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Ultrasound-Guided Hydrodissection Combined with Small Pluripotent Stem Cells (SPSCs) and SPSC-Derived Exosomes in Chronic Nerve Pain: A Clinical Case Series

Torbjörn Ogéus DC, PgD, MSc, ScA* and Emil Sandström, PT, MSc

Abstract

Background: Chronic peripheral nerve pain is a common and often disabling condition associated with nerve entrapment, post-inflammatory neuropathic irritation, mechanical tethering, and radicular or peripheral nerve-related pain syndromes. Conventional treatments, including pharmacological therapy, corticosteroid injections, and physical rehabilitation, may provide incomplete or temporary relief. Ultrasound-guided hydrodissection has emerged as a minimally invasive technique intended to mechanically separate irritated or entrapped nerves from surrounding fascia, adhesions, or fibrotic tissue. In parallel, regenerative approaches using small pluripotent stem cells (SPSCs) and SPSC-derived exosomes may offer biological effects through paracrine signaling, immunomodulation, and support of tissue repair.

Case presentations: Six patients with chronic peripheral nerve pain of varying etiologies, including suspected nerve entrapment, post-inflammatory neuropathic pain, and disc herniation-associated nerve irritation, were treated with ultrasound-guided hydrodissection combined with local administration of autologous SPSCs and SPSC-derived exosomes. All patients had persistent symptoms despite prior conservative management. The procedure involved ultrasound identification of the symptomatic nerve or perineural target area, hydrodissection to separate the nerve from adjacent tissue planes, and targeted local administration of SPSCs and exosomes. Across the case series, patients reported clinically meaningful reductions in pain and improvements in function during follow-up. No serious adverse events were observed.

Conclusion: This preliminary case series suggests that ultrasound-guided hydrodissection combined with SPSCs and SPSC-derived exosomes may represent a promising multimodal approach for selected patients with chronic peripheral nerve pain. The rationale is based on combining mechanical nerve release with potential regenerative, anti-inflammatory, and paracrine effects. These findings should be interpreted cautiously because of the uncontrolled design, small sample size, heterogeneous indications, and absence of blinding. Controlled prospective studies are warranted to evaluate efficacy, safety, mechanisms of action, and long-term outcomes.

Keywords: Small pluripotent stem cells; SPSC; Ogéus Sparq cells platform; ultrasound-guided hydrodissection; peripheral nerve pain; nerve entrapment; nerve root hydrodissection; SPSC-derived exosomes; extracellular vesicles; peripheral blood; regenerative medicine; brachial plexus; ulnar nerve; cell viability; numerical rating scale

Affiliation:
Stockholms led- & smärtklinik, 114 24 Stockholm, Sweden

***Corresponding Author:**
Torbjörn Ogéus DC, PgD, MSc, ScA, Stockholms led- & smärtklinik, 114 24 Stockholm, Sweden.

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Abbreviations: SPSC: Small Pluripotent Stem Cell; Sparq: Ogéus Sparq cells platform; EV: Extracellular vesicle; HD: Hydrodissection; MRI: Magnetic resonance imaging; NRS: Numerical rating scale; NSAID: Non-steroidal anti-inflammatory drug; OA: Osteoarthritis; D5W: Dextrose 5% in Water; MISEV: Minimal information for studies of extracellular vesicles; TEM: Transmission electron microscopy; CD9: Cluster of differentiation 9; CD63: Cluster of differentiation 63; CD81: Cluster of differentiation 81

Introduction

Peripheral nerve pain represents a clinically important and frequently disabling condition that may arise from nerve entrapment, inflammatory irritation, trauma, post-surgical scarring, radiculopathy, or chronic mechanical compression [1,2]. Entrapment neuropathies and mechanically mediated nerve pain may occur when a peripheral nerve becomes compressed or tethered by adjacent fascia, scar tissue, fibrotic adhesions, or other anatomical structures [1-13,14-16]. This may impair normal nerve gliding, alter intraneural or perineural vascular supply, increase mechanosensitivity, and contribute to persistent neuropathic symptoms such as burning pain, paresthesia, dysesthesia, allodynia, weakness, or functional limitation [1,15,16].

Conventional treatment options include analgesic and neuropathic pain medication, physical rehabilitation, neurodynamic exercises, corticosteroid injections, local anesthetic injections, and, in selected cases, surgical decompression. Although these approaches may benefit many patients, a subset continues to experience persistent symptoms or only temporary improvement. Pharmacological therapies may be limited by adverse effects or incomplete symptom control, whereas corticosteroid injections are primarily anti-inflammatory and may not address mechanical tethering or impaired nerve mobility. Surgical decompression may be appropriate for severe or refractory entrapment neuropathies, but it is invasive and not always indicated in patients with diffuse, multifocal, inflammatory, or early-stage nerve irritation.

Ultrasound-guided nerve hydrodissection (HD) has emerged as a promising minimally invasive treatment option for peripheral nerve pain and nerve entrapment syndromes [1,2,14,15]. The procedure involves high-resolution ultrasound-guided injection of fluid around a nerve to separate it from surrounding fascia, scar tissue, fibrotic adhesions, collagen bands, ligaments, or tight fascial tunnels [1,15]. HD may thereby mechanically release the nerve, improve nerve gliding, reduce perineural mechanical irritation, and decompress the vasa nervorum and nervi nervorum surrounding the nerve trunk [1,15,16-22].

The clinical rationale for HD is supported by both anatomical and biomechanical observations. Histological findings in carpal tunnel syndrome have demonstrated fibrosis of the subsynovial connective tissue, which may reduce median nerve mobility and gliding capacity [17]. In a cadaveric model, ultrasound-guided HD with 5% dextrose in water (D5W) immediately reduced gliding resistance of the median nerve within the carpal tunnel [18].

The vasa nervorum and nervi nervorum may be relevant to the pain-relieving effects of HD. The vasa nervorum contribute to neural blood supply, nutrient delivery, and clearance of metabolites, whereas the nervi nervorum are small sensory nerve fibers that innervate the nerve sheath and may contribute to neurogenic inflammation and neuropathic pain [19-22]. Mechanical compression, tethering, or fibrosis around a peripheral nerve may therefore impair both neural vascular supply and nociceptive regulation of the perineural environment [1,21,22]. These findings support the concept that mechanical separation of the nerve from restrictive perineural tissue can directly influence nerve dynamics and local mechanosensitivity.

Different injectates used for HD may provide additional pharmacological or biological effects beyond mechanical separation. Corticosteroids may reduce edema, inflammation, and granulation tissue formation [23], while platelet-rich plasma may provide growth factors with potential tissue-repair effects [24]. D5W is commonly used in nerve HD research and has shown favorable outcomes in randomized trials for carpal tunnel syndrome [25-27]. Although the mechanisms of D5W-mediated pain relief remain incompletely understood, one proposed mechanism involves modulation or downregulation of transient receptor potential vanilloid 1 (TRPV1)-related nociceptive signaling [28,29]. Commonly studied injectates include D5W, local anesthetics, corticosteroids, platelet-rich plasma, hyaluronic acid, normal saline, and hyaluronidase [1,2].

Clinical studies have shown that HD can be feasible and safe in selected peripheral nerve and nerve root applications. Ultrasound-guided lumbar nerve root HD has been reported as feasible, reproducible, and safe, with favorable injectate spread and clinical outcomes [30]. Ultrasound-guided HD or selective injection of cervical nerve roots has also been described as feasible in patients with cervical radicular pain, including patients with stenosis [31]. However, available evidence remains heterogeneous, and further controlled studies are required to determine optimal indications, injectates, volumes, and long-term outcomes [1-4,14].

Regenerative medicine approaches have also attracted interest in the treatment of musculoskeletal and nerve-related disorders. Small pluripotent stem cells (SPSCs) are described here as a population of very small, non-manipulated stem cells derived from peripheral blood using the author's established isolation protocol [5]. Pluripotent stem cells

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possess the defining property of pluripotency, characterized by the capacity to differentiate into cell lineages spanning all three embryonic germ layers: ectoderm, mesoderm, and endoderm [32]. Consequently, pluripotent or pluripotency-associated cell populations may represent a versatile cellular substrate in regenerative medicine, with theoretical potential for tissue repair across multiple somatic tissues [5,32].

SPSCs constitute a novel peripheral blood-derived progenitor cell population characterized in prior work by small size, high viability, and expression of pluripotency-associated markers [5-7]. This population overlaps conceptually with previously described very small embryonic-like stem cells and small blood stem cells, which have been reported to express markers associated with early developmental potency and to mobilize in response to stress or tissue injury [5-8]. However, the biological identity, potency, and therapeutic mechanisms of SPSCs remain under investigation, and claims regarding pluripotency or regenerative function should be interpreted cautiously and supported by further phenotypic and functional validation.

In this case series, SPSCs were used in combination with SPSC-derived exosomes. Exosomes are a specialized class of nanoscale extracellular vesicles generated through the endocytic pathway and released by most cell types [13,33,34]. Exosomes and extracellular vesicles are increasingly recognized as mediators of intercellular communication and tissue repair through the transfer of proteins, lipids, cytokines, microRNAs, and other bioactive molecules [9-13,33,34]. In nerve-related disorders, extracellular vesicles may influence inflammation, angiogenesis, axonal growth, Schwann cell activity, remyelination, and neuropathic pain signaling [9-12,33].

Amniotic fluid derived exosomes have demonstrated therapeutic effects in preclinical models of osteoarthritis, including improved cartilage-related outcomes and increased pain tolerance [35]. Exosome-based therapy has also been explored clinically in osteoarthritis and musculoskeletal disorders [36]. More broadly, exosomes and their molecular cargo have emerged as promising therapeutic candidates for the modulation of inflammatory and neuropathic pain phenotypes [9,33]. These findings provide a biological rationale for investigating extracellular vesicle-enriched preparations in chronic nerve pain, although direct clinical evidence remains limited.

The rationale for combining HD with SPSCs and SPSC-derived exosomes is therefore twofold. First, HD may mechanically release the affected nerve from restrictive tissue planes, reduce compression or tethering, improve nerve gliding, and relieve local mechanical irritation [1,15,18]. Second, SPSCs and SPSC-derived exosomes may provide local biological signaling that could modulate inflammation, support tissue repair, and potentially improve the perineural microenvironment [5-13,33]. This multimodal approach may be particularly relevant in chronic nerve pain, where both mechanical and biological drivers may coexist.

Although HD has shown promising results in peripheral nerve entrapment and in selected cervical and lumbar nerve root applications, to our knowledge no prior clinical studies have evaluated ultrasound-guided HD using SPSCs and SPSC-derived exosomes as active biological agents. The present study describes six cases in which HD combined with an autologous SPSC/SPSC-derived exosome mixture was used to treat chronic peripheral, cervical radicular, and lumbar radicular nerve pain.

Methods

Study design

This is a retrospective descriptive case series of six patients treated for chronic peripheral nerve pain using ultrasound-guided HD combined with local administration of SPSCs and SPSC-derived exosomes. The report was prepared in accordance with the principles of transparent case-series reporting. Because this is an uncontrolled retrospective case series, no causal conclusions regarding treatment efficacy can be drawn.

Patient selection

Patients were eligible for inclusion if they had chronic peripheral nerve pain or nerve-related pain symptoms lasting more than 6 months, had persistent symptoms despite prior conservative management, and underwent ultrasound-guided HD combined with SPSCs and SPSC-derived exosomes. Patients were excluded if they had active local infection, systemic infection, uncontrolled coagulopathy, severe uncontrolled systemic disease, or contraindications to injection therapy.

The six included patients represented a heterogeneous clinical population with suspected nerve entrapment, post-inflammatory neuropathic pain, and disc herniation-associated nerve irritation. Both male and female patients were included.

Ethical considerations

All procedures were performed as part of clinical care after discussion of potential risks, benefits, alternatives, and the experimental nature of the combined regenerative approach. Written informed consent for treatment and use of anonymized clinical data for publication was obtained from all patients. The report contains anonymized retrospective clinical observations from routine clinical care.

SPSC preparation

Small Pluripotent Stem Cells (SPSCs) were extracted through the Ogéus Sparq cells® platform: peripheral blood

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was collected from each patient using 60 mL of whole blood. Sodium citrate was used as anticoagulant at 1 mL per tube. The blood was first centrifuged at 600 x g to separate the plasma fraction. The supernatant plasma was then transferred to new tubes and centrifuged at 1200 x g for 10 minutes. The resulting pellet and supernatant plasma were placed in cold storage for 4.5 hours. After cold storage, SPSCs were observed as a pellet at the bottom of the tube, while the supernatant plasma was considered exosome-rich. The final treatment mixture consisted of resuspended SPSC pellet combined with the exosome-rich plasma fraction, yielding the SPSC/EV mixture used for injection.

The SPSC isolation approach was based on the author's prior work describing isolation and characterization of SPSCs from peripheral blood, self-organization of SPSCs into embryoid body-like structures, and mobilization of circulating SPSCs following vacuum-stabilized palmar cooling [5-7]. The preparation was used fresh and was not culture expanded, enzymatically digested, genetically modified, or otherwise substantially manipulated.

The total SPSC cell dose and viability were recorded for each patient. Case 1 received 178 million cells with 98% viability; Case 2 received 156 million cells with 98% viability; Case 3 received 201 million cells with 97% viability; Case 4 received 167 million cells with 99% viability; Case 5 received 245 million cells with 98% viability; and Case 6 received 195 million cells with 97% viability.

SPSC-derived exosome preparation

SPSC-derived exosomes were obtained from the exosome-rich plasma supernatant generated during the SPSC isolation process. After centrifugation and cold storage, the SPSC pellet was combined with the exosome-rich supernatant plasma to create the final SPSC/EV mixture. This mixture was administered locally as part of the HD procedure or into disc-related target regions depending on the clinical indication.

Extracellular vesicle content was assessed using Myriade VideoDrop analysis, which demonstrated a mean total extracellular vesicle particle number of 2.3 trillion particles per preparation, with a mean particle size of 133 nm. Additional third-party extracellular vesicle characterization is being performed in a separate study. For future prospective studies, further extracellular vesicle characterization should follow international EV reporting recommendations and include nanoparticle tracking analysis or equivalent particle analysis, protein concentration, transmission electron microscopy, and expression of EV-associated markers such as CD9, CD63, and CD81 [13]. Sterility and endotoxin testing should also be reported when available.

Ultrasound-guided procedure

All procedures were performed under sterile conditions using high-resolution musculoskeletal (LOGIQ Fortis; GE HealthCare, Chicago, IL, USA). The symptomatic nerve or target perineural region was identified in short-axis and/or long-axis view. Relevant anatomical landmarks, areas of tenderness, nerve swelling, reduced nerve mobility, fascial thickening, or suspected adhesions were documented when present.

After skin disinfection and local anesthesia as appropriate, a needle was advanced under continuous ultrasound visualization using an in-plane technique. HD was performed by slowly injecting fluid around the nerve to separate it from surrounding tissue planes while avoiding intraneural injection. Successful HD was defined sonographically by circumferential or partial separation of the nerve from adjacent fascia or scar tissue, with visible expansion of the perineural plane.

The injectate composition varied according to the treated anatomical target. For spinal nerve root HD, the injectate consisted of 1 mL Xylocaine combined with 1ml of D5W and 2 mL of the SPSC/EV mixture. For cervical nerve root HD, the injectate consisted of 1 mL Xylocaine combined with 1ml of D5W and 1 mL of the SPSC/EV mixture. For disc-related target regions injections, 3 mL of the SPSC/EV mixture was administered. For brachial plexus HD, the injectate consisted of 4 mL of the SPSC/EV mixture combined with 1 mL of D5W and 1 mL Xylocaine. For ulnar nerve HD, 1 mL Xylocaine, 1 mL D5W and 3 mL of the SPSC/EV mixture were administered at each injection point. After the procedure, patients were observed for immediate adverse events and received standardized post-procedure instructions. Post-treatment rehabilitation consisted of simple pain-free nerve-flossing movements and basic pain-free body-weight exercises.

Outcome measures

Clinical outcomes were assessed using patient-reported pain and functional status. Pain was measured using the 0-10 numerical rating scale (NRS), where 0 represents no pain and 10 represents worst imaginable pain. Functional improvement was assessed descriptively based on patient-reported changes in activity tolerance, neurological symptoms, strength, sensory function, walking ability, sleep disturbance, and bladder control when relevant. Follow-up was performed at 1, 3, and 6 months. In all six cases, the reported NRS improvement occurred within the first month after treatment and remained stable at 3 and 6 months.

The primary descriptive outcome was change in pain from baseline to final available follow-up. Secondary outcomes included patient-reported functional improvement, reduction in analgesic use when available, return to activity, and adverse events.

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Case Presentations

Case 1

A 40-year-old woman presented with a 15-year history of chronic neck pain with radiating nerve pain into the right arm. Prior conservative treatments included physiotherapy, muscle-relaxing medication, and amitriptyline, all with only moderate effects. Magnetic resonance imaging (MRI) demonstrated nerve entrapment associated with a C5/C6 disc herniation. The patient underwent ultrasound-guided treatment with SPSCs and SPSC-derived exosomes at the C5/C6 disc-related target region, combined with HD of the right C6 nerve root. Baseline pain was NRS 5. After treatment, pain decreased to NRS 0. Three days after treatment, the patient reported no restrictions or residual symptoms. No recurrence of symptoms was reported at 1, 3, or 6 months.

Case 2

A 62-year-old woman presented with a 10-year history of sensory and motor loss affecting bladder control. She had used incontinence pads for many years. Prior conservative treatments included physiotherapy and anti-inflammatory medication without meaningful effect. MRI demonstrated a large L5/S1 disc herniation and facet joint osteoarthritis. The patient received SPSCs and SPSC-derived exosomes at the L4-S1 disc-related target region and underwent bilateral HD of the L5 nerve roots. Baseline pain was NRS 3 and decreased to NRS 1 within 1 month. At 1 month after treatment, the patient also reported return of motor and sensory control of bladder function. No recurrence of symptoms was reported at 1, 3, or 6 months.

Case 3

A 50-year-old man presented with a 3-year history of neck and shoulder pain, loss of strength, and sensory symptoms affecting the right arm and fingers. Prior conservative treatments included physiotherapy, muscle-relaxing medication, and anti-inflammatory medication with low effect. MRI did not show a clear correlation between the patient's symptoms and cervical spine findings. The patient received ultrasound-guided HD of the right brachial plexus with SPSCs and SPSC-derived exosomes. Baseline pain was NRS 6 and decreased to NRS 1 after treatment. Improvement in symptoms and function was reported 4 weeks after treatment. No recurrence of symptoms was reported at 1, 3, or 6 months, and strength had normalized by 3 months.

Case 4

A 33-year-old man presented with a 10-year history of pain and functional loss due to left-sided ulnar nerve entrapment. Prior treatments included physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs), nerve pain medication, and five surgical procedures, including ulnar nerve transposition and later surgical removal of scar tissue. Despite these procedures, he remained substantially symptomatic at presentation, with severe nerve pain, frequent nocturnal awakenings, and inability to work in static positions because of pain. The patient underwent ultrasound-guided HD of the left ulnar nerve at two sites, below and above the elbow joint, using SPSCs and SPSC-derived exosomes. Baseline pain was NRS 8 and decreased to NRS 2 after treatment. Improvement was reported within 1 week. No recurrence of symptoms was reported at 1, 3, or 6 months.

Case 5

A 63-year-old man presented with a 6-month history of nerve pain involving the neck, shoulder, left arm, and fingers. Prior conservative treatments included physiotherapy and NSAIDs. MRI demonstrated a left-sided C5/C6 disc herniation. The patient received SPSCs and SPSC-derived exosomes at the C5/C6 disc-related target region combined with HD of the left C6 nerve root. Baseline pain was NRS 4 and decreased to NRS 0 after treatment. Two weeks after the procedure, the patient reported no restrictions or residual symptoms. No recurrence of symptoms was reported at 1, 3, or 6 months.

Case 6

A 52-year-old woman presented with a 10-year history of complex nerve pain associated with multiple disc herniations and suspected nerve entrapments in both the cervical spine and lower back. Prior conservative treatments included physiotherapy, NSAIDs, and muscle-relaxing medication. Symptoms included loss of sensation in the left leg, loss of sensation in both arms, and nerve pain in the neck, arms, and left leg. The patient underwent ultrasound-guided HD with SPSCs and SPSC-derived exosomes at the bilateral brachial plexus and left L4 nerve root. Baseline pain was NRS 7 and decreased to NRS 1 after treatment. The patient experienced immediate symptom relief within 10 minutes of treatment and reported improved walking ability and muscle function on the same day. No recurrence of symptoms was reported at 1, 3, or 6 months.

Results

Six patients were included in the case series: three women and three men, aged 33-63 years. Symptom duration ranged from 6 months to 15 years. The treated conditions were heterogeneous and included cervical disc herniation-associated nerve root irritation, lumbar disc herniation-associated nerve dysfunction, brachial plexus-related pain, chronic post-surgical ulnar nerve entrapment, and complex multifocal nerve pain involving both cervical and lumbar regions (Figure 1).

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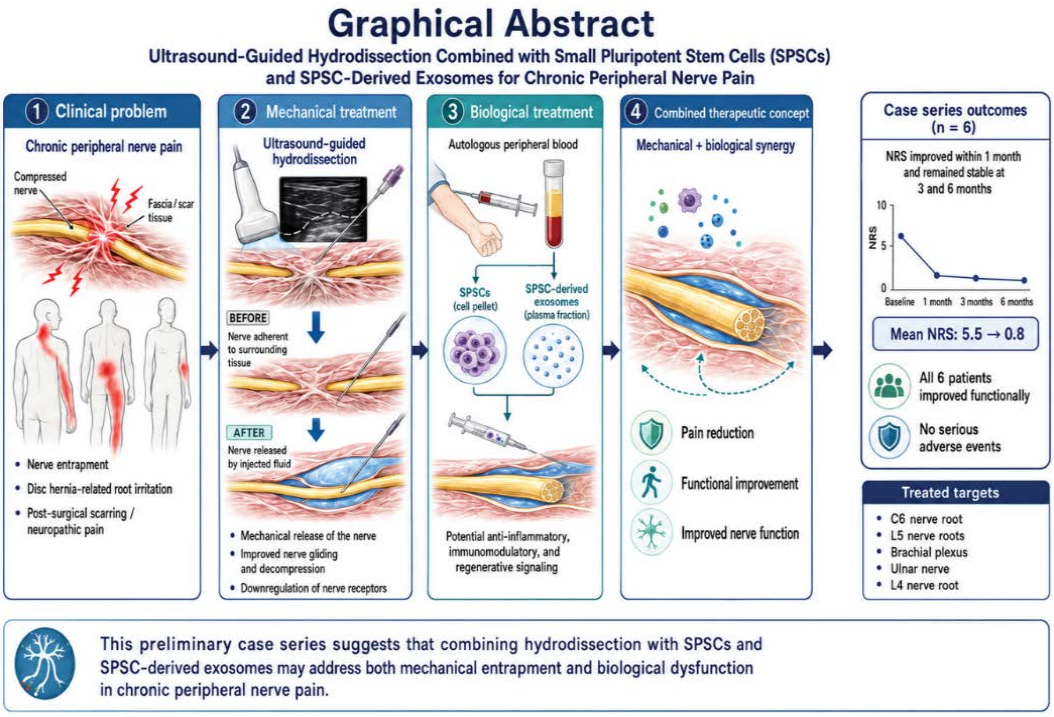

Figure 1: Graphical abstract.

Baseline pain scores ranged from NRS 3 to NRS 8. After treatment, pain scores ranged from NRS 0 to NRS 2. The reduction in NRS occurred within 1 month in all six patients and remained stable at both 3- and 6-month follow-up. Four patients reported complete or near-complete pain relief, and all six patients reported clinically meaningful functional improvement. Reported improvements included absence of restrictions, return of bladder motor and sensory control, improved arm strength and sensation, reduced nocturnal awakenings, improved walking ability, and improved muscle function. No recurrence of symptoms was reported at 1, 3, or 6 months in any patient.

No serious adverse events, infections, neurological deterioration, or treatment-related worsening were observed. Mild local inflammation and soreness at the injection site occurred but resolved within 48 hours (Table 1).

Schematic overview of the combined treatment concept: ultrasound-guided hydrodissection for mechanical nerve release, combined with locally administered SPSCs and SPSC-derived exosomes for potential anti-inflammatory, immunomodulatory, and regenerative signaling. In this six-patient case series, NRS pain scores improved within 1 month and remained stable through 6 months, with functional improvement in all patients and no serious adverse events (Table 2).

Table 1: Patient characteristics and clinical presentation.

Case	Age/sex; duration	Diagnosis / suspected etiology	Target region and prior treatment
1	40/F; 15 years	C5/C6 disc herniation with right C6 nerve root irritation	C5/C6 disc-related target region, right C6 nerve root. Prior: physiotherapy, muscle relaxant, amitriptyline; moderate effect only.
2	62/F; 10 years	Large L5/S1 disc herniation, facet joint osteoarthritis, sensory and motor bladder dysfunction	L4-S1 disc-related target region and bilateral L5 nerve roots. Prior: physiotherapy and anti-inflammatory medication without effect; long-term incontinence pads.
3	50/M; 3 years	Right-sided brachial plexus-related pain; MRI without clear cervical correlation	Right brachial plexus. Prior: physiotherapy, muscle relaxant, and anti-inflammatory medication with low effect.
4	33/M; 10 years	Chronic left ulnar nerve entrapment after multiple surgeries	Left ulnar nerve above and below elbow. Prior: five surgeries, physiotherapy, NSAIDs, and nerve pain medication without sufficient effect.
5	63/M; 6 months	Left-sided C5/C6 disc herniation with C6 nerve root irritation	C5/C6 disc-related target region and left C6 nerve root. Prior: physiotherapy and NSAIDs.
6	52/F; 10 years	Complex multifocal nerve pain with multiple disc herniations and suspected cervical/lumbar entrapments	Bilateral brachial plexus and left L4 nerve root. Prior: physiotherapy, NSAIDs, and muscle relaxant.

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Table 2: Treatment dose, outcomes, and safety.

Case	Cell dose / viability	Injectate	Outcome and safety
1	178 million cells; 98% viability	C6 nerve root: 1 mL Xylocaine + 2 mL SPSC/EV mixture; disc-region: 3 mL SPSC/EV mixture	NRS 5 to 0 within 1 month; no restrictions or symptoms after 3 days; stable at 3 and 6 months. Mild local soreness/ inflammation only, resolved within 48 h.
2	156 million cells; 98% viability	L5 nerve roots: 1 mL Xylocaine + 2 mL SPSC/ EV mixture per nerve root; disc-region: 3 mL SPSC/EV mixture	NRS 3 to 1 within 1 month; return of motor and sensory bladder control at 1 month; stable at 3 and 6 months. Mild local soreness/inflammation only, resolved within 48 h.
3	201 million cells; 97% viability	Brachial plexus: 4.5 mL SPSC/EV mixture + 1.5 mL Xylocaine	NRS 6 to 1 within 1 month; improved symptoms/function by 4 weeks; normal strength by 3 months; stable at 6 months. Mild local soreness/inflammation only, resolved within 48 h.
4	167 million cells; 99% viability	Each ulnar nerve injection point: 1 mL Xylocaine + 3 mL SPSC/EV mixture	NRS 8 to 2 within 1 month; improvement within 1 week with reduced disabling nerve pain; stable at 3 and 6 months. Mild local soreness/inflammation only, resolved within 48 h.
5	245 million cells; 98% viability	C6 nerve root: 1 mL Xylocaine + 2 mL SPSC/EV mixture; disc-region: 3 mL SPSC/EV mixture	NRS 4 to 0 within 1 month; no restrictions or symptoms after 2 weeks; stable at 3 and 6 months. Mild local soreness/ inflammation only, resolved within 48 h.
6	195 million cells; 97% viability	Brachial plexus: 4.5 mL SPSC/EV mixture + 1.5 mL Xylocaine; L4 nerve root: 1 mL Xylocaine + 2 mL SPSC/EV mixture	NRS 7 to 1 within 1 month; immediate relief within 10 min; improved walking and muscle function same day; stable at 3 and 6 months. Mild local soreness/inflammation only, resolved within 48 h.

Note. SPSC/EV mixture refers to the combined SPSC pellet and extracellular vesicle-rich plasma fraction

Discussion

This case series describes six patients with chronic peripheral nerve pain treated with ultrasound-guided hydrodissection combined with SPSCs and SPSC-derived exosomes. The main observations were clinically meaningful reductions in pain, functional improvement, and absence of serious adverse events during the available 6-month follow-up period. Baseline NRS pain scores ranged from 3 to 8 and improved to 0–2 within 1 month, with stable results at both 3 and 6 months. These findings are encouraging, particularly because symptom duration ranged from 6 months to 15 years and all patients had persistent symptoms despite prior conservative treatment. However, because this is a small, uncontrolled, heterogeneous case series, the results should be interpreted as hypothesis-generating rather than confirmatory.

The treatment concept used in this study was based on the assumption that chronic nerve pain may involve both mechanical and biological components. Mechanically, nerve entrapment, post-surgical scarring, disc herniation-related root irritation, and fascial restriction may impair nerve gliding, increase perineural tension, and alter the function of the vasa nervorum and nervi nervorum [1,15,19-22]. Ultrasound-guided HD may address this component by mechanically separating the affected nerve from surrounding fascia, scar tissue, collagen bands, or tight tissue planes [1,15]. This may reduce local compression, improve nerve mobility, restore perineural tissue planes, and decrease mechanosensitive irritation. The rapid symptom relief reported in some cases, including improvement within minutes in Case 6 and within days or weeks in other patients, is consistent with a potential immediate mechanical effect of nerve release.

Previous studies support the plausibility of a mechanical effect from HD. Histological studies in carpal tunnel syndrome have demonstrated fibrosis of subsynovial connective tissue, which may reduce nerve gliding capacity [17]. In a cadaveric model, ultrasound-guided HD reduced gliding resistance of the median nerve within the carpal tunnel [18]. Clinical studies have also reported favorable outcomes after HD in peripheral nerve entrapment syndromes and selected nerve root applications [1-4,25-27,30,31]. The present case series extends this rationale to a broader clinical population, including cervical and lumbar nerve root irritation, brachial plexus-related symptoms, and chronic post-surgical ulnar nerve entrapment.

In addition to mechanical release, the biological component may have contributed to the sustained improvement observed at 3 and 6 months. The SPSC/SPSC-exosome mixture used in this study contained a high viable cell dose, ranging from 156 to 245 million cells per patient, with viability between 97% and 99%. Extracellular vesicle analysis using Myriade VideoDrop demonstrated a mean total extracellular vesicle particle number of 2.3 trillion particles per preparation, with a mean particle size of 133 nm. These characteristics suggest that the injected preparation delivered both a viable cellular component and a substantial extracellular vesicle-rich fraction to the perineural environment.

Extracellular vesicles and exosomes are increasingly recognized as mediators of intercellular communication and tissue repair [9-13,33,34]. They may transfer bioactive proteins, lipids, cytokines, and microRNAs capable of influencing inflammation, angiogenesis, Schwann cell behavior, axonal regeneration, and neuropathic pain signaling

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[9-12,33]. In peripheral nerve injury models, exosome-based approaches have been associated with modulation of neuroinflammation, promotion of Schwann cell activity, support of axonal regeneration, and improved nerve repair [9-12]. Although these mechanisms remain largely preclinical, they provide a plausible biological rationale for the sustained clinical improvements observed in the present series.

The local perineural microenvironment in chronic nerve pain may include inflammatory mediators, fibrosis, altered vascular supply, and nociceptive sensitization. HD may create physical space around the affected nerve, while the SPSC/SPSC-exosome mixture may provide paracrine signaling within this newly opened perineural plane. This combination could theoretically produce synergy: HD may reduce mechanical stress and improve local tissue perfusion, while SPSCs and SPSC-derived exosomes may modulate inflammation, support tissue remodeling, and contribute regenerative signals. The stable improvement through 6 months may therefore reflect more than transient anesthetic or purely mechanical effects, although this cannot be proven from the present design.

The improvement in neurological function in several cases is particularly notable. Case 2 reported return of motor and sensory bladder control after treatment of L4–S1 discr-related target region and bilateral L5 nerve root HD. Case 3 reported normalization of strength by 3 months after right brachial plexus HD. Case 6 reported immediate improvement in walking ability and muscle function after treatment of the bilateral brachial plexus and left L4 nerve root. These observations may reflect reduced nerve irritation, improved nerve gliding, improved perineural vascular or metabolic function, or modulation of local inflammatory signaling. However, given the uncontrolled nature of the case series, these findings should be interpreted cautiously and require confirmation in prospective studies with objective neurological testing.

A further biological consideration is nociceptor sensitization. D5W HD has been hypothesized to reduce pain partly through modulation of TRPV1-related nociceptive signaling [28,29]. Although D5W was not the main active injectate in the present study, the concept that perineural injectates may influence receptor-mediated pain signaling is relevant. The observed pain reduction may have involved both mechanical downregulation of nerve irritation and biological modulation of inflammatory or nociceptive signaling. Future studies should consider measuring biomarkers of neuroinflammation, nociceptor sensitization, and extracellular vesicle cargo to better clarify these mechanisms.

SPSCs are described in this study as a peripheral blood-derived population of very small, non-manipulated cells isolated using the author's cold-enrichment protocol [5-7]. Prior work has reported expression of pluripotency-associated markers and self-organization into embryoid body-like structures under autologous plasma conditions [5,6]. This concept overlaps with prior descriptions of small blood stem cells and very small embryonic-like stem cells [5,8]. In the present study, the clinical use of SPSCs should be understood primarily as an autologous, minimally manipulated, peripheral blood-derived cellular preparation with potential paracrine activity. Further studies are needed to define the identity, potency, reproducibility, and mechanism of action of the SPSC fraction, particularly in relation to nerve repair and perineural inflammation.

An important biological distinction is that pluripotent or pluripotency-associated cells may have a broader developmental and paracrine profile than conventional mesenchymal stromal/stem cells (MSCs). MSCs and MSC-derived exosomes have been widely studied in peripheral nerve injury and may promote Schwann cell proliferation, axonal regeneration, angiogenesis, immunomodulation, and remyelination [10-12]. However, MSCs are generally considered multipotent mesenchymal-lineage cells, whereas pluripotent cells are defined by the capacity to generate derivatives of all three embryonic germ layers, including neuroectodermal lineages [32]. This distinction is biologically relevant in nerve-related disorders, because nerve repair involves not only mesenchymal tissue remodeling but also Schwann cell activation, axonal regrowth, remyelination, vascular support, and modulation of neuroinflammatory and nociceptive signaling.

Extracellular vesicles derived from pluripotent stem cells may therefore carry cargo that differs from MSC-derived vesicles and may be more closely linked to early developmental, neurotrophic, angiogenic, and cell-fate regulatory signaling [37]. Preclinical studies of induced pluripotent stem cell-derived exosomes have reported effects on peripheral nerve regeneration, including Schwann cell internalization and proliferation, axonal regeneration, remyelination, angiogenesis, reduced neuroinflammation, and improved sensory and motor recovery in sciatic nerve injury models [38,39]. In one peripheral nerve reconstruction model, acellular nerve grafts supplemented with iPSC-derived exosomes promoted motor functional recovery and histological nerve regeneration comparable to autologous nerve transplantation [38]. These findings suggest that pluripotent stem cell-derived extracellular vesicles may have substantial neuroregenerative potential.

This distinction may be relevant to the present case series. The observed improvements in pain, strength, sensory symptoms, walking ability, and bladder control could theoretically be influenced by biological mechanisms that extend beyond the more commonly described anti-inflammatory and trophic effects of MSC-derived exosomes.

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The SPSC/SPSC-derived exosome mixture may have provided a paracrine environment enriched in pluripotency-associated and repair-associated signaling, potentially supporting nerve recovery through modulation of Schwann cell behavior, axonal integrity, perineural inflammation, vascular support, and nociceptive sensitization. Nevertheless, the present study did not directly compare SPSCs or SPSC-derived exosomes with MSCs or MSC-derived exosomes, and no causal conclusion can be made regarding superiority. Future comparative studies should directly evaluate SPSC-derived versus MSC-derived extracellular vesicles using standardized potency assays, cargo profiling, nerve-specific in vitro models, and controlled clinical outcomes.

The safety profile in this case series was favorable. No serious adverse events, infections, neurological deterioration, or treatment-related worsening were observed. Mild local inflammation and soreness at the injection site resolved within 48 hours. This is consistent with the generally favorable safety profile reported for ultrasound-guided HD in the literature [1-4,14]. However, the addition of biological preparations introduces additional considerations, including sterility, endotoxin testing, extracellular vesicle characterization, cell viability, cell dose standardization, and regulatory classification. Future studies should include standardized release criteria and third-party characterization of both the cellular and extracellular vesicle components.

Overall, these findings support the hypothesis that combining ultrasound-guided HD with SPSCs and SPSC-derived exosomes may address both mechanical entrapment and biological dysfunction in chronic peripheral nerve pain. The consistent improvement across six heterogeneous cases suggests that this approach may be clinically relevant in selected patients with chronic nerve pain refractory to conservative treatment. Nevertheless, the relative contribution of HD, Xylocaine, SPSCs, SPSC-derived exosomes, rehabilitation, natural history, and placebo effects cannot be determined in this case series. Controlled prospective studies are needed to evaluate efficacy, durability, safety, mechanism of action, and optimal patient selection.

Limitations

This study has several important limitations. First, the sample size was small and included only six patients. Second, the treated conditions were heterogeneous, limiting generalizability. Third, there was no control group, placebo group, or hydrodissection-only comparator, making it impossible to determine the relative contribution of mechanical HD, SPSCs, exosomes, natural history, rehabilitation, or placebo effects. Fourth, outcomes were based primarily on clinical follow-up and patient-reported improvement. Fifth, the SPSC and exosome preparations require detailed characterization to support reproducibility and mechanistic interpretation. Finally, follow-up duration was limited and may not capture late recurrence or delayed adverse events.

Conclusion

This six-patient case series suggests that ultrasound-guided hydrodissection combined with SPSCs and SPSC-derived exosomes may be a feasible and potentially beneficial approach for selected patients with chronic peripheral nerve pain. The treatment concept is based on combining mechanical perineural release with local regenerative and anti-inflammatory signaling. The absence of serious adverse events and the observed clinical improvements support further investigation, but no efficacy conclusions can be drawn from this uncontrolled preliminary series. Prospective controlled studies are warranted to assess clinical efficacy, durability, safety, optimal patient selection, and mechanisms of action.

Declaration

Ethics approval: According to the Ethics Commission of Stockholm, Sweden, case reports with biological medicinal products do not require ethical approval for publication. This applies to the present study. The study was conducted following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication: Written informed consent was obtained from the patients for the publication of these case reports and any accompanying images. Copies of the written consent forms are available for review by the Editor-in-Chief of this journal.

Acknowledgment: The two authors were the main and only contributors to the manuscript.

Authors' contributions: TO and ES were the patient's primary caregiver regarding the specific injuries. All texts, design, literature review, and drafting of this case report were done by TO and ES, responsible for the submitted manuscript.

Competing Interests: Ogéus Sparq cells® is a trademarked platform developed by the main author (TO). The present study reports biological observations obtained using this platform.

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Availability of data and materials: All data generated or analyzed during this study are included in this published article [and its supplementary information files]. Radiographic and ultrasound images are stored at the clinic and are available for review by the Editor-in-Chief of this journal.

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