on 3/13/2025

Search	Terms	Number of Results
1	"Back pain"[tw] OR "Lumbar pain"[tw] OR Radiculopathy[tw] OR "Discogenic back pain"[tw] OR "Discogenic low back pain"[tw] OR "Discogenic pain"[tw] OR "Discogenic syndrome"[tw] OR "Vertebrogenic pain"[tw] OR "Sacroiliac joint dysfunction"[tw] OR "Spinal stenosis"[tw] OR "Lumbar spinal stenosis"[tw] OR "Back pain"[Mesh] OR "Intervertebral disc degeneration"[Mesh] OR "Low back pain"[Mesh] OR "Chronic pain"[Mesh] OR Radiculopathy[Mesh] OR "Spinal stenosis"[Mesh]	130,795
2	"Platelet-rich plasma"[tw] OR "PRP therapy"[tw] OR "Bone marrow concentrate"[tw] OR "Intradiscal biologics"[tw] OR "Leukocyte-rich prp"[tw] OR "Autologous conditioned serum"[tw] OR "Autologous protein solution"[tw] OR "Autologous chondrocytes"[tw] OR "Progenitor cells"[tw] OR "Mesenchymal stem cells"[tw] OR "Stem cell therapy"[tw] OR "Embryonic stem cells"[tw] OR "Platelet rich plasma"[Mesh] OR "Bone marrow cells"[Mesh] OR "Mesenchymal stem cell transplantation"[Mesh]	482, 555

	OR "Transplantation, autologous"[Mesh] OR "Embryonic stem cells"[Mesh] OR "Genetic therapy"[Mesh]	
3	"Conservative treatment"[tw] OR "Epidural injection"[tw] OR "Spinal cord stimulation"[tw] OR DMARDS[tw] OR "Facet injection"[tw] OR "facet joint injection"[tw] OR "Spinal cord stimulation"[tw] OR "Disease-modifying anti-rheumatic drugs"[tw] OR "Intra-articular injection"[tw] OR Neurostimulation[tw] OR "Thermal annular procedures"[tw] OR "Percutaneous adhesiolysis"[tw] OR "Conservative treatment"[Mesh] OR "Radiofrequency ablation"[Mesh] OR Conservative[Mesh] OR Interventional[Mesh] OR "Methylene blue"[Mesh] OR "Spinal cord stimulation"[Mesh] OR "Epidural injection"[Mesh] OR "Antirheumatic agents"[Mesh]	979,499
4	1 AND 2 AND 3	94