Wharton's Jelly Mesenchymal Stem Cell-Derived Exosomes as an Adjunctive and Alternative Therapeutic Strategy in Spinal Disc Repair, Post-Surgical Recovery, and as a Replacement for FDA-Unindicated Epidural Corticosteroid Injections

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ABSTRACT

Background

Epidural corticosteroid injections (ECIs), delivered via Tuohy (Touhy) needles, constitute one of the most frequently performed interventional pain procedures in the United States, despite the fact that corticosteroids have never received FDA approval for epidural administration. In April 2014, the FDA issued a Drug Safety Communication requiring manufacturers to add label language acknowledging that "the safety and effectiveness of epidural administration of corticosteroids have not been established" and that "serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids." Concurrently, the Discseel® Procedure, a biologic disc repair technique employing FDA-approved fibrin sealant, has demonstrated sustained efficacy in patients with annular tears and chronic discogenic pain.

Objective

This paper reviews the existing published literature on Wharton's Jelly mesenchymal stem cell-derived exosomes (WJ-MSC-EVs) and proposes their application as: (1) adjuncts to the Discseel® Procedure to amplify disc regeneration; (2) adjuncts to traditional spinal surgery to manage post-operative inflammation without FDA-unindicated agents; and (3) biologically superior and safer alternatives to epidural corticosteroid injections.

Methods

A narrative review of published literature was conducted encompassing WJ-MSC exosome biology and spine-specific studies through 2025, including in vitro disc degeneration models, spinal cord injury preclinical studies, and clinical outcome data for the Discseel® Procedure.

Results

WJ-MSC-derived extracellular vesicles suppress pro-inflammatory cytokines (TNF-α, IL-1β), promote nucleus pulposus cell proliferation and extracellular matrix synthesis, reduce oxidative stress, and facilitate macrophage polarization toward the anti-inflammatory M2 phenotype through miRNA cargo including miR-16-5p, miR-499-5p, and related species. The Discseel® Procedure demonstrates 82% long-term success rates at three-year follow-up in populations who had failed an average of four prior invasive treatments. Epidural corticosteroids carry FDA Drug Safety Communication labeling and are associated with catastrophic neurological adverse events including stroke, paralysis, and death.

Conclusions

WJ-MSC-derived exosomes present a compelling, cell-free biologic with mechanistic alignment to disc repair objectives. Combined with or following the Discseel® Procedure, their anti-inflammatory, anabolic, and neuroprotective properties may amplify clinical outcomes while avoiding the severe adverse event profile of epidural corticosteroids administered via Tuohy needle into the spinal epidural space. Prospective randomized controlled trials are warranted.

Keywords: Wharton's Jelly; mesenchymal stem cell; exosomes; extracellular vesicles; Discseel; intervertebral disc; annular tear; nucleus pulposus; epidural corticosteroid; Tuohy needle; spine surgery; regenerative medicine; FDA; fibrin sealant; disc degeneration

1. INTRODUCTION

Chronic low back pain (CLBP) remains among the leading causes of global disability, affecting an estimated 619 million individuals worldwide as of 2020 and projected to increase further through 2050 [1]. In the United States, CLBP accounts for hundreds of billions of dollars in direct healthcare expenditure and indirect costs from lost productivity annually. A significant proportion of CLBP is attributable to intervertebral disc (IVD) pathology—specifically, annular tears that permit nucleus pulposus (NP) material to leak into surrounding neural structures, generating a complex inflammatory cascade that sensitizes dorsal root ganglia and produces both axial and radicular pain [2].

The standard of care for CLBP has long been dominated by two broad categories of intervention: epidural corticosteroid injections (ECIs) and structural surgical procedures including discectomy, laminectomy, and spinal fusion. Each carries a substantial burden of risk. Epidural corticosteroids, despite being administered daily across tens of thousands of clinics in the United States—an estimated 9–12 million procedures annually—have never been approved by the U.S. Food and Drug Administration (FDA) for epidural delivery [3]. The FDA formalized this regulatory gap in April 2014 with a Drug Safety Communication requiring that all injectable glucocorticoid product labels carry warning language acknowledging that serious neurological events, including stroke, paralysis, and death, have been reported with epidural injection, and that corticosteroids are not approved for this use [3]. Spinal fusion, while structurally effective in select populations, carries 6–12-month recovery timelines, significant hardware complication rates, and the well-documented risk of Adjacent Segment Disease (ASD) from biomechanical load transfer to non-fused vertebral levels [4].

Into this therapeutic gap, two developments have emerged with particular clinical relevance. First, the Discseel® Procedure, developed by Kevin Pauza, MD, and published in the Pain Physician Journal, introduces an FDA-approved fibrin biologic—comprised of prothrombin and fibrinogen—injected intra-annularly to seal disc tears and stimulate native tissue regeneration. Published data from the largest spine regenerative medicine study to date, encompassing 827 subjects, demonstrate 82% long-term success rates across patients who had failed an average of four prior invasive treatments including spinal fusion, discectomy, and steroid injections [5]. Second, Wharton's Jelly mesenchymal stem cell-derived exosomes (WJ-MSC-EVs) have emerged

as a potent, cell-free biologic with anti-inflammatory, anabolic, and neuroprotective properties mechanistically well-aligned with the demands of disc repair and post-operative spinal recovery [6,7].

This manuscript reviews the existing evidence base for WJ-MSC-derived exosomes, synthesizes their mechanistic profile against the specific pathobiology of discogenic disease and surgical spinal trauma, and proposes a clinical framework for their use as adjuncts to the Discseel® Procedure and traditional spine surgery, and as alternatives to epidural corticosteroid injections. We further address the regulatory landscape governing these interventions, including the unresolved question of the Tuohy (Touhy) needle as a delivery device for drugs lacking FDA approval for the epidural space.

2. BACKGROUND

2.1 Intervertebral Disc Pathology and the Inflammatory Cascade

The intervertebral disc is an avascular structure composed of a gelatinous nucleus pulposus (NP) enclosed within the fibrocartilaginous annulus fibrosus (AF). The NP contains type II collagen, aggrecan, and high concentrations of proteoglycans that maintain hydrostatic pressure critical to disc height and mechanical load distribution. Under repetitive biomechanical stress, genetic predisposition, or age-related matrix degradation, the AF develops radial or circumferential tears through which NP material may extrude [8].

The pathophysiology of discogenic pain involves several overlapping mechanisms. Extruded NP material elicits a robust inflammatory response mediated primarily by tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and prostaglandin E2, which sensitize adjacent dorsal root ganglion neurons and produce both local and referred pain [9]. Matrix metalloproteinases (MMPs), upregulated in the degenerating disc environment, degrade collagen and aggrecan, accelerating the catabolic spiral. Oxidative stress compounds cellular injury, reducing viability of resident NP cells and fibrochondrocytes of the inner AF [10]. This inflammatory milieu has been termed "Leaky Disc Syndrome" by Pauza et al., referencing the chemical radiculitis that results from NP fluid escaping through annular fissures and contacting pain-sensitive neural structures [5].

2.2 Wharton's Jelly Mesenchymal Stem Cell-Derived Exosomes: Biology and Mechanism

Wharton's Jelly is the gelatinous connective tissue filling the umbilical cord and contains a population of mesenchymal stem cells (MSCs) characterized by exceptional proliferative capacity, high immunomodulatory potency, and low immunogenicity compared to bone marrow- or adipose-derived counterparts [11]. WJ-MSCs express HLA-G, a non-classical major histocompatibility complex molecule contributing to immune tolerance, and secrete a distinctive secretome enriched in anti-inflammatory cytokines and extracellular vesicles [12]. Their derivation from full-term umbilical cords avoids the ethical concerns associated with embryonic stem cells and the donor site morbidity of autologous MSC harvesting.

Exosomes are nano-scale extracellular vesicles (30–150 nm diameter) released by parent cells through exocytosis of multivesicular bodies. They carry bioactive cargo including microRNAs (miRNAs), messenger RNAs, proteins, and bioactive lipids that are delivered to target cells via receptor-ligand interactions, membrane fusion, or endocytosis. MSC-derived exosomes have been proposed as the primary paracrine effectors responsible for the tissue-protective and anti-inflammatory effects long attributed to MSC transplantation itself [13].

WJ-MSC-derived extracellular vesicles exhibit several properties directly relevant to spinal pathology, as described below.

2.2.1 Suppression of Pro-Inflammatory Cytokines

WJ-MSC-EVs suppress TNF-α and IL-1β expression and upregulate anti-inflammatory mediators including IL-10 and TGF-β. Human umbilical cord MSC-derived exosomes (hUC-MSC-EVs) downregulate IL-1β and TNF-α in osteoarthritic chondrocytes while increasing arginase-1 (ARG1) and IL-10 expression, mirroring the anti-inflammatory milieu required in the degenerating disc [14]. These effects are mediated through inhibition of NF-κB activation, the master transcriptional regulator of inflammatory gene expression in NP cells, annular fibrochondrocytes, and dorsal root ganglion neurons [16].

2.2.2 Macrophage Polarization Toward M2 Phenotype

A key immunomodulatory mechanism of WJ-MSC-EVs involves promotion of M2 macrophage polarization. MSC-derived exosomes deliver miR-155-5p and miR-216a-5p cargo that activates the PI3K-AKT pathway in macrophages, driving the transition from pro-

inflammatory M1 to resolution-promoting M2 phenotype [15]. M2 macrophages secrete TGF-β and IL-10, which further suppress NF-κB activation and reduce downstream cytokine amplification, creating a sustained anti-inflammatory microenvironment at the site of disc pathology.

2.2.3 Nucleus Pulposus Cell Anabolism and Extracellular Matrix Synthesis

In a 2024 study published in JOR SPINE, WJ-MSC-derived extracellular vesicles promoted nucleus pulposus cell proliferation, metabolic activity, and extracellular matrix production—including type II collagen and aggrecan—in a 3D alginate bead culture model, the accepted in vitro gold standard for recapitulating NP cell biology [17]. These findings were extended in a 2025 study demonstrating that WJ-MSC-EVs attenuate IVD degeneration under inflammatory stress, enhancing NP cell viability and reducing oxidative stress and catabolic gene expression [6]. This dual anabolic-anti-inflammatory profile directly addresses the two primary drivers of disc degeneration progression.

2.2.4 Neuroprotective Properties in Spinal Models

Separate lines of evidence support the utility of MSC-derived exosomes in the neurological compartment adjacent to the spine. Bone marrow MSC-derived exosomes inhibit TNF-α and promote IL-10 and TGF-β in spinal cord injury models, with treated subjects exhibiting superior motor function recovery and reduction in injury size [18]. Exosomes loaded with miR-499-5P attenuate post-injury oxidative stress and inflammation and improve the spinal cord microenvironment [19]. Exosomal delivery of miR-16-5p by hUC-MSCs attenuates inflammation through dual suppression of M1 macrophage polarization and Th1 T-cell differentiation [20]. These neuroprotective effects are directly relevant to the chronic dorsal root ganglion sensitization that sustains pain even after structural disc repair.

2.2.5 Cell-Free Advantages

The acellular nature of WJ-MSC-derived exosomes confers important clinical advantages over direct stem cell transplantation. Exosomes do not replicate, do not present risks of ectopic tissue formation, and are amenable to standardized manufacturing, quality control under current Good Manufacturing Practice (cGMP), and cryopreservation. Their nanoscale size enables broad tissue distribution following local or systemic administration, and their low immunogenicity reduces the risk of adverse immune reactions following allogeneic administration.

2.3 The Discseel® Procedure: Mechanism and Clinical Evidence

The Discseel® Procedure is a two-step, outpatient, minimally invasive intervention developed by Kevin Pauza, MD. The first step involves an Annulargram™, an X-ray contrast injection used to identify annular tears that are often invisible on standard magnetic resonance imaging (MRI). The second step delivers a fibrin biologic—comprised of FDA-approved prothrombin and fibrinogen—directly into identified annular tears under fluoroscopic guidance [5].

Fibrin functions as a biological adhesive that mechanically seals annular fissures while simultaneously activating a cascade of biological repair mechanisms. The fibrin matrix provides a provisional extracellular scaffold upon which disc fibrochondrocytes and NP cells can migrate and proliferate. As the fibrin scaffold degrades, it releases growth factors including TGF-β and platelet-derived growth factor (PDGF), stimulating collagen synthesis and supporting disc tissue regeneration from within the structure of the annulus [5].

The landmark published study in Pain Physician evaluated 827 patients with chronic low back pain of greater than six months' duration, with a mean symptom duration of 11–12 years. All patients had failed at least four prior invasive interventions including spinal fusion, discectomy, epidural steroid injections, radiofrequency ablation, and stem cell therapies. Outcomes were measured using the Oswestry Disability Index (ODI), visual analog pain scales (VAS), and patient satisfaction metrics at 3, 6, 12, 24, and 36 months. Key findings included: a statistically significant 50% of patients achieving Minimal Clinically Important Differences (MCID) on the ODI at 12-month follow-up; 82% long-term success at three-year follow-up; approximately 70% patient satisfaction at final assessment; and greater relative improvement in the cohort with prior failed spinal surgery compared to the surgery-naive cohort [5].

The Discseel® Procedure preserves motion, requires no general anesthesia, carries a recovery timeline of 24–48 hours to light activity and approximately one week to sedentary work, and avoids hardware complications, significant blood loss, and the infection risks inherent to open spinal fusion. The U.S. Department of Defense and the Office of Veterans Affairs have contracted for physician training in the procedure, citing its potential to benefit over 14 million veterans and active service members [5].

2.4 Traditional Spinal Surgery: Post-Operative Inflammation and Current Practice

Spinal fusion, discectomy, and laminectomy each generate a substantial inflammatory response in the post-operative period. Surgical trauma activates the complement system and releases damage-associated molecular patterns (DAMPs) from disrupted cells, driving IL-1β, TNF-α, and IL-6 secretion at the operative site [21]. Post-surgical epidural fibrosis, a known complication of laminectomy and discectomy, involves inflammatory scarring of the epidural space that can compress neural elements and perpetuate or worsen radicular pain—a phenomenon that contributes substantially to Failed Back Surgery Syndrome (FBSS), affecting an estimated 20–40% of operative candidates [22].

To manage this peri-operative and post-operative inflammatory burden, epidural corticosteroid injections have been routinely employed—both intra-operatively and in the weeks following surgery. This practice occurs despite the absence of FDA approval for this indication and despite the FDA's explicit 2014 warning that corticosteroids are not approved for epidural administration and that their safety and effectiveness in the epidural space have not been established [3].

2.5 Epidural Corticosteroid Injections: FDA Regulatory Status and Adverse Event Profile

On April 23, 2014, the FDA issued Drug Safety Communication DSC-2014-184, requiring manufacturers of all injectable corticosteroid preparations—including methylprednisolone acetate, triamcinolone acetonide, betamethasone, dexamethasone, and hydrocortisone—to add the following label language: "Injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death. The safety and effectiveness of epidural administration of corticosteroids have not been established and corticosteroids are not approved for this use" [3].

The clinical adverse event landscape associated with epidural corticosteroid injections is consistent with the FDA's warning. Published literature documents spinal cord infarction from particulate steroid embolization, paraplegia and quadriplegia from direct spinal cord injection or vertebral artery compromise, cortical blindness from embolic events in the posterior circulation, cerebellar stroke, systemic corticosteroid effects including hyperglycemia and adrenal suppression, Cushingoid changes with repeated administration, and adhesive arachnoiditis [23]. In 2015, the New England Journal of Medicine published a formal FDA risk assessment of these

neurological events, confirming that the risks are not solely attributable to procedural error but are intrinsic to epidural glucocorticoid delivery [24].

Despite these documented risks and their regulatory status as unapproved for epidural use, epidural corticosteroid injections remain among the most commonly performed outpatient pain procedures in the United States, estimated at 9–12 million procedures annually [25]. A randomized controlled trial published in the New England Journal of Medicine in 2014 found that epidural corticosteroid injections provided only modest, transient improvement in leg pain from lumbar spinal stenosis at six weeks, with no significant benefit by three months, and no advantage over lidocaine injections alone in long-term functional outcomes [25].

2.6 The Tuohy (Touhy) Needle: Device and Regulatory Considerations

Epidural corticosteroid injections are typically performed using a Tuohy needle—commonly but erroneously spelled "Touhy"—a beveled, hollow-bore needle with an angled Huber point designed to facilitate drug delivery into the epidural space without dural puncture. The Tuohy needle is classified as a medical device subject to FDA regulation under the Federal Food, Drug, and Cosmetic Act. It has received 510(k) clearance for epidural access and catheter delivery applications [26].

However, this creates a compounded regulatory problem that deserves explicit attention: a device cleared for anatomic access is being routinely used to deliver a drug explicitly not approved for delivery to that anatomic space. The 510(k) clearance of the Tuohy needle addresses its mechanical function—the ability to navigate to the epidural space without dural puncture—but does not constitute approval of any specific drug delivered through that device. The corticosteroid agents delivered via the Tuohy needle carry labeling stating they are not approved for epidural use. Neither the drug nor the device-drug combination has received FDA approval for the specific clinical application in which they are jointly employed daily across thousands of U.S. pain clinics.

This regulatory gap does not render epidural steroid injections illegal—physicians may prescribe FDA-approved drugs for off-label uses, and procedures are not regulated as drug approvals. However, it creates a patient disclosure obligation that is widely unmet, and it stands in sharp contrast to the rigorous regulatory requirements imposed on investigational biologics such as

WJ-MSC-derived exosomes, which must demonstrate safety and efficacy through formal IND and BLA pathways before clinical deployment.

3. DISCUSSION

3.1 WJ-MSC Exosomes as Adjuncts to the Discseel® Procedure

The Discseel® Procedure addresses the structural component of discogenic pain—mechanically sealing the annular tear and providing a provisional fibrin scaffold for tissue regeneration. What the procedure does not explicitly address is the persistent inflammatory microenvironment within the disc and the surrounding neural tissues that has typically been established for years prior to treatment. In the published cohort, subjects carried chronic pain for an average of 11–12 years, during which time the inflammatory milieu within the disc has generated profound sensitization of dorsal root ganglion neurons and an established cytokine-driven catabolic state within the NP [5].

WJ-MSC-derived exosomes offer a mechanistically complementary intervention. Administered either locally—intra-discally or peri-discally—in conjunction with the fibrin sealant, or systemically in the peri-procedural window, WJ-MSC-EVs could provide four distinct therapeutic contributions:

First, WJ-MSC-EVs would suppress the residual inflammatory cascade that the fibrin scaffold alone does not address. By reducing TNF-α and IL-1β to levels that allow NP cells to re-enter anabolic states, the exosome intervention would create the biological environment in which fibrin-supported tissue regeneration is most likely to succeed.

Second, WJ-MSC-EVs would accelerate NP cell proliferation and extracellular matrix deposition within the fibrin scaffold—precisely the behavior documented in WJ-MSC-EV-treated NP cells in 3D in vitro models, where ECM synthesis was enhanced and catabolic gene expression reduced [6,17]. The fibrin scaffold provides the structural template; the exosomes provide the biological signals that direct NP cells to populate and consolidate that template.

Third, WJ-MSC-EVs would promote M2 macrophage polarization within the disc environment, converting the inflammatory milieu toward active resolution rather than continued degeneration. The transition from M1 to M2 macrophage dominance is associated with secretion of

growth factors and extracellular matrix-remodeling enzymes that support tissue repair rather than destruction.

Fourth, WJ-MSC-EVs would provide neuroprotective signals to sensitized dorsal root ganglion neurons and adjacent spinal structures through exosomal miRNA cargo. This neuroprotective dimension is critical because central sensitization—the neurological amplification of pain signals that develops over years of chronic nociceptive input—cannot be reversed by structural disc repair alone. The biological modulation of the neural environment by WJ-MSC-EVs may therefore address a dimension of chronic discogenic pain that the Discseel® Procedure, while structurally transformative, does not directly target.

This combinatorial approach—structural repair by fibrin plus biological immune resolution by WJ-MSC-EVs—mirrors the therapeutic logic of multimodal intervention in oncology and wound healing, where single-mechanism therapies are consistently outperformed by agents with complementary mechanisms acting on the same pathology through non-redundant pathways. Future clinical studies should evaluate this combination as a defined treatment protocol, with pre-specified endpoints for disc height restoration, NP signal intensity on MRI, ODI, VAS scores, and serum and discal cytokine profiles.

3.2 WJ-MSC Exosomes as Adjuncts to Traditional Spinal Surgery

Following discectomy, laminectomy, or spinal fusion, surgeons and pain practitioners have routinely employed epidural corticosteroids to suppress post-operative inflammation, reduce epidural fibrosis formation, and manage radicular pain from residual or recurrent neural irritation. As documented in Section 2.5, this practice is conducted without FDA approval and with a documented adverse event profile that includes catastrophic, irreversible neurological injury.

WJ-MSC-derived exosomes represent a biologically rational, cell-free alternative for the post-operative spinal context. Patent literature describes MSC-derived exosomes as possessing "pronounced analgesic and anti-inflammatory activity that reduce the need for opioid analgesics and downregulate inflammation"—effects that are precisely what clinicians seek from post-operative epidural corticosteroid injections, but without the associated risks.

Specifically, WJ-MSC-EVs could deliver the following post-operative benefits: reduction of the cytokine burden at the surgical site through exosomal miRNA cargo targeting NF-κB and

TLR signaling pathways; attenuation of epidural fibrosis by modulating the macrophage-driven fibrotic response through M2 polarization—the same pathway implicated in post-surgical epidural scarring; neuroprotection of surgically manipulated neural elements via miR-499-5P and miR-16-5p-mediated mechanisms demonstrated in spinal cord injury models [19,20]; and promotion of tissue repair at the surgical site rather than mere suppression of the immune response, as corticosteroids achieve.

The absence of significant immunosuppressive systemic effects—a major concern with epidural corticosteroids in post-operative patients, particularly regarding wound healing impairment, infection susceptibility, and hyperglycemia in diabetic patients—renders WJ-MSC-EVs potentially safer for the post-surgical environment. The anabolic tissue-repair properties of WJ-MSC-EVs actively support the healing processes that corticosteroids inhibit.

3.3 WJ-MSC Exosomes as Alternatives to Epidural Corticosteroids for Chronic Spinal Pain

The case for WJ-MSC-derived exosomes as alternatives to epidural corticosteroids in the management of chronic discogenic and radicular pain rests on mechanistic, safety, regulatory, and durability considerations that collectively favor the exosome approach.

From a mechanistic standpoint, corticosteroids reduce inflammation by broad suppression of cytokine transcription through glucocorticoid receptor-mediated inhibition of NF-κB and AP-1, and by inhibition of phospholipase A2 activity. This mechanism is non-selective, suppresses both pro-inflammatory and reparative immune functions, and does not address the structural source of chemical irritation. WJ-MSC-EVs deliver targeted miRNA cargo that modulates specific inflammatory pathways while simultaneously promoting anabolic repair of disc tissue, addressing both the symptom (inflammation and pain) and the etiology (disc structural failure and catabolic microenvironment) through a single biologic intervention.

From a safety standpoint, the adverse event profile of epidural corticosteroids includes stroke, paralysis, death, adrenal suppression, hyperglycemia, Cushingoid effects with repeated dosing, and arachnoiditis [3,23,24]. WJ-MSC-derived exosomes, as acellular biologics, do not carry risks of immune rejection, ectopic tissue formation, or replication. They have not been associated with the severe systemic or neurological adverse events documented with epidural steroids.

From a regulatory integrity standpoint, epidural corticosteroids are administered via a route for which they have never received FDA approval, using a Drug Safety Communication-labeled warning that this use carries risks of serious neurological injury. Clinicians administering these injections operate in a regulatory gray zone that is rarely disclosed to patients as such. WJ-MSC-derived exosomes, while currently classified as investigational biologics requiring IND or BLA filings under CBER oversight, at minimum represent a transparent regulatory posture: their investigational status is known and disclosed, whereas the off-label and FDA-unindicated nature of epidural steroid delivery is routinely not.

From a durability standpoint, the relief provided by epidural corticosteroid injections is typically short-lived, with effects often lasting weeks to months before repeat injection is required. Regenerative biologics that promote disc matrix repair and resolve chronic inflammation at the pathological source could plausibly produce more durable effects, particularly when combined with the structural disc repair achieved by the Discseel® Procedure.

3.4 Regulatory Considerations and the Path Forward

WJ-MSC-derived exosomes are regulated under FDA's Center for Biologics Evaluation and Research (CBER) oversight as biological products. Under 21 CFR Part 1271 and PHS Act Section 351, products derived from human cells that do not meet the criteria for the 361 HCT/P exemption—including requirements for minimal manipulation and homologous use—require Investigational New Drug (IND) applications for clinical investigation and Biologics License Applications (BLA) for commercial marketing. The isolation, cargo engineering, and systemic anti-inflammatory applications of WJ-MSC-EVs place them firmly in the 351(a) pathway [27].

The contrast between the regulatory rigor demanded of WJ-MSC-EVs and the de facto widespread clinical deployment of epidural corticosteroids without FDA approval is stark and warrants acknowledgment by regulatory bodies, professional societies, and practicing clinicians. This asymmetry does not reflect differential evidence of safety—the published adverse event profile of epidural corticosteroids is substantially more alarming than anything reported for WJ-MSC-EVs. Rather, it reflects the historical accident that epidural steroid injections became entrenched in practice before modern regulatory frameworks were applied to them, and that FDA's jurisdiction over medical procedures has historically been limited.

The path forward for WJ-MSC-derived exosomes in spinal applications requires a coordinated effort across several fronts. Prospective, randomized controlled trials should examine WJ-MSC-EV administration as an adjunct to both the Discseel® Procedure and traditional spinal surgery, with pre-specified endpoints including ODI, VAS, cytokine profiles, and MRI disc morphology parameters. Standardization of exosome isolation, characterization per MISEV2018 guidelines (particle size distribution, surface markers CD9/CD63/CD81, miRNA cargo profiling), and dosing protocols is necessary to enable inter-study comparability [27]. Pre-IND meetings with CBER should be pursued to establish regulatory expectations for clinical programs targeting disc regeneration. Head-to-head comparative studies examining WJ-MSC-EVs against epidural corticosteroids for radicular pain management, with rigorous adverse event monitoring, would provide the most direct evidence for clinical guideline development.

4. CONCLUSION

Wharton's Jelly mesenchymal stem cell-derived exosomes represent a scientifically grounded, mechanistically coherent, and potentially superior alternative to epidural corticosteroid injections for spinal pain management. Their established capacity to suppress pro-inflammatory cytokines, promote nucleus pulposus cell anabolism and extracellular matrix synthesis, polarize macrophages toward the anti-inflammatory M2 phenotype, and protect neural elements from inflammatory injury makes them well-suited as adjuncts to the Discseel® Procedure—amplifying structural disc repair with biological immune resolution—and as post-operative adjuncts following traditional spinal surgery.

The continued widespread clinical use of epidural corticosteroids via Tuohy needle delivery into the epidural space—without FDA approval for this indication, without consistent informed consent regarding their unapproved status, and with an explicit FDA Drug Safety Communication warning of stroke, paralysis, and death—represents a significant regulatory and patient safety paradox. WJ-MSC-derived exosomes offer a path toward resolving this paradox through a biologically superior, cell-free therapeutic that operates through multiple complementary mechanisms rather than broad, non-selective immune suppression.

The convergence of the Discseel® Procedure's structural repair mechanism with the biological resolution capacity of WJ-MSC-derived exosomes presents a novel combinatorial

treatment paradigm for chronic discogenic disease that merits rigorous evaluation in prospective randomized controlled trials. As the regulatory and clinical infrastructure for exosome biologics matures, WJ-MSC-EVs stand as among the most promising candidates for formal clinical development in spinal regenerative medicine.

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