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Intradiscal injection for the management of low back pain

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Abstract

Low back pain (LBP) is a common clinical problem and a major cause of physical disability, imposing a prominent socioeconomic burden. Intervertebral disc degeneration (IDD) has been considered the main cause of LBP. The current treatments have limited efficacy because they cannot address the underlying degeneration. With an increased understanding of the complex pathological mechanism of IDD, various medications and biological reagents have been used for intradiscal injection for the treatment of LBP. There is increasing clinical evidence showing the benefits of these therapies on symptomatic relief and their potential for disc repair and regeneration by targeting the disrupted pathways underlying the cause of the disease. A brief overview of the potential and limitations for these therapies are provided in this review, based on the recent and available data from clinical trials and systematic reviews. Finally, future perspectives are discussed.

KEYWORDS
intervertebral disc degeneration, intradiscal injection, low back pain

1 | INTRODUCTION

Low back pain (LBP) is a common symptom that occurs below the costal margin and above the inferior gluteal fold, which refers to pain, muscle tension, or stiffness. The global prevalence of LBP in 2017 was 7.83%, and 577 million people were affected at any time.[1] In 2019, a systematic review of 13 studies from northern Europe, North America, and Israel reported that the prevalence of LBP ranged between 14% and 20%.[2] A systematic review and meta-analysis revealed that the lifetime prevalence of LBP was 47% in low-, lower-

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middle-, and upper-middle-income countries in Africa.[3] LBP is a major cause of physical disability in people of all ages and socioeconomic statuses, which places a prominent socioeconomic burden on public health.[4] In a recent study assessing the incidence, prevalence, and years lived with disability associated with 354 diseases, LBP was identified as the leading cause of worldwide productivity loss and of years lived with disability in 126 countries.[5] Moreover, the economic burden of LBP is approximately £2.8 billion in the United Kingdom and more than $100 billion in the United States per year.[6,7]

Intervertebral disc degeneration (IDD) is considered a major cause of LBP,[8] which also causes other musculoskeletal and spine diseases, such as disc herniation, spinal stenosis, structural instability, and spondylosis. The etiology of IDD is multifactorial, including genetic predisposition, abnormal biomechanical loading, decreased nutrient transport, aging, and lifestyle factors.[9] The development of IDD is characterized by certain pathological features, including elevated inflammatory cytokine levels, progressive loss of the extracellular matrix (ECM), changes in cell phenotype, and increased cell senescence and death. These cellular and biochemical changes further lead to progressive functional and structural impairment.

Treatment for LBP can be divided into three stages. Conservative therapy should be considered as the first line of care in case of an acute episode, including the use of nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, opioids, and antitumor necrosis factor antagonists, in conjunction with nonpharmacological strategies such as traction, manipulation, and physical therapy, all of which lead to improvement in most patients.[10] If the symptoms do not subside after the conservative therapy, more invasive treatments are generally considered, including epidural injections, facet injections, and radiofrequency ablations. Finally, if patients are refractory to the above treatments or experience progressive neurological deficits, surgery is recommended, such as endoscopic lumbar discectomy, posterior lumbar interbody fusion, and disc replacement. Unfortunately, to date, all treatments have limited efficacy, and no specific therapies for IDD exist.

Hence, there is a strong clinical demand for the development of regenerative therapy to restore and maintain the native disc structure and mechanical function. Based on the ongoing investigations and understanding of the pathological mechanism of IDD, increasing biological approaches have shown their benefit for disc repair and regeneration.[11] Presently, the regenerative therapy for IDD can be divided into three categories: gene therapy, cell therapy, and tissue engineering biomaterials.[12,13] Especially, cell therapy and tissue engineering approach targeting the multiple disrupted pathways underlying the cause of IDD are considered to be potential therapeutic strategies.[14] There are growing clinical investigations and trials illuminating the potential for these therapies in pain control and disc regeneration.

Intradiscal injection is a minimally invasive outpatient procedure for the treatment of LBP. In this procedure, a needle is inserted in the nucleus pulposus (NP) via a percutaneous approach. Usually, this procedure is performed under imaging guidance such as real-time multiplanar fluoroscopy and computed tomography (CT), to improve the success rate and reduce adverse events. Recently, the use of ultrasound for guiding intradiscal injection has made this procedure more convenient, safer, and decreased the physical load and radiation exposure.[15,16]

The common medications used for intradiscal injection include oxygen-ozone (O_2-O_3) mixture, steroids, methylene blue, and thermal decompression device, to reduce the inflammatory response or remove the degenerated disc by dehydration and dissolution of the NP tissues.[17] In recent years, various biological reagents and biomaterials, including platelet-rich plasma (PRP), stem cells, and hydrogel, have been used for intradiscal injection, drawing increased attention for the screening of the ideal injectable medications for IDD. These therapies target the multiple disrupted pathways underlying the cause of the disease and have the potential for disc repair and regeneration.[18] With the increasing variety of biological reagents used for intradiscal injection, there is an urgent need for a review to better illuminate the potential and limitations of these therapies in the treatment of LBP.

Many reports have identified the benefit of intradiscal injection using many biological reagents for disc regeneration in vitro and animal experiments, such as senolytic targeting cellular senescence, antioxidant targeting mitochondrial dysfunction, small molecule natural compound, and some ingredients extracted from the traditional Chinese medicine herb.[19-22] However, their efficacy and feasibility for intradiscal injection are not confirmed by clinical trials; therefore, these studies were excluded from our review.

Therefore, this article aimed to distill the most recent and available data from clinical trials and systematic reviews, combined with the targeting pathways underlying the pathological mechanism of IDD, to illustrate the effectiveness of intradiscal injection of different medications or biological reagents in the treatment of LBP, and provide more comprehensive and authentic evidence for the selection of these treatments.

2 | GLUCOCORTICOIDS

Inflammatory response is considered to be an important cause of LBP. Glucocorticoids are widely used in the treatment of LBP, such as epidural injection,[23,24] sacroiliacs joint,[25] nerve root block,[26] injections following discectomy,[27] because of their powerful anti-inflammatory effects.

In a randomized controlled trial (RCT) conducted by Cao et al,[28] after intradiscal glucocorticoid injection, the visual analog scale (VAS) and Oswestry Disability Index (ODI) scores improved significantly at 3 or 6 months compared to those observed with saline injection. Recently, Nguyen et al[29] revealed in a multicenter RCT that intradiscal injection of methylprednisolone acetate can effectively alleviate the symptoms of LBP at 1 month, but without long-term efficacy. Moreover, for LBP with active discopathy, intradiscal injection of prednisolone acetate can reduce pain intensity at 1 month but not at 3 and 6 months.[30] Due to the half-life of glucocorticoids, their anti-inflammatory effects and efficacy are difficult to maintain for a long time. However, it is unclear whether multiple injections can maintain long-term efficacy.

3 | OXYGEN-OZONE

Ozone is a strong oxidizing gas that normally exists in the atmosphere with antiseptic, analgesic, immunomodulating, and anti-inflammatory properties.[31] The intradiscal injection of O_2-O_3 mixture, with a concentration range from 10 to 40 μg O_3/mL O_2, has been widely used in the treatment of LBP in many countries since the 1990s, especially in Europe and Asia, as an alternative minimally invasive, safe, and cost-effective choice.[32,33] Multiple studies have demonstrated its significant improvement of symptoms, because of the following properties: (a) stimulating the activity of fibroblasts to repair the damaged disc by deposition of collagen; (b) increasing the concentration of oxygen in tissues; (c) interrupting the inflammatory cascade of the arachidonic acid; (d) reducing the disc volume by breaking the glycosaminoglycan chains.[34,35]

A previous meta-analysis including 12 studies and almost 8000 patients ranging from 13 to 94 years showed that after treatment by oxygen/ozone, the mean improvement was 3.9 for VAS and 25.7 for ODI, the pain and function outcomes were similar to the outcomes treated by a surgical discectomy. Moreover, O_2-O_3 treatment had a lower complication rate of 0.064% and a significantly shorter recovery time.[36] A recent systematic review and meta-regression including 22 articles also highlighted the positive effects in reducing pain and improving function for patients with LBP.[37] Several studies have reported that intradiscal O_2-O_3 injection can reduce the disc herniation size and improve the pain quality in the short term,[38] although its benefit can span across 10 years.[39] Furthermore, some studies and meta-analyses reported that ozone therapy was more effective than other therapies, such as laser disc decompression and steroid injection.[40,41] Moreover, a recent RCT reported that intradiscal O_2-O_3 injection alone was sufficient to treat LBP and radicular pain, additional periforaminal steroid injection was not beneficial.[42]

Although many studies have demonstrated that intradiscal O_2-O_3 injection plays a relevant role in the improvement of pain quality for patients with LBP or lumbar disc herniation (LDH), there is insufficient evidence to reinforce strong recommendations.[37] Additionally, to obtain a successful clinical outcome, the indications and selection criteria should be fully understood. The radicular pain caused by LDH is considered the best clinical indication of O_2-O_3 treatment, rather than LBP; and patients with neurological motor deficit, cauda equina syndrome, or spinal infection are not recommended for O_2-O_3 treatment.[35]

4 | METHYLENE BLUE

Nociceptive nerves grow into the NP extending from the outer layer of the annulus fibrosis or endplate, which is one of the main causes of chronic discogenic LBP.[43,44] Since the first synthesis in 1876, methylene blue has been used for the treatment of many painful ailments and idiopathic pruritus ani, because of its neurolytic effect by blocking nerve conduction or damage to nerve endings.[45] Meanwhile, methylene blue is known to have an anti-inflammatory effect by inhibiting the synthesis of nitric oxide and generation of free radicals, which is beneficial for relieving pain.[46]

Intradiscal methylene blue injection was first reported by Peng et al[47] and was considered an effective and minimally invasive treatment for LBP. Subsequently, its short-term efficacy was found in other studies by Kim et al[48] and Zhang et al.[49] A meta-analysis including five clinical studies concluded that intradiscal methylene blue injection can relieve pain symptoms and improve ODI score, which is a safe and effective procedure for the treatment of chronic LBP.[50] However, a recent multicentre RCT showed that, compared to placebo injection, intradiscal methylene blue injection did not exhibit better efficacy, and could not be recommended for patients with chronic discogenic LBP.[51] Further, an in vitro study found that a high concentration of methylene blue can inhibit proliferation and paracrine function of annulus fibrosus cells, even induce cell apoptosis, suggesting that its practical application for the treatment of discogenic LBP should be carefully considered.[52] In the past 2 years, no clinical study was conducted to confirm the efficacy of intradiscal methylene blue injection. Therefore, its safety and efficacy, especially in the long-term, need to be further assessed.

5 | MESENCHYMAL STEM CELLS

IDD usually involves a decrease in cell density, increase in inflammatory factors, and an overall reduction in the synthesis of ECM.[9] Use of cell-based therapies, especially implantation of autologous or allogeneic mesenchymal stem cells (MSCs) may be a potential therapeutic strategy for early disc degeneration.[53] MSCs from various adult tissues, such as the bone marrow, adipose tissue, and umbilical cord, have become highly topical for disc regeneration in experimental and clinical investigations, because of their potential for differentiating into NP cells (NPCs), promoting the proliferation of NPCs, and promoting the synthesis of the ECM. Meanwhile, MSCs have powerful immunomodulatory properties and the ability to reduce the inflammatory response in the disc by promoting the production of anti-inflammatory factors.[54]

Pang et al[55] reported that intradiscal injection of umbilical cord MSCs can improve the patient's pain symptoms and functional scores. Orozco et al's study[56] reported that 26 patients suffering from degenerative disc disease, as well as candidates for surgical treatment, were selected. After intradiscal injection of bone marrow-derived MSCs, 40% of patients improved one modified Pfirrmann grade at 12 months, the VAS and ODI scores decreased significantly at 36 months, and only six patients eventually progressed to surgery. Moreover, its long-term efficacy was reported in a study with a follow-up period of up to 6 years.[57]

Considering that MSCs have an immune privilege or immune evasion ability, and can inhibit the immune response in a manner not restricted by the human leukocyte antigen (HLA) system, the injection of allogeneic MSCs would not cause apparent immune rejection, and would be logistically more convenient than the autologous MSC. Noriega et al[58] showed in an RCT that intradiscal injection of allogeneic bone marrow MSCs can improve disc quality quantified by Pfirrmann grading, pain symptoms, and quality of life, without causing

severe adverse events, and confirmed that allogeneic MSCs therapy was a valid alternative for the treatment of IDD. A recent systematic review including seven clinical studies identified that MSCs injection was a safe and feasible option for IDD in patients at the early-degeneration stage, evidenced by an overall clinical and radiological improvement and very low complication rate during the follow-up.[59] However, how to maintain the viability of MSCs, and how to promote their proliferation and differentiation under the conditions of low pH, low glucose, low oxygen, and high inflammatory conditions of the degenerating intervertebral disc (IVD), remains a challenge to be further resolved in future research.[60]

6 | PLATELET-RICH PLASMA

PRP is an autologous blood concentrate acquired from centrifuged whole blood, which contains a natural concentration of growth factors and cytokines, including vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor, transforming growth factor β-1, and platelet-derived growth factor.[61] Recently, increasing studies have demonstrated the repair and regenerative ability of PRP in many damaged or degenerated tissues, including tendons, ligaments, and cartilage, because of its potential for promoting cell proliferation, differentiation, migration, and synthesis of ECM proteins and collagen.[62-65] Moreover, PRP has exhibited an anti-inflammatory effect by preventing the activation of inflammatory mediators and inhibiting metalloproteinases, making it a potential strategy for the management of LBP.[66,67]

In a prospective observational study by Levi et al,[68] 22 patients with discogenic LBP underwent intradiscal injection of PRP. If the patient's VAS improved by at least 50% and ODI decreased by at least 30%, the treatment was considered successful. Finally, the treatment success rate was 14% at 1 month, 32% at 2 months, and 47% at 6 months follow-up. The first double-blind RCT using PRP for discogenic LBP was reported by Tuakli-Wosornu et al.[69] Forty-seven patients were treated by the intradiscal injection of PRP (treatment group) or contrast agent (control group). At the 8-week follow-up, there were statistically significant improvements in the treatment group with numeric rating scale (NRS) best pain, functional rating index (FRI), and patient satisfaction (North American Spine Society Outcome Questionnaire) compared to the control group. No adverse events were reported, such as disc infection, neurologic injury, or progressive herniation. Furthermore, the long-term efficacy of intradiscal PRP injection for symptomatic degenerative intervertebral discs was confirmed in an RCT with 5 to 9 years follow-up,[70] and a positive correlation between platelet concentration of PRP and clinical outcomes was identified in a recent prospective clinical trial.[71]

Recently, several meta-analyses demonstrated that intradiscal PRP injection had shown beneficial effects in controlling pain and improving disabilities in patients with LBP, but there was a paucity of high-quality studies to give conclusive evidence.[72,73] Therefore, more clinical studies, especially RCTs with multiple outcome parameters, are necessary for evaluating the true efficacy of this treatment.[74] Moreover, according to the American Society of Interventional Pain Physicians guidelines, the qualitative evidence for intradiscal PRP injection in the treatment of LBP has been assessed as level III, based on the available evidence including RCT, observational studies, meta-analysis, and systematic review.[75]

7 | CONDOLIASE

During disc degeneration, lumbosacral nerve compression induced by herniated NP tissues is an important factor causing LBP and radicular pain. Chemonucleolysis was first described by Smith[76] in 1964, to dissolve the herniated NP by injection of proteolytic enzymes. Chymopapain, a nonspecific proteoglycanase derived from the papaya plant, was the main enzyme used for this procedure. Subsequently, chemonucleolysis was approved by the US Food and Drug Administration in 1982 and is widely used for the treatment of LDH in the United States and Europe, although accompanied by considerable controversy and vocal opposition. However, since the early 2000s, chymopapain was gradually withdrawn from the market and chemonucleolysis has not been available for LDH, due to safety concerns and other factors.

Chondroitin sulfate ABC endolyase (condoliase), derived from the gram-negative rod, *Proteus vulgaris*, is a pure mucopolysaccharidase with high substrate specificity for hyaluronic acid and chosulphaten sulfate, which are the main proteoglycans of NP tissues. Unlike chymopapain, the target of condoliase is chondroitin sulfate, which is distributed in the NP tissues but not in the nerves and vascular tissues. Therefore, condoliase can be safely and specifically used for the treatment of LDH.[77]

In an RCT conducted by Matsuyama et al,[78] 192 patients with LDH were included. After the intradiscal injection of different doses of condoliase, the clinical symptoms were significantly improved without causing severe adverse drug reactions. Moreover, three doses had similar efficacy, but the incidence of adverse events and decrease in disc height was dose-dependent. Therefore, a small dose of condoliase (1.25 U) was recommended for intradiscal injection. Okada et al[79] reported that, after the intradiscal injection of condoliase, 85.4% of patients reported an improvement in pain symptoms, and no severe adverse event was observed. Furthermore, injecting condoliase into the center of the NP is recommended for obtaining better clinical effectiveness. Intradiscal injection of condoliase for the treatment of LDH has been approved by the drug regulatory authority in Japan,[80] after its efficacy and safety were confirmed in clinical phases II/III and III studies.[78,81] Although current studies suggest that the intradiscal injection of condoliase is a potential new, effective, and minimally invasive therapeutic strategy for patients with LDH,[82] its long-term efficacy and side effects remain unclear, and the best clinical indications need to be further identified.

8 | CYTOKINE ANTAGONIST

Cytokines, as regulatory proteins and proinflammatory biomarkers, play an important role in the occurrence and development of disc degeneration, by amplification of inflammatory response and promoting ECM

degradation.[83] Especially, tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) are presumed to be critical drivers of IDD.[84] Advances in experimental and clinical research have identified that specific cytokine antagonists may be a novel treatment strategy for LBP or early-stage IDD,[85-87] including anti-TNF: infliximab, etanercept, and adalimumab; anti-IL-6: tocilizumab; antinerve growth factor: tanezumab, fulranumab; anti-Janus kinase: tofacitinib.

A previous double-blind, placebo-controlled pilot study reported that a single low dose (0.1-1.5 mg) of intradiscal etanercept injection imparted no significant improvement in pain scores and function, although no severe side effects were observed.[88] However, in an RCT conducted by Sainoh et al,[89] the intradiscal injection dose of etanercept was increased to 10 mg. After 8 weeks of follow-up, the patient's pain symptoms and function scores improved without adverse reactions such as infection and nerve damage. Additionally, the intradiscal injection of tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, was shown to exert a short-term analgesic effect in patients with discogenic LBP.[90] However, there is limited evidence on cytokine antagonists for the treatment of LBP, and it cannot be currently recommended for clinical practice. Therefore, larger sample sizes and better-designed studies are required to determine the safety and efficacy, especially, the long-term effects.

9 | HYDROGEL-BASED BIOMATERIALS

During degeneration, the synthesis of ECM components such as type II collagen and proteoglycan decreases, which impairs the NP mechanical function, and decreases the swelling capacity and pressurization potential. Therefore, how to restore and maintaining the native disc structure and mechanical function is the key to biological-based therapies. With the development of tissue engineering technology, various hydrogels have been made using natural or synthetic materials.[91] Natural hydrogels include hyaluronic acid, chitosan, alginate, and fibrin.[92] Generally, these materials are economical and exhibit low levels of cytotoxicity, bioactivity, and bioactive degradation.

Especially, hyaluronic acid-based hydrogels have been drawing increasing attention as the ideal candidates for IDD,[92] because of their potential to repair and regenerate the NP through providing a three-dimensional microenvironment for the implanted cells,[93] restoring biomechanical properties,[94] reducing inflammation response, and nociceptive behavior,[95] promoting ECM synthesis,[96] and promoting stem cell differentiation to NP-like cells.[97]

Animal experiments revealed that the injection of hyaluronic acid hydrogel not only restored the height of the intervertebral disc but also reduced inflammation and promoted the synthesis of ECM.[98,99] Priyadarshani et al[100] showed that crosslinking of type II collagen-hyaluronic acid hydrogel can provide a growth-permissive environment for NPCs and be transplanted into the disc as cell carriers. Moreover, the combined injection of hydrogel and stem cells provides a carrier for stem cells and also reduces the risk of adverse reactions such as ligament and bone hyperplasia caused by stem cell leakage. In a phase I clinical trial conducted by Kumar et al,[101] intradiscal injections of hyaluronic acid combined with autologous adipose-derived MSCs relieved the pain symptoms of patients with LBP and also improve the functional score and quality of life, and no adverse event was observed during the 1-year follow-up period. In a prospective randomized, placebo-controlled 36-month study,[102] compared with the control groups, intradiscal injection of allogeneic mesenchymal precursor cells (MPCs) with hyaluronic acid demonstrated significant improvements in pain and function at various time points from baseline to 36 months, and there were no clinical symptoms of immune reactions to allogeneic MPCs, or other severe adverse events. However, the current research on the treatment of IDD with hydrogel-based biomaterials is mainly conducted in vitro and animal experiments; the safety and feasibility of this option still need to be confirmed by more clinical studies.

Synthetic hydrogels are made from synthetic polymers such as polyamides and polyethylene glycol. Compared to natural hydrogels, synthetic hydrogels have better reproducibility, controllability, and customizable properties. However, potential biocompatibility and cytotoxicity are big concerns of synthetic hydrogels. While these materials displayed promising clinical application potential in cell tests and animal experiments, only a few synthetic hydrogel devices have been studied in clinical research.[92] For example, GelStix Nucleus Augmentation Device is a modified polyacrylonitrile hydrogel that reconstructs the disc function by increasing hydration and IVD height. Ceylan et al[103] implanted GelStix in 29 patients with IDD and found that the VAS scores were decreased from 7.14 to 2.48 and the ODI scores were decreased from 28.14 to 17.35 after 12 months following treatment. Moreover, another randomized, double-blind, placebo-controlled, multicentre study has been conducted to evaluate the efficacy of treatment with the GelStix device in patients with chronic discogenic LBP, which is expected to conclude in August 2021.[104]

10 | SIDE EFFECTS

Generally, minimal intradiscal injection may offer good results with patient compliance and low cost, but some side effects have been reported, including discitis,[105] disc collapse,[106] and impairment of sensitivity in the lower ipsilateral limb.[107] With the application of imaging guidance, this procedure became more feasible and safer, with an overall complication rate of ~0.47%.[32] Meanwhile, IDD is considered a major concern in intradiscal injection. Theoretically, a needle puncture injury can cause increased cell death, metabolic dysfunction, annulus fibrosus integrity impairment, and NP depressurisation.[108,109] Therefore, some authors have highlighted small-diameter puncture needle and minimum dose of agent to avoid disc degeneration.[110,111] Moreover, disc degeneration caused by intradiscal injection was rarely reported. A recent narrative review on the techniques of intradiscal injection including 6843 patients reported that only two discs showed a collapse after injection of corticosteroid.[32]

TABLE 1 Mechanism and clinical efficacy of medications/biological agents used for intradiscal injection

Medications/biological agents	Mechanism and effects	Clinical outcomes	Study type
Glucocorticoids	Anti-inflammation effect[23-27]	Improving VAS, NRS, ODI scores, and LBP-related limitations in activities (Quebec Back Pain Disability Scale) in the short term Reducing the HADS depression scores in the long term	Prospective trial, prospective randomized controlled trial[28-30]
O_2-O_3	(1) Stimulating the activity of fibroblasts to repair the damaged disc by deposition of collagen; (2) Increasing the concentration of oxygen in tissues; (3) Interrupting the inflammatory cascade of the arachidonic acid; (4) Reducing the disc volume by breaking the glycosaminoglycan chains.[31-35]	Improving VAS, ODI scores in the short and long term Reducing the size of the disc herniation in the long term.	Prospective trial, prospective randomized controlled trial, systematic review, meta-analysis.[36-41]
Methylene blue	(1) Blocking nerve conduction or damage to nerve endings[45]; (2) Anti-inflammation effect.[46]	Reducing the NRS, ODI scores and improving patient satisfaction rates in the short term Improving disc degeneration condition assessed by apparent diffusion coefficient and T2 values on MRI in the long term Decreasing the usage of NSAIDs or opioid medications in the long term.	Prospective trial, prospective randomized controlled trial, meta-analysis.[47-50]
MSCs	(1) Differentiating into NP cells; (2) Promoting the synthesis of ECM; (3) Immunomodulatory properties.[53,54]	Improving VAS, ODI, FRI, SF-36 scores in the short and long term Improving disc quality quantified by Pfirrmann grading in the long term.	Prospective trial, prospective randomized controlled trial, systematic review.[55-59]
PRP	(1) Promoting cell proliferation, differentiation, migration; (2) Promoting the synthesis of ECM; (3) Preventing the activation of inflammatory mediators and inhibiting metalloproteinases.[62-67]	Improving VAS, ODI, NRS best pain, FRI scores, and patient satisfaction (North American Spine Society Outcome Questionnaire) in the short and long term.	Prospective trial, prospective randomized controlled trial, systematic review; meta-analysis.[68-74]
Condoliase	Specifically dissolve the chondroitin sulfate in NP tissue and relieve the compression on nerve roots.77	Improving VAS (worst leg pain), ODI, and SF-36 scores in the short term.	Prospective trial, prospective randomized controlled trial.[78-82]
Cytokine inhibitor	Anti-inflammation effect.[85-87]	Improving NRS and ODI scores in the short term.	Prospective randomized controlled trial.[89,90]
Hydrogel-based biomaterials combined with stem cells	(1) Providing a three-dimensional microenvironment for the implanted cells (2) Restoring biomechanical properties; (3) Reducing inflammation response and nociceptive behavior; (4) Promoting the synthesis of ECM; (5) Promoting stem cell differentiation to NP-like cells.[92-97]	Improving VAS, ODI, SF-36 scores, and disc quality quantified by Pfirrmann grading and apparent diffusion coefficient on diffusion MRI in the short and long term.	Prospective trial, prospective randomized controlled trial.[101-103]

Abbreviations: ECM, extracellular matrix; FRI, functional rating index; HADS, Hospital Anxiety and Depression Scale; LBP, low back pain; MRI, Magnetic Resonance Imaging; MSC, mesenchymal stem cell; NP, nucleus pulposus; NRS, numerical rating scale; NSAID, nonsteroidal anti-inflammatory drugs; O_2-O_3, oxygen-ozone; ODI, Oswestry Disability Index; PRP, platelet-rich plasma; SF-36, 36-Item Short Form Survey; VAS, visual analog scale.

11 | CONCLUSION AND FUTURE PERSPECTIVES

Intradiscal injection is a minimally invasive technique widely used in the management of patients with LBP, and its safety, efficacy, and feasibility are identified by growing clinical trials. Although there are various medications or biological agents used for intradiscal injection to treat LBP, their efficacy and safety are not easily comparable because of differences in the study designs and their limited number of cases, and there is insufficient evidence to support strong recommendations for their clinical application.

Increasing reports are revealing the benefits of these medications or biological agents in relieving the clinical symptoms and their potential for disc regeneration (Table 1). However, they all have some limitations. For example, the injection of glucocorticoids, methylene blue, and cytokine inhibitors can reduce inflammation and relieve symptoms in the short-term, but their efficacy is difficult to maintain for a long period due to their half-lives. Although previous studies suggested that the intradiscal injection of PRP and condoliase can alleviate pain symptoms, larger-sample and high-quality clinical trials are still needed to confirm their efficacy. MSCs have the potential to differentiate into NPCs and promote the synthesis of the ECM; however, it is difficult for the implanted MSCs to maintain their viability in the hypoxic and acidic environment of the degenerated disc.

Therefore, combined injections are expected to compensate for their individual components' limitations. Especially, the combination of cell therapy and tissue engineering technology may be the ideal medications for IDD, because of their potential for restoring the native function of IVD and disc regeneration. For example, stem cell-embedded hydrogel injection maintains the mechanical properties of IVD and provides a carrier for stem cells, which is beneficial for their survival, proliferation, and differentiation. Although the current evidence is mainly derived from animal experiments, preclinical experiments, and limited clinical trials, there are certain challenges for its clinical application. With the growing clinical data and future systematic reviews, it is not unrealistic to hypothesize that this option can provide longer relief and greater clinical benefits to this patient population, and play an important role in the management of LBP.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Fu Zhang and Songjuan Wang contributed equally to the concept of the paper and the writing of the article. Baoliang Li contributed to the article revision. Zhiyu Zhou and Shaoyu Liu provided substantial contributions to reviewing the format, revising the article critically, and its final approval. All authors have read and approved the final submitted article.

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