# Intranasal Dental Pulp Stem Cell Exosomes for Chronic Spinal Cord Injury

**Introduction**

Spinal cord injury (SCI) is a life-altering neurological condition with over 180,000 new cases reported annually worldwide, and an acute-phase mortality rate of up to 16% [1]. Chronic SCI is characterized by persistent neuroinflammation, glial scarring, and loss of axonal connectivity, with few available therapies capable of reversing damage once the acute phase has passed. While current strategies such as surgical decompression and high-dose corticosteroids can mitigate immediate deterioration, they provide limited functional restoration in chronic stages.

Emerging regenerative strategies focus on modulating the post-injury microenvironment. Mesenchymal stem cells (MSCs) have demonstrated immunomodulatory and trophic support effects, but direct cell transplantation faces obstacles such as poor survival, tumorigenic risk, and ethical concerns [2]. A promising alternative lies in exosomes—nano-sized extracellular vesicles released by stem cells that carry bioactive cargo, including growth factors, cytokines, and regulatory miRNAs.

Dental pulp stem cells (DPSCs), derived from neural crest origins, produce exosomes (DPSC-Exos) with robust neuroregenerative potential. These exosomes are rich in neurotrophic proteins like BDNF, NGF, and GDNF, as well as anti-inflammatory miRNAs [1]. In rodent models of SCI, intranasally delivered DPSC-Exos reduced lesion volume, improved motor scores, and downregulated key inflammatory cytokines including TNF-α, IL-1β, and IL-6. Importantly, the exosomes were shown to downregulate glial markers GFAP and IBA1 and increase expression of neuronal integrity markers such as MAP2 and Tuj1, suggesting they help reestablish a pro-regenerative environment at the injury site [1].

Intranasal delivery offers a non-invasive route to bypass the blood–spinal cord barrier and target central nervous system (CNS) tissues directly. This route has proven successful in previous preclinical trials using bone marrow MSC-derived exosomes, such as ExoPTEN, which demonstrated functional and histological improvements in rat SCI models following intranasal administration [2]. Based on these findings, we propose a pilot clinical study to assess the safety and preliminary efficacy of intranasal DPSC-Exos for chronic SCI in human patients.

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## Specific Aim

Assess intranasal DPSC-exosomes for neuroinflammatory suppression and regeneration.

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## Rationale

DPSC-Exos combine the regenerative signals of stem cells with the safety of a cell-free therapeutic. Their enrichment in neurotrophic and immunomodulatory cargo, delivered intranasally to bypass systemic barriers, presents a novel and minimally invasive strategy for chronic SCI, a stage largely refractory to current treatments [1][2].

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## Methods

This single-center, double-blind pilot study will enroll 10–20 adults with chronic SCI (≥12 months post-injury), ASIA grade A–C. Participants will be randomized 1:1 into treatment or placebo groups, with each patient's baseline data serving as an internal control.

DPSC-derived exosomes will be harvested from cultured human DPSCs using differential ultracentrifugation and characterized via nanoparticle tracking analysis (NTA), transmission electron microscopy (TEM), and Western blotting for CD63, CD9, and TSG101 to confirm exosomal identity. Treatment participants will receive approximately $10^9$–$10^{10}$ particles per dose intranasally once weekly for 4 weeks. The placebo group will receive sterile saline in identical administration. All doses will be delivered via a nasal spray device under medical supervision.

Primary outcomes include changes in ASIA motor and sensory scores at 1, 3, and 6 months post-treatment. Secondary endpoints will examine serum and/or CSF levels of TNF-α, IL-1β, IL-6, GFAP, and MAP2. Exploratory endpoints include spinal MRI for lesion structure, quality-of-life surveys, and adverse event monitoring. Statistical analysis will involve paired t-tests or Wilcoxon signed-rank tests for within-group changes and unpaired t-tests or Mann–Whitney U-tests for between-group comparisons, with $p < 0.05$ considered significant.

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## Pitfalls and Alternative Approaches

Exosome delivery via intranasal administration may exhibit variability in CNS uptake in human subjects. Should efficacy prove insufficient, delivery may be optimized using increased dosing frequency, intrathecal injection, or exosome-embedded biomaterial scaffolds to enhance retention and bioavailability [1][2].

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## References

[1] Wang, Y., Liu, C., Wang, X., Zhang, M., & Yang, Y. (2025). *Dental pulp stem cell-derived exosomes promote axonal repair in spinal cord injury by suppressing neuroinflammation and apoptosis*. Journal of Neurobiology, 520, 102215. https://www.sciencedirect.com/science/article/abs/pii/S0040816625004574

[2] Zhou, Z., et al. (2025). *ExoPTEN: Allogeneic Exosome Therapy for Spinal Cord Injury with Strong Therapeutic Potential and Clinical Promise*. Cytotherapy, 27(1), 75–88. https://www.sciencedirect.com/science/article/pii/S146532492500132X