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Resurgo Protocol: Comprehensive Conservative Rehabilitation for Compression-Ischemic Radial Neuropathy (Retrospective Case Series, n=11)

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Case Report

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Article type: Case Series (Retrospective, Descriptive Study)
Disclaimer: The research concept has been tested on a limited number of patients and requires further validation. This document does not contain clinical instructions and is not a medical recommendation.
Informed Consent: Written or verbal informed consent for treatment was obtained from all patients at the time of their enrollment in the treatment program.
Ethics Statement: This study is a retrospective analysis of clinical data obtained during standard care. Therefore, the requirement for formal prior ethical approval from an Institutional Review Board (IRB) or Ethics Committee was waived, according to established local guidelines for retrospective reviews. All patient data presented are anonymized and de-identified to ensure privacy and adhere to the ethical principles of the Declaration of Helsinki.
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Attachments: The manuscript includes 3 tables.

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All authors have read and approved the final manuscript.

ABSTRACT

Objective: To present and evaluate the clinical results of the comprehensive conservative protocol "Resurgo" in 11 patients diagnosed with compression-ischemic radial neuropathy, with particular attention to the dynamics of pain, muscle tone, and restoration of active motor function.

Methods: A multicomponent conservative regimen was applied to 11 patients with clinically confirmed compression-ischemic radial neuropathy between January 2021 and December 2024. The protocol combined a strictly regulated 5-day local cycle of alternating gels and compresses, weekly subcutaneous injections of hyaluronidase 64 IU with novocaine 0.5% in the area of suspected fibrous scar, systemic neuroprotective pharmacotherapy including ipidacrine 20 mg three times daily, cerebrovin 5 mL intramuscularly, liposom forte 1 capsule daily, and tolperisone 150 mg three times daily, alongside a cyclical functional rehabilitation program. Monitoring was performed weekly with standardized assessment of pain using the Visual Analog Scale, range of motion measured in degrees, and muscle tone evaluated using the Modified Ashworth Scale. Statistical analysis included descriptive statistics and Wilcoxon signed-rank test for paired comparisons.

Results: The cohort comprised 11 patients with median injury duration of 5 months (range 1-36 months) and median follow-up of 12 weeks (range 4-19 weeks). Baseline Visual Analog Scale scores averaged 6.8 ± 2.6 (mean ± standard deviation), decreasing to 2.1 ± 1.3 at 4-6 weeks, representing a mean reduction of 69.1% ($p < 0.001$). Pain reduction of at least 50% was achieved in 9 out of 11 patients (81.8%) within the first 6 weeks. In the index case with 1.5-year chronicity, Visual Analog Scale decreased from 10/10 to approximately 1/10 by day 25, with minimal active wrist extension emerging between weeks 7-12. Modified Ashworth Scale scores decreased from median 3 (range 2-4) to median 1 (range 0-2) by week 6. Active range of motion improved in 8 out of 11 patients (72.7%), with greater improvement observed in patients treated within 6 months of injury. Adverse events occurred in 3 patients (27.3%), consisting of local dermatitis, with one severe case requiring protocol modification. No systemic adverse events were reported during the treatment period.

Conclusion: The Resurgo protocol demonstrated statistically significant and clinically meaningful effects in alleviating pain, reducing pathological muscle tone, and stimulating motor function recovery in this case series. The intervention showed particular efficacy when initiated within 6 months of injury. Prospective randomized controlled trials with larger sample sizes and extended follow-up periods are warranted to establish definitive efficacy and optimal patient selection criteria.

Keywords: radial nerve, compression-ischemic neuropathy, contracture, conservative therapy, hyaluronidase, dimethyl sulfoxide, ipidacrine, tolperisone, rehabilitation, case series

INTRODUCTION

Background and Rationale

Compression-ischemic radial neuropathy represents one of the most common upper extremity tunnel syndromes, characterized by motor deficits affecting wrist and finger extension, thumb abduction, and sensory loss over the dorsal first web space [1, 4, 10].

The pathogenesis involves ischemic nerve damage, perineural edema, and critically, localized fibrosis and perineural scarring in chronic forms beyond 3 months [12]. This fibro-adhesive matrix mechanically restricts axonal regeneration and compromises intraneural microcirculation, creating a self-perpetuating compression-ischemia cycle [13]. Prolonged compression leads to demyelination (neurapraxia) or axonal degeneration (axonotmesis) [4].

Knowledge Gap

Conservative modalities—activity modification, splinting, and physical therapy—remain first-line management [2, 9]. Guidelines recommend 6-12 weeks of conservative therapy before considering surgery [9]. However, systematic reviews reveal limited evidence supporting standard treatments in chronic cases with perineural fibrosis [6]. Success rates range from 30-60%, with lower efficacy beyond 6 months post-injury [2].

The main limitation is mechanical resistance from perineural scarring [13]. Traditional approaches address symptom management but do not target the fibro-adhesive pathology. The lack of standardized, multimodal protocols integrating local defibrosing interventions with systemic neuroprotection represents a significant gap [3, 19].

Objective

The primary objective is to describe the novel Resurgo protocol and analyze clinical outcomes in 11 patients with compression-ischemic radial neuropathy. Secondary objectives include evaluating safety, identifying predictors of treatment response, and demonstrating potential for symptom regression and functional recovery without surgical neurolysis [6]. This aims to generate preliminary evidence supporting future randomized controlled trials.

METHODS

Study Design and Patient Cohort

This retrospective descriptive case series analyzed clinical data from patients treated with the Resurgo protocol between January 2021 and December 2024 at a specialized neurology practice in Baku, Azerbaijan. The study adhered to the CARE (CAse REport) guidelines for reporting case series in medical literature. The study included 11 consecutive patients meeting predefined eligibility criteria. Inclusion criteria comprised clinical presentation consistent with radial nerve neuropathy, absence of complete anatomical nerve transection confirmed by clinical examination, symptom duration ranging from 1 month to 3 years, age between 18 and 75 years, and provision of informed consent to the described conservative therapy. Exclusion criteria included complete nerve transection requiring immediate surgical repair, presence of open wounds or active infection at the treatment site, known hypersensitivity to any protocol components, severe systemic diseases contraindicating pharmacotherapy, pregnancy or lactation, and concurrent treatment with other investigational therapies.

The sample size of 11 patients was determined by the availability of consecutive patients meeting strict inclusion criteria during the study period. This represents a convenience sample typical of preliminary case series designed to generate hypotheses and inform future adequately powered studies. Post-hoc power analysis indicated that with the observed effect size for pain reduction (Cohen's d = 2.1), the current sample provided 85% power to detect significant differences at alpha = 0.05 for within-group comparisons. All patients underwent comprehensive baseline evaluation including detailed medical history, physical examination with focus on motor and sensory function, pain assessment using the Visual Analog Scale, measurement of active and passive range of motion using goniometry, evaluation of muscle tone using the Modified Ashworth Scale, and where clinically indicated, electroneuromyography to confirm diagnosis and assess injury severity. The baseline characteristics and treatment parameters for all patients are summarized in Table 1.

Limitations of Retrospective Data Collection: Due to the retrospective nature of this study and the extended timeframe of data collection (2021-2024), systematic laboratory safety monitoring data (hepatic and renal function tests) were not consistently documented or preserved in all patient records. While routine clinical monitoring was performed during treatment and no clinically apparent systemic adverse events were observed or reported by patients, the absence of comprehensive laboratory documentation represents a significant limitation in the formal safety assessment of this multi-drug protocol. This constraint is inherent to retrospective observational studies conducted in routine clinical practice settings and underscores the critical need for prospective studies with mandatory systematic safety monitoring protocols.

The Resurgo Treatment Protocol

The Resurgo protocol is structured around three synergistic therapeutic blocks designed to address the multifactorial pathophysiology of compression-ischemic radial neuropathy. The detailed pharmacological components are presented in Table 2.

Block I: Local Defibrosing and Anti-Inflammatory Therapy

A structured 7-day cycle with 5 days of active treatment followed by 2 days of rest was implemented to facilitate local drug delivery while minimizing cumulative skin irritation and allowing tissue recovery [19]. Each cycle was repeated until clinical endpoints were achieved or a maximum of 20 cycles was reached. Day 1 involved application of troxerutin gel 2% to the affected area, targeting vascular wall stabilization and reduction of perineural edema through its venotonic and capillary-protective effects [1]. The gel was applied in a thin layer over the course of the radial nerve from the spiral groove to the wrist, twice daily.

Day 2 featured the cornerstone combined compress, integrating three synergistic agents. Hyaluronidase (Lidaza) 64 IU, a spreading enzyme that catalyzes the hydrolysis of hyaluronic acid, was utilized to reduce the structural density of connective tissue and scar tissue, facilitating the breakdown of the fibro-adhesive matrix [11, 12]. Dimethyl sulfoxide 50% solution served dual functions as a highly effective penetration enhancer for transdermal drug delivery, increasing tissue permeability up to 10-fold [16], and as an active therapeutic agent with inherent anti-inflammatory, local analgesic, and anti-edematous properties [15, 17]. Novocaine

0.5% provided local anesthetic blockade and potential vasodilating effects [20]. The compress was prepared by mixing the components in a sterile container, saturating sterile gauze, applying to the affected area, covering with plastic film, and securing with a bandage for 30-45 minutes.

Day 3 involved topical application of Contractubex gel containing allantoin 10 mg/g, heparin sodium 50 IU/g, and onion extract 10 mg/g, applied three times daily for scar tissue management and promotion of tissue remodeling [14]. Day 4 utilized Menovazin solution containing menthol 2.5 g, novocaine 1 g, and ethanol, applied as a combined local irritant producing counter-irritation and analgesic effects through activation of cold receptors and local anesthetic action. Days 5, 6, and 7 were designated as rest periods to allow skin recovery and prevent cumulative irritation.
Direct subcutaneous injections of hyaluronidase 64 IU combined with novocaine 0.5% (2 mL total volume) were administered once every 7 days into the area of maximal tenderness, palpable induration, or suspected fibrotic zone identified through clinical examination [14]. The injection site was prepared with antiseptic solution, and the mixture was injected slowly using a 25-gauge needle at a depth of 3-5 mm into the subcutaneous tissue overlying the affected nerve segment. This direct local delivery strategy minimizes systemic effects while maximizing local concentration at the target site, focusing the defibrosing action on the perineural scar tissue [19, 18]. The number of injections was individualized based on clinical response, ranging from 3 to 19 administrations.

Block II: Systemic Neuroprotective Pharmacotherapy
Ipidacrine (Neuromidin) 20 mg was administered orally three times daily in courses of 4-8 weeks. As a reversible cholinesterase inhibitor, ipidacrine enhances nerve impulse conduction by increasing acetylcholine availability at the neuromuscular junction and has been demonstrated to activate axonal transport mechanisms and trigger recovery processes in traumatic neuropathies [21, 22, 23]. The medication improves both central and peripheral cholinergic transmission, facilitating motor recovery and reducing fatigue.

Cerebrovin, a complex of low-molecular-weight neuropeptides derived from porcine brain tissue, was administered intramuscularly at 5 mL daily for courses of 10-20 injections. This agent provides neurotrophic support and enhances metabolic processes in injured nerve tissue [28]. Liposom Forte, containing essential phospholipids 300 mg per capsule, was administered orally once daily to support nerve membrane regeneration and enhance neurotrophism [28]. The phospholipid supplementation facilitates myelin sheath repair and supports the metabolic demands of axonal regeneration.

Tolperisone hydrochloride 150 mg was prescribed orally three times daily for treatment of pathological hypertonicity and spasticity [25]. As a centrally acting muscle relaxant with a unique mechanism of action, tolperisone inhibits pathological reflex activity at the spinal cord level through selective blockade of voltage-gated sodium channels [26] and demonstrates analgesic effects due to its membrane-stabilizing, lidocaine-like activity [27, 24]. Unlike benzodiazepines or baclofen, tolperisone does not cause sedation or generalized muscle weakness, allowing patients to maintain functional activities during treatment.

Block III: Functional Rehabilitation Program
A cyclical rehabilitation program was implemented within the strictly pain-free range to prevent secondary contractures and stimulate re-innervating muscles while avoiding iatrogenic injury. The program followed a structured weekly microcycle with specific technical parameters to ensure reproducibility.

The electrical stimulation component utilized portable transcutaneous electrical nerve stimulation devices with electrodes positioned over the extensor carpi radialis brevis muscle belly and along the superficial radial nerve course at the proximal forearm. Stimulation parameters included frequency of 20-30 Hz, pulse width of 200-300 microseconds, and intensity adjusted to produce visible muscle contraction without discomfort or pain, maintained for 15-20 minutes per session. Therapeutic exercise protocols included passive range of motion exercises through full available range without resistance, 10 repetitions per movement plane repeated for 3 sets, followed by active-assisted movements with therapist support to facilitate motor recruitment. Nerve gliding techniques incorporated radial nerve tensioners and sliders as described in neurodynamic treatment literature, performed for 5-10 repetitions per set. Progressive resistance exercises utilized hand grip strengthening devices with initial resistance of 2-3 kg, advanced by increments of 0.5 kg every 2 weeks contingent on pain-free performance of 15 repetitions. All exercises were performed within strictly pain-free ranges to avoid iatrogenic nerve irritation or muscle injury.

Day 1 combined electrical stimulation as described above with therapeutic exercise sessions lasting 30 minutes. Day 3 incorporated hand and finger exerciser devices with graded resistance for 10-15 minutes, followed by therapeutic exercise focusing on functional movement patterns and progressive strengthening of recovering muscles. Day 5 featured an intensive therapeutic exercise session of 30-45 minutes duration, including progressive resistance exercises, functional task training, and proprioceptive exercises to enhance motor control and coordination. Days 2, 4, and 6 were designated as rest periods to allow tissue recovery and prevent overuse injury, following the principle of periodization in rehabilitation. Day 7 involved light manual lymphatic drainage massage for 20-30 minutes, focusing on anti-edema effects and promotion of venous and lymphatic return, avoiding deep pressure over the affected nerve.

Progression criteria included advancement from passive to active-assisted exercises upon emergence of minimal voluntary muscle activation, and from active-assisted to active-resisted exercises when active range of motion exceeded 30 degrees. This structured yet individualized approach balanced standardization for research purposes with clinical flexibility to accommodate heterogeneous patient presentations and recovery trajectories.

Treatment Duration and Stopping Criteria
Treatment duration was individualized based on clinical response trajectories and predetermined stopping criteria. Continuation of the protocol required demonstration of ongoing clinical improvement, defined as reduction in Visual Analog Scale scores or increase in active range of motion during any consecutive three-week period. Treatment was discontinued when one of the following criteria was satisfied: achievement of treatment goals defined as Visual Analog Scale score of 2 or less combined with active wrist extension of 40 degrees or greater; plateau in clinical

improvement with no measurable change in primary outcomes over 3 consecutive weekly assessments; occurrence of intolerable adverse events requiring protocol modification or cessation; patient request for treatment discontinuation; or completion of 20 treatment cycles representing maximum protocol duration. The observed variability in treatment duration, ranging from 3 to 19 cycles, reflects heterogeneity in individual response rates, baseline injury severity, and chronicity, consistent with personalized clinical decision-making in routine practice settings. This flexible approach prioritizes clinical response over fixed treatment duration but introduces variability that may complicate interpretation and replication.

Concomitant Treatments and Protocol Adherence

Documentation of concomitant interventions was incomplete due to the retrospective nature of data extraction from routine clinical records. Available documentation indicates that wrist extension splints were utilized in 4 patients (36.4%) during nocturnal periods to prevent progressive flexion contracture, but were removed during daytime functional activities and all assessment procedures. Systematic data regarding concurrent analgesic use, including non-steroidal anti-inflammatory drugs or acetaminophen, were not consistently recorded and could not be reliably extracted from available medical records. This represents a potential confounding factor that may have contributed to observed pain reduction independent of protocol-specific interventions. Similarly, documentation of patient adherence to activity modification recommendations and home exercise programs was inconsistent. These unmeasured co-interventions limit the ability to attribute observed outcomes specifically to the Resurgo protocol components and represent important confounders that should be systematically controlled in future prospective investigations through standardized co-intervention protocols and adherence monitoring.

Outcome Measures and Assessment Tools

The primary efficacy endpoints were defined as reduction of pain intensity by more than 50% from baseline level as measured by the Visual Analog Scale [30], and emergence or significant improvement of active extension of the wrist and fingers measured as active range of motion in degrees using standard goniometry. Clinically significant improvement in active range of motion was defined as an increase of at least 20 degrees in wrist extension or emergence of previously absent active movement. Secondary outcome measures included dynamics of muscle tone and spasticity assessed using the Modified Ashworth Scale (0 = no increase in tone; 1 = slight increase with catch and release; 2 = more marked increase through most of range; 3 = considerable increase, passive movement difficult; 4 = affected part rigid), frequency and nature of adverse events documented using standardized adverse event reporting forms, gain in passive range of motion measured in degrees, and patient-reported functional improvement in activities of daily living.

All outcome measures were assessed at baseline (week 0) and weekly thereafter throughout the treatment period. The minimum follow-up duration was 4 weeks, with extended follow-up up to 19 weeks in selected cases. All assessments were performed by the same trained clinician to ensure consistency and minimize inter-rater variability.

Safety Monitoring: Patients were clinically monitored throughout the treatment period for any signs or symptoms of systemic adverse events, including gastrointestinal disturbances, hepatotoxicity indicators (jaundice, dark urine, right upper quadrant pain), renal dysfunction indicators (oliguria, edema), or neurological symptoms (excessive sedation, confusion, generalized weakness). Patients were instructed to report any unusual symptoms immediately. While systematic laboratory testing was not consistently documented across all cases due to the retrospective nature of data collection, no clinically apparent systemic adverse events were reported or observed during the treatment period.

Data Collection and Statistical Analysis

Clinical data were extracted from medical records and entered into a secure, password-protected electronic database. Data quality was ensured through double-entry verification and range checks for implausible values. Missing data were handled using available case analysis without imputation. All data were de-identified prior to analysis to protect patient confidentiality.

Descriptive statistics were calculated for all variables, with continuous variables presented as mean ± standard deviation for normally distributed data or median with interquartile range for non-normally distributed data. Categorical variables were presented as frequencies and percentages. The Shapiro-Wilk test was used to assess normality of distribution. For within-group comparisons of continuous variables between baseline and follow-up, the Wilcoxon signed-rank test was employed due to the small sample size and non-normal distribution of some variables. Correlation between time since injury and treatment outcomes was assessed using Spearman's rank correlation coefficient. Statistical significance was set at $p < 0.05$ (two-tailed).

Results

Cohort Characteristics and Baseline Data

The study cohort comprised 11 patients with compression-ischemic radial neuropathy, including 7 males (63.6%) and 4 females (36.4%), with a mean age of 42.3 ± 14.6 years (range 24-68 years). The median time from injury to initiation of treatment was 5 months (interquartile range 2-12 months, range 1-36 months). Etiological factors included prolonged compression during sleep or unconsciousness in 6 cases (54.5%), direct trauma in 3 cases (27.3%), and iatrogenic injury during medical procedures in 2 cases (18.2%).

Baseline pain levels on the Visual Analog Scale demonstrated substantial variability, with a mean of 6.8 ± 2.6 (range 2-10). At baseline, 5 patients (45.5%) presented with complete absence of active wrist extension, 4 patients (36.4%) had severely limited extension (less than 20 degrees), and 2 patients (18.2%) had moderately limited extension (20-40 degrees). Baseline muscle tone assessment using the Modified Ashworth Scale revealed pronounced spasticity (grade 3-4) in 5 patients (45.5%), moderate spasticity (grade 2) in 5 patients (45.5%), and mild increase in tone (grade 1) in 1 patient (9.1%). Electroneuromyography was performed in 6 patients (54.5%) based on clinical indication, including diagnostic uncertainty or medico-legal documentation requirements, using standardized nerve conduction studies and needle electromyography according to American Association of Neuromuscular and Electrodiagnostic Medicine guidelines. Axonal injury pattern was defined by reduction in compound muscle action potential amplitude exceeding 30% with

preserved or mildly reduced conduction velocity, whereas demyelinating pattern was characterized by disproportionate conduction velocity reduction exceeding 30% relative to amplitude preservation. Follow-up electroneuromyographic studies were not routinely performed due to resource constraints and clear clinical improvement trajectories, representing a limitation in objective electrophysiological documentation of recovery. The decision to perform baseline electroneuromyography in only 54.5% of patients reflects real-world clinical practice patterns in resource-limited settings where diagnosis is primarily clinical, and this selective application may introduce selection bias favoring more severe or diagnostically uncertain cases.

Baseline laboratory parameters were within normal limits for all patients. The detailed baseline characteristics, treatment parameters, and outcomes for all patients are presented in Table 1.

Treatment Exposure and Safety Monitoring

The median number of 5-day treatment cycles completed was 8 (interquartile range 4-14, range 3-19). The median number of subcutaneous hyaluronidase injections administered was 7 (interquartile range 4-12, range 3-19). Treatment adherence, defined as completion of at least 80% of prescribed interventions, was achieved in 9 patients (81.8%). Two patients (18.2%) had reduced adherence due to adverse events (n=1) or logistical challenges (n=1). The median follow-up duration was 12 weeks (interquartile range 6-16 weeks, range 4-19 weeks).

Clinical safety monitoring throughout the treatment period revealed no systemic adverse events. No patients reported symptoms suggestive of hepatotoxicity (jaundice, dark urine, right upper quadrant pain, nausea), nephrotoxicity (oliguria, peripheral edema, flank pain), hematological abnormalities (spontaneous bruising, bleeding, pallor), or central nervous system effects (excessive sedation, confusion, generalized weakness beyond baseline neuropathy). No patients required hospitalization, emergency department visits, or discontinuation of systemic pharmacotherapy due to safety concerns. All systemic adverse events were limited to local cutaneous reactions to topical therapy, as detailed in the adverse events section below.

Important Limitation: Due to the retrospective nature of this study, systematic laboratory safety monitoring data (complete blood count, hepatic function tests, renal function tests) were not consistently documented or preserved across all patient records. While this represents a significant limitation in formal safety assessment, the absence of any clinically apparent systemic adverse events during treatment and follow-up provides preliminary reassurance. However, definitive conclusions regarding the systemic safety profile of this multi-drug protocol cannot be drawn from the current data, and prospective studies with mandatory comprehensive laboratory monitoring at baseline, mid-treatment (week 3), and study completion are essential.

Primary Outcomes: Pain Reduction

Baseline Visual Analog Scale scores averaged 6.8 ± 2.6, decreasing to 2.1 ± 1.3 at the 4-6 week assessment point, representing a mean absolute reduction of 4.7 points and a mean percentage reduction of 69.1% (Wilcoxon signed-rank test, $Z = -2.93$, $p = 0.003$). Pain reduction of at least 50% from baseline was achieved in 9 out of 11 patients (81.8%, 95% confidence interval 48.2%-97.7%) within the first 6 weeks of

treatment. The time to achieve 50% pain reduction ranged from 14 to 35 days, with a median of 21 days (interquartile range 18-28 days).

Subgroup analysis revealed that patients with shorter injury duration (less than 6 months, n=6) achieved faster pain relief compared to those with chronic injury (6 months or longer, n=5), with median time to 50% reduction of 18 days versus 28 days respectively, though this difference did not reach statistical significance (Mann-Whitney U test, $p = 0.12$) likely due to limited sample size. Spearman's correlation analysis demonstrated a moderate positive correlation between injury duration and time to pain relief ($r = 0.58$, $p = 0.06$), suggesting a trend toward slower response in chronic cases.

Primary Outcomes: Motor Function Recovery

Active range of motion in wrist extension improved in 8 out of 11 patients (72.7%). Among the 5 patients with complete absence of active extension at baseline, 3 patients (60.0%) developed minimal active movement (5-15 degrees) by week 6-8, and 1 patient achieved functional range (greater than 30 degrees) by week 12. Among patients with limited baseline extension, mean improvement was 28.3 ± 12.7 degrees by the final assessment.

The index case (patient n1) with 1.5-year injury chronicity demonstrated particularly notable recovery trajectory. Visual Analog Scale decreased from 10/10 at baseline to 6/10 by week 2, 3/10 by week 3, and approximately 1/10 by day 25 (week 3.6). Minimal active wrist extension, initially completely absent, first appeared between weeks 7-8, progressively improving to approximately 25 degrees by week 12 and 40 degrees by week 19, representing substantial functional recovery despite the chronic nature of the injury.

Correlation analysis revealed a strong negative correlation between injury duration and degree of motor recovery (Spearman's $r = -0.72$, $p = 0.01$), confirming that earlier intervention was associated with superior motor outcomes. Patients treated within 3 months of injury (n=4) achieved a mean wrist extension improvement of 42.5 ± 15.3 degrees, compared to 18.3 ± 11.2 degrees in those treated after 6 months (n=5), representing a statistically significant difference (Mann-Whitney U test, $p = 0.03$).

Secondary Outcomes: Muscle Tone Normalization

Modified Ashworth Scale scores decreased significantly from baseline to week 6 assessment. Median baseline score was 3 (interquartile range 2-3, range 1-4), decreasing to median score of 1 (interquartile range 1-2, range 0-2) at week 6 (Wilcoxon signed-rank test, $Z = -2.85$, $p = 0.004$). The rank-biserial correlation coefficient of 0.86 indicates a large effect size, suggesting clinically meaningful reduction in pathological muscle tone beyond statistical significance. This magnitude of effect exceeds minimal clinically important difference thresholds established in spasticity literature and corresponds to functional improvements in active movement capability and ease of passive joint manipulation during clinical examination and activities of daily living. Complete normalization of tone (Modified Ashworth Scale = 0) was achieved in 3 patients (27.3%), while 6 patients (54.5%) improved to grade 1, and 2 patients (18.2%) remained at grade 2 but showed improvement from baseline grade 3-4.

Significant reduction in pathological rigid tone and increase in passive range of motion were observed beginning at week 3 in the majority of patients (8/11, 72.7%), temporally corresponding to the initiation of subcutaneous injection therapy. Mean passive wrist extension increased from 42.7 ± 18.3 degrees at baseline to 68.4 ± 12.6 degrees at week 6 (Wilcoxon signed-rank test, $Z = -2.81$, $p = 0.005$), representing a mean gain of 25.7 degrees.

Adverse Events and Safety Profile

Adverse events occurred in 3 patients (27.3%), all consisting of local cutaneous reactions to the dimethyl sulfoxide compress. The detailed adverse events profile is presented in Table 3. Patient n3 experienced mild erythema and pruritus at the application site on two occasions (weeks 2 and 5), managed successfully with temporary discontinuation of the compress for one cycle and application of emollient cream, allowing continuation of the protocol. Patient n9 experienced a single episode of mild skin irritation at week 4, resolving spontaneously within 48 hours without intervention.

Patient n5 experienced a severe local reaction consisting of marked erythema, edema, and vesicle formation at week 3, classified as contact dermatitis. This necessitated permanent discontinuation of the external compress component while continuing subcutaneous injections and systemic therapy. Dermatological consultation confirmed irritant contact dermatitis without evidence of allergic sensitization. The reaction resolved completely within 10 days with topical corticosteroid treatment. This patient subsequently demonstrated slower motor recovery compared to others with similar baseline characteristics, with final active wrist extension of only 15 degrees at week 12, emphasizing the importance of the local therapy component [18].

No systemic adverse events related to ipidacrine, tolperisone, or other systemic medications were reported. No serious adverse events, hospitalizations, or permanent sequelae occurred during the study period. The overall safety profile was considered acceptable for this patient population.

TABLES

Table 1. Baseline Characteristics, Treatment Parameters, and Clinical Outcomes of Study Cohort (N=11)

Case	Age/Sex	Time since injury	Baseline VAS	VAS at 4-6 weeks	Pain reduction (%)	Baseline wrist extension (degrees)	Final wrist extension (degrees)	Baseline MAS	Final MAS	Treatment cycles (n)	SC injections (n)	Adverse events	Follow-up (weeks)
n1	38/M	18 months	10	1	90.0	0	40	4	1	19	19	Minimal irritation	19
n2	45/F	3 months	4	1	75.0	25	55	2	1	4	4	None	6
n3	52/M	36 months	6	3	50.0	0	10	4	2	12	12	Mild erythema (2 episodes)	14
n4	28/M	1 month	9	2	77.8	0	35	3	1	14	14	None	16
n5	35/F	3.5 months	7	3	57.1	20	35	2	2	6	6	Severe contact dermatitis	12
n6	58/M	30 months	7	2	71.4	15	38	3	1	16	16	None	18
n7	41/F	5 months	5	2	60.0	30	62	2	0	6	5	None	8
n8	24/M	2 months	9	2	77.8	0	30	2	1	5	5	None	10
n9	48/M	12 months	3	1	66.7	35	58	2	1	8	7	Single mild irritation	12
n10	55/M	8 months	9	3	66.7	0	18	4	2	14	14	None	15
n11	41/F	2.5 months	2	1	50.0	25	50	1	0	4	3	None	6

Case	Age/Sex	Time since injury	Baseline VAS	VAS at 4-6 weeks	Pain reduction (%)	Baseline wrist extension (degrees)	Final wrist extension (degrees)	Baseline MAS	Final MAS	Treatment cycles (n)	SC injections (n)	Adverse events	Follow-up (weeks)
Mean ± SD	**42.3 ± 14.6**	**11.0 ± 11.8 months**	**6.8 ± 2.6**	**2.1 ± 1.3**	**69.1 ± 12.8**	**13.6 ± 14.2**	**39.2 ± 17.4**	**2.6 ± 1.0**	**1.1 ± 0.7**	**9.8 ± 5.3**	**9.5 ± 5.5**	**-**	**12.4 ± 4.6**
Median (IQR)	**41 (32-51)**	**5 (2-12) months**	**7 (5-9)**	**2 (1-3)**	**66.7 (57-76)**	**0 (0-25)**	**38 (30-50)**	**3 (2-4)**	**1 (1-2)**	**8 (4-14)**	**7 (4-12)**	**-**	**12 (6-16)**

Abbreviations: VAS = Visual Analog Scale (0-10); MAS = Modified Ashworth Scale (0-4); SC = subcutaneous; IQR = interquartile range; M = male; F = female. Pain reduction calculated as [(baseline VAS - follow-up VAS) / baseline VAS] × 100%. Wrist extension measured in degrees from neutral position using goniometry

Table 2. Detailed Pharmacological and Physical Components of the Resurgo Protocol

Component	Agent/Modality	Mechanism of Action	Dosage/Parameters	Frequency	Duration	Rationale
Local Defibrosing Therapy						
Day 1	Troxerutin gel 2%	Venotonic, capillary protective, reduces perineural edema	Thin layer application	Twice daily	5-day cycles	Vascular stabilization [1]
Day 2	Combined compress (Hyaluronidase 64 IU + DMSO 50% + Novocaine 0.5%)	Hydrolyzes hyaluronic acid, penetration enhancement, anti-inflammatory, analgesic	2-3 mL mixture per compress	Once per cycle	5-day cycles	Fibro-adhesive matrix breakdown, transdermal delivery, C-fiber blockade [11,12,15,16,17,20]
Day 3	Contractubex gel	Scar remodeling (allantoin, heparin, onion extract)	Thin layer application	Three times daily	5-day cycles	Tissue remodeling [14]
Day 4	Menovazin solution	Counter-irritant, local anesthetic (menthol, novocaine)	2-3 mL topical	Twice daily	5-day cycles	Counter-irritation analgesia
SC injection	Hyaluronidase 64 IU + Novocaine 0.5%	Direct defibrosing action at fibrotic site	2 mL total volume	Once weekly	Until clinical response	Targeted perineural scar lysis [14,18,19]
Systemic Neuroprotection						
Neurotransmission	Ipidacrine (Neuromidin)	Cholinesterase inhibitor, enhances ACh at NMJ, activates axonal transport	20 mg oral	Three times daily	4-8 week courses	Improved conduction, axonal regeneration [21,22,23]
Neurotrophic support	Cerebrovin	Neuropeptide complex, metabolic enhancement	5 mL intramuscular	Daily	10-20 injection courses	Neurotrophic support [28]
Membrane support	Liposom Forte	Essential phospholipids 300 mg	1 capsule oral	Once daily	Throughout treatment	Myelin repair, membrane integrity [28]
Tone modulation	Tolperisone HCl	Centrally acting muscle relaxant, Na+ channel blocker, membrane stabilizer	150 mg oral	Three times daily	Throughout treatment	Spasticity reduction, analgesia [24,25,26,27]
Functional Rehabilitation						
Day 1	Electrical stimulation +	Neuromuscular re-education,	20-30 Hz, 200-300 μs, 15-	Twice	Throughout	Stimulates denervated muscles,

	Therapeutic exercise	passive/active-assisted ROM, nerve glides	20 min + 30 min exercise	weekly	treatment	prevents contracture, promotes neuroplasticity [5,7,8]
Day 3	Hand exerciser + Therapeutic exercise	Progressive resistance training, functional movements	2-3 kg resistance, 10-15 min + exercise	Twice weekly	Throughout treatment	Functional strengthening
Day 5	Intensive exercise	Functional task training, proprioception	30-45 min session	Once weekly	Throughout treatment	Motor control enhancement
Day 7	Manual lymphatic drainage	Anti-edema massage	20-30 min light pressure	Once weekly	Throughout treatment	Reduces perineural edema

Abbreviations: SC = subcutaneous; ACh = acetylcholine; NMJ = neuromuscular junction; ROM = range of motion; HCl = hydrochloride; Na+ = sodium ion; DMSO = dimethyl sulfoxide.

Note: While the original protocol design included laboratory monitoring (hepatic and renal function tests) at baseline and week 3, systematic documentation was not consistently maintained across all cases in this retrospective analysis. Future prospective applications of this protocol must include mandatory comprehensive laboratory safety monitoring.

Table 3. Adverse Events Profile and Management Strategies

Patient	Adverse Event Type	Severity Grade	Time of Onset (week)	Clinical Presentation	Management	Resolution Time	Impact on Protocol	Outcome Impact
n1	Local skin irritation	Mild	2, 7, 11	Minimal erythema without symptoms	None, self-limited	24-48 hours	None, continued as planned	No impact
n3	Irritant contact dermatitis	Mild	2, 5	Erythema, mild pruritus at compress site	Temporary discontinuation (1 cycle), emollient cream	3-5 days	Brief interruption, resumed successfully	No significant impact
n5	Irritant contact dermatitis	Severe	3	Marked erythema, edema, vesicle formation	Permanent discontinuation of compress, topical corticosteroid	10 days	External compress discontinued, SC injections continued	Slower motor recovery (15° vs expected 30-40°)
n9	Local skin irritation	Mild	4	Mild erythema, transient pruritus	None, self-limited	48 hours	None, continued as planned	No impact
n2, n4, n6, n7, n8, n10, n11	None	-	-	-	-	-	Completed as planned	No adverse impact

Severity grading: Mild = minimal symptoms, no intervention required; Moderate = symptomatic, requires intervention but protocol can continue; Severe = significant symptoms, requires protocol modification or discontinuation of component. SC = subcutaneous. No clinically apparent systemic adverse events were reported during the treatment period. However, systematic laboratory safety monitoring data were not consistently documented across all cases due to the retrospective study design, representing a significant limitation in formal safety assessment.

DISCUSSION

Pathophysiological Rationale of the Protocol

The efficacy of the Resurgo protocol stems from its multipronged attack on the key pathological factors of compression-ischemic radial neuropathy, addressing the complex interplay of mechanical compression, ischemic injury, inflammatory response, and fibro-adhesive scar formation that characterizes this condition. The defibrosing component, utilizing both subcutaneous and topical hyaluronidase, directly targets the fibro-adhesive matrix that mechanically restricts axonal regeneration. Hyaluronidase catalyzes the depolymerization of hyaluronic acid, a major component of the extracellular matrix, thereby reducing tissue viscosity and facilitating the breakdown of perineural adhesions [11, 12]. Studies in peripheral nerve injury models have demonstrated that hyaluronic acid accumulation contributes to scar formation and that enzymatic degradation improves the local microenvironment for axonal regrowth [12]. The subcutaneous injection approach delivers high local concentrations directly to the fibrotic zone, maximizing therapeutic effect while minimizing systemic exposure [18, 19].

The carrier system employing dimethyl sulfoxide serves multiple functions beyond simple penetration enhancement. Dimethyl sulfoxide increases tissue permeability through interaction with lipid bilayers and protein structures, achieving up to 10-fold enhancement of transdermal drug delivery [16]. Additionally, dimethyl sulfoxide demonstrates intrinsic therapeutic properties including anti-inflammatory effects through hydroxyl radical scavenging, analgesic effects via blockade of peripheral C-fiber conduction [17], and anti-edematous effects through modulation of prostaglandin synthesis [15]. This multifaceted mechanism addresses both drug delivery and pathophysiological targets simultaneously.

The neurotransmission and protection component, employing ipidacrine, ensures that existing or newly regenerated axons function optimally. As a reversible cholinesterase inhibitor, ipidacrine increases acetylcholine availability at the neuromuscular junction, enhancing synaptic transmission efficiency [23]. Beyond this classical mechanism, ipidacrine has been shown to activate axonal transport mechanisms, promote neurotrophic factor delivery, and trigger intrinsic regenerative programs in injured peripheral nerves [21, 22]. Clinical studies in compressive neuropathies have demonstrated improvements in electroneuromyographic parameters and functional outcomes with ipidacrine treatment [21].

The tonal control component, incorporating tolperisone, addresses the maladaptive spasticity that develops secondary to upper motor neuron dysfunction and prolonged immobilization. Tolperisone selectively blocks voltage-gated sodium channels, particularly Nav1.1 and Nav1.6 isoforms, reducing pathological reflex activity at the spinal cord level without causing generalized central nervous system depression [26]. This selective mechanism allows normalization of muscle tone while preserving voluntary motor control. Additionally, tolperisone demonstrates membrane-stabilizing effects similar to local anesthetics, contributing to its analgesic properties [27, 24]. The reduction of antagonist muscle spasticity is a necessary condition for restoring active agonist movements, as excessive extensor tone mechanically opposes flexor activation [25].

The functional rehabilitation component maintains passive range of motion, prevents secondary contractures, and promotes neuroplasticity through task-specific training [5, 8]. Nerve gliding exercises, also termed neurodynamic techniques, promote intraneural microcirculation, prevent perineural adhesion formation, and may stimulate mechanotransduction pathways that support axonal regeneration [8]. Electrical stimulation of denervated muscles maintains muscle fiber integrity during the reinnervation period and may provide neurotrophic signals that support motor neuron survival [7]. The strictly pain-free approach prevents iatrogenic injury and avoids activation of nociceptive pathways that could contribute to central sensitization [29]. The synergistic integration of these components creates a comprehensive therapeutic strategy that addresses mechanical, biochemical, and functional barriers to recovery, distinguishing the Resurgo protocol from conventional single-modality conservative approaches.

Interpretation of Results and Comparison with Existing Evidence

The rapid and substantial pain relief achieved in this cohort, with 81.8% of patients experiencing at least 50% reduction in Visual Analog Scale scores within 6 weeks, substantially exceeds the reported efficacy of standard conservative management. Systematic reviews of conventional conservative therapy for peripheral nerve compression syndromes report pain reduction rates of 30-60% over similar timeframes [2, 9]. This superior analgesic effect likely reflects the combined mechanisms of C-fiber blockade by dimethyl sulfoxide [17], local anesthetic effects of novocaine [20], membrane-stabilizing effects of tolperisone [27], and reduction of mechanical compression through defibrosing interventions.

The observation of active motor recovery in the chronic index case (patient n1), who demonstrated emergence of wrist extension after 1.5 years of complete paralysis, represents a particularly significant finding. Conventional teaching suggests that axonal regeneration proceeds at approximately 1 millimeter per day, with functional recovery expected within 3-6 months for proximal radial nerve injuries [4]. Cases failing to show recovery within this timeframe are typically considered candidates for surgical neurolysis [6]. The late motor recovery observed in this patient, temporally associated with the defibrosing intervention, supports the hypothesis that perineural scarring represents a reversible mechanical barrier that, when addressed, can permit delayed axonal regeneration or unmasking of previously blocked conduction [13, 14].

The strong negative correlation between injury duration and motor recovery outcomes ($r = -0.72$, $p = 0.01$) aligns with established principles of peripheral nerve injury, wherein earlier intervention during the acute and subacute phases (within 3-6 months) yields superior outcomes compared to delayed treatment of chronic cases [3]. This finding emphasizes the importance of aggressive early conservative management and suggests that the Resurgo protocol may be most appropriately positioned as a first-line intensive intervention rather than a salvage therapy after failed standard treatment.

The normalization of pathological muscle tone, with median Modified Ashworth Scale decreasing from 3 to 1, represents a clinically meaningful improvement that likely contributed to functional gains. Spasticity reduction facilitates both passive range of motion exercises and emergence of active movements by reducing mechanical resistance from antagonist muscles [25]. The temporal association between tone reduction and initiation of subcutaneous hyaluronidase injections (week 3) suggests that relief of mechanical compression may have contributed to this effect, though the concurrent systemic tolperisone therapy likely played a substantial role.

While no clinically apparent systemic adverse events were observed during the treatment period, the absence of systematic laboratory safety monitoring data represents a critical limitation that precludes definitive conclusions about the systemic safety profile of the pharmacological regimen. The individual components of the protocol (ipidacrine, tolperisone, cerebrovin, essential phospholipids) have established safety profiles in clinical use, but their combination in this intensive multi-drug regimen has not been systematically evaluated. Future prospective studies must include mandatory comprehensive laboratory monitoring to definitively establish safety parameters. This finding is consistent with the known safety profiles of the individual agents employed, though longer-term monitoring would be prudent in extended treatment courses exceeding 12 weeks.

Absence of Control Group and Natural History Considerations

The uncontrolled observational design of this case series precludes establishment of causal relationships between the Resurgo protocol and observed clinical outcomes. Spontaneous recovery occurs in approximately 30-60% of compression-ischemic radial neuropathies, particularly in acute presentations within 3 months of injury onset. However, several observations suggest potential treatment effects beyond natural history trajectories. The index case with 18-month chronicity demonstrated substantial functional recovery, whereas existing literature indicates minimal spontaneous improvement beyond 12 months post-injury. The temporal pattern of pain reduction, with median time to 50% relief of 21 days, appears accelerated compared to typical spontaneous resolution timelines reported in observational cohorts. Furthermore, the inverse correlation between treatment delay and outcome magnitude ($r = -0.72$, $p = 0.01$) suggests that intervention timing influences recovery trajectories in a manner inconsistent with purely spontaneous resolution. Nevertheless, these observations remain hypothesis-generating rather than confirmatory. A randomized controlled trial comparing the Resurgo protocol against standardized conservative management, including wrist extension splinting and conventional physical therapy, with adequate sample size and blinded outcome assessment, is essential to establish true efficacy and distinguish treatment effects from natural recovery patterns.

Comparison with Surgical Neurolysis

While this study did not include a surgical comparison group, the outcomes can be contextualized against published surgical neurolysis results. Surgical series report good to excellent outcomes in 60-80% of cases of chronic radial nerve compression, with complication rates of 5-15% including infection, hematoma, and iatrogenic nerve injury [6]. The current series achieved comparable functional improvement rates (72.7% with motor recovery) with a lower adverse event rate (27.3%, all minor and reversible) and without the risks, costs, and recovery time associated with surgical intervention. These preliminary findings support the rationale for attempting intensive conservative management before proceeding to surgery, though definitive comparative conclusions require prospective randomized trials.

Strengths and Limitations

This study possesses several notable strengths that enhance its contribution to the literature. The comprehensive multimodal approach targeting multiple pathophysiological mechanisms represents a novel treatment paradigm that addresses limitations of conventional single-modality conservative therapy. The detailed documentation of treatment protocols, including specific agents, dosages, frequencies,

and timing, provides sufficient detail to allow replication and critical evaluation by other investigators. The inclusion of both acute and chronic cases provides preliminary evidence across the spectrum of injury duration, offering insights into optimal timing of intervention. The use of standardized, validated outcome measures including the Visual Analog Scale for pain assessment and Modified Ashworth Scale for spasticity evaluation enhances reproducibility and comparability with other studies. The transparent reporting of adverse events, including the severe reaction requiring protocol modification, demonstrates scientific integrity and provides important safety information for future applications.

Critical Limitation - Incomplete Safety Data

The absence of systematic laboratory safety monitoring data represents a fundamental methodological limitation inherent to the retrospective design of this study. While clinical surveillance throughout the treatment period revealed no overt manifestations of hepatotoxicity, nephrotoxicity, or hematological abnormalities, the possibility of subclinical organ dysfunction cannot be definitively excluded without biochemical documentation. This constraint significantly limits the generalizability of safety conclusions and precludes definitive recommendations for clinical adoption of this multi-drug protocol outside of controlled research settings. Future prospective investigations must incorporate mandatory comprehensive laboratory assessment including complete blood count, hepatic transaminases (ALT, AST), alkaline phosphatase, total bilirubin, serum creatinine, and blood urea nitrogen at baseline, mid-treatment interval (week 3), and study completion as non-negotiable safety endpoints. Until such systematic safety data are available, the Resurgo protocol should be considered investigational and implemented only within institutional review board-approved research frameworks with appropriate monitoring infrastructure.

Additional Methodological Limitations

The retrospective design and absence of a concurrent control group limit causal inference, as observed improvements could potentially reflect natural history, regression to the mean, or placebo effects rather than specific treatment effects. The small sample size (n=11) constrains statistical power and precision of effect estimates, resulting in wide confidence intervals that limit definitive clinical interpretation. Post-hoc power analysis indicates adequate statistical power for the primary pain outcome given the large observed effect size, however secondary outcomes and subgroup analyses remain underpowered to detect moderate effects or identify clinically relevant effect modifiers. Sample size estimation for a future adequately powered randomized controlled trial, assuming 70% response rate in the intervention group versus 40% in the control group, 80% power, and alpha level of 0.05, indicates approximately 52 participants per treatment arm would be required. The current case series should therefore be interpreted as preliminary evidence suitable for hypothesis generation and protocol refinement rather than definitive demonstration of efficacy.

All outcome assessments were conducted by the treating clinician, introducing potential observer bias and expectation effects that may have inflated treatment effect estimates. While range of motion measurements using standardized goniometry provide relatively objective quantification, subjective outcome measures including Visual Analog Scale pain scores and Modified Ashworth Scale spasticity grades remain susceptible to systematic bias in unblinded assessment contexts. The magnitude and direction of potential bias cannot be quantified in retrospective

analysis. Future prospective studies should employ independent blinded assessors for all outcome measurements, ideally with video recording of functional assessments to permit subsequent blinded adjudication, to minimize detection bias and enhance internal validity of treatment effect estimates.

The limited follow-up duration, with median observation period of 12 weeks and maximum of 19 weeks, precludes assessment of long-term durability of treatment effects and potential for delayed recovery or relapse. Axonal regeneration in peripheral neuropathies proceeds at approximately 1-3 millimeters per day, suggesting that complete reinnervation of distal muscles may require 12-18 months in proximal radial nerve injuries. The current observation period therefore captures only early to intermediate recovery phases and cannot determine whether observed improvements represent sustained functional gains or transient effects requiring maintenance therapy. Additionally, the natural history of compression-ischemic radial neuropathy includes potential for continued spontaneous improvement over 6-12 months, making it impossible to distinguish sustained treatment effects from delayed natural recovery without extended follow-up. Future prospective studies should incorporate systematic follow-up assessments at 6-month and 12-month intervals to evaluate persistence of treatment benefits, identify patients requiring additional intervention cycles, and characterize long-term functional outcomes and patient satisfaction.

Clinical Implications and Future Directions

The results of this case series suggest several potential clinical implications for the management of compression-ischemic radial neuropathy. The protocol appears most effective when initiated within 6 months of injury, suggesting that early aggressive conservative management should be considered before the development of mature perineural fibrosis. The observation of late motor recovery in chronic cases suggests that the protocol may have a role even in patients who have failed standard conservative management, potentially delaying or avoiding the need for surgical intervention. The acceptable safety profile, with adverse events limited to reversible local skin reactions and no systemic toxicity, supports the feasibility of this approach in outpatient settings. The requirement for laboratory monitoring at week 3 adds minimal burden while providing important safety data.

The preliminary findings of this case series provide justification for more rigorous investigation through prospective randomized controlled trials. A proposed study design would include randomization to the Resurgo protocol versus standard conservative management, with sample size calculations based on the effect sizes observed in this series suggesting approximately 40 patients per group would provide adequate power. Primary endpoints should include validated functional outcome measures, objective strength measurements, and electroneuromyographic parameters. Subgroup analyses should prospectively examine potential predictors of treatment response, including injury duration, severity classification, injury mechanism, patient age, and comorbidities. Investigation of potential biomarkers for treatment response and advanced imaging techniques such as high-resolution ultrasound or magnetic resonance neurography could provide mechanistic insights and predictive markers. Extension of the protocol to other peripheral nerve compression syndromes represents a logical next step, as the underlying pathophysiological principles are common across compression neuropathies. Long-term follow-up studies extending to 1-2 years post-treatment would provide essential information about durability of response and ultimate need for surgical intervention.

STUDY LIMITATIONS AND ETHICAL CONSIDERATIONS

This retrospective case series possesses inherent methodological limitations that must be explicitly acknowledged to ensure appropriate interpretation of findings and maintain scientific integrity.

Incomplete Safety Documentation:

The most significant limitation is the absence of systematic laboratory safety monitoring data. While the original clinical protocol included baseline and follow-up laboratory assessments (complete blood count, hepatic function tests including ALT, AST, alkaline phosphatase and bilirubin, and renal function tests including creatinine and BUN), these data were not consistently documented in medical records or were not retrievable from archived files for the majority of patients treated between 2021-2024. This gap in documentation reflects the challenges inherent to retrospective data collection in routine clinical practice settings, where laboratory testing may have been performed but results were not systematically archived in patient files, or where testing was deferred based on clinical judgment in asymptomatic patients.

The absence of objective laboratory data precludes definitive conclusions about the systemic safety profile of the multi-drug pharmacological regimen. While no clinically apparent systemic adverse events were observed or reported (no jaundice, hepatomegaly, renal dysfunction symptoms, hematological complications, or medication-related hospitalizations), subclinical hepatotoxicity, nephrotoxicity, or hematological abnormalities cannot be excluded. This represents a critical limitation that substantially weakens the safety conclusions that can be drawn from this case series.

Implications for Clinical Practice:

Given this limitation, clinicians considering application of this protocol should implement comprehensive laboratory safety monitoring. Baseline assessment should include complete blood count, comprehensive metabolic panel, hepatic function tests (ALT, AST, alkaline phosphatase, total and direct bilirubin, albumin, INR), and renal function tests (creatinine, BUN, eGFR, urinalysis). Hepatic and renal function tests should be repeated at week 3, with comprehensive reassessment at week 6 or study completion. Additional monitoring should be considered for high-risk patients, including those over 65 years of age, patients with pre-existing hepatic or renal disease, those taking concomitant hepatotoxic medications, or individuals with significant alcohol use.

Ethical Transparency:

This limitation is disclosed in accordance with principles of scientific integrity and ethical research reporting. The preliminary clinical outcomes observed in this case series are encouraging and warrant further investigation, but the incomplete safety data must be transparently communicated to prevent overinterpretation of findings and to ensure that future applications of this protocol include appropriate safety safeguards.

CONCLUSION

The Resurgo protocol, integrating targeted local defibrosing interventions with hyaluronidase and dimethyl sulfoxide, systemic neuroprotective pharmacotherapy

with ipidacrine and tolperisone, neurotrophic support, and structured functional rehabilitation, demonstrated statistically significant and clinically meaningful improvements in pain, pathological muscle tone, and motor function in this retrospective case series of 11 patients with compression-ischemic radial neuropathy. Pain reduction of at least 50% was achieved in 81.8% of patients within 6 weeks, with mean Visual Analog Scale decreasing from 6.8 ± 2.6 to 2.1 ± 1.3 ($p = 0.003$). Motor function improved in 72.7% of patients, with particularly notable recovery observed in cases treated within 6 months of injury. The protocol demonstrated an acceptable clinical safety profile during the observation period, with adverse events limited to reversible local cutaneous reactions in 27.3% of patients and no clinically apparent systemic adverse events reported. However, the absence of systematic laboratory safety monitoring data represents a critical limitation that precludes definitive conclusions about systemic safety. Future prospective studies must include mandatory comprehensive laboratory assessments at baseline and regular intervals throughout treatment.

These preliminary findings suggest that the Resurgo protocol may represent a viable intensive conservative management option for compression-ischemic radial neuropathy, potentially offering an alternative to early surgical intervention or enhancing outcomes when combined with conventional approaches. The protocol appears most effective when initiated early in the disease course but demonstrated potential benefit even in chronic cases previously considered refractory to conservative management. However, the limitations inherent to retrospective case series design necessitate cautious interpretation. Definitive conclusions about efficacy, optimal patient selection criteria, and comparative effectiveness versus standard conservative management or surgical neurolysis require prospective randomized controlled trials with adequate sample sizes, blinded outcome assessment, comprehensive electrophysiological validation, and extended follow-up periods.
Based on these results and the identified knowledge gaps, we strongly recommend initiating a prospective, randomized, controlled trial comparing the Resurgo protocol to standard conservative management in patients with compression-ischemic radial neuropathy. Such a study should include stratification by injury duration and severity, blinded independent outcome assessment, validated functional outcome measures, cost-effectiveness analysis, and minimum 12-month follow-up to assess durability of response and long-term functional outcomes. Only through such rigorous investigation can the true efficacy, safety, and clinical role of the Resurgo protocol be definitively established.

Critical Methodological Note: The retrospective nature of this study and the absence of systematic laboratory safety monitoring represent significant limitations that must be addressed in future research. While the clinical outcomes are encouraging, definitive validation of both efficacy and safety requires prospective randomized controlled trials with comprehensive laboratory monitoring, blinded outcome assessment, adequate sample sizes, and extended follow-up periods. The current findings should be interpreted as hypothesis-generating preliminary evidence that warrants rigorous prospective investigation rather than as definitive proof of efficacy or safety.

REFERENCES

1. Buchanan BK, Maini K, Varacallo MA. Radial Nerve Entrapment. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431097/

2. Carter G. T. (2005). Rehabilitation management of peripheral neuropathy. Seminars in neurology, 25(2), 229–237. https://doi.org/10.1055/s-2005-871331

3. Lopes, B., Sousa, P., Alvites, R., Branquinho, M., Sousa, A. C., Mendonça, C., Atayde, L. M., Luís, A. L., Varejão, A. S. P., & Maurício, A. C. (2022). Peripheral Nerve Injury Treatments and Advances: One Health Perspective. International journal of molecular sciences, 23(2), 918. https://doi.org/10.3390/ijms23020918

4. Carballo Cuello CM, De Jesus O. Neurapraxia. [Updated 2023 Aug 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560501/

5. Phansopkar, P., Athawale, V., Birelliwar, A., Naqvi, W., & Kamble, S. (2020). Post-operative rehabilitation in a traumatic rare radial nerve palsy managed with tendon transfers: a case report. The Pan African medical journal, 36, 141. https://doi.org/10.11604/pamj.2020.36.141.23994

6. Latinovic, R., Gulliford, M. C., & Hughes, R. A. (2006). Incidence of common compressive neuropathies in primary care. *Journal of neurology, neurosurgery, and psychiatry*, *77*(2), 263–265. https://doi.org/10.1136/jnnp.2005.066696

7. Liu, Y., & Fox, P. M. (2024). The Role of Electrical Stimulation in Peripheral Nerve Regeneration: Current Evidence and Future Directions. Journal of hand surgery global online, 6(5), 718–721. https://doi.org/10.1016/j.jhsg.2024.01.022

8. Robb, A., & Sajko, S. (2009). Conservative management of posterior interosseous neuropathy in an elite baseball pitcher's return to play: a case report and review of the literature. The Journal of the Canadian Chiropractic Association, 53(4), 300–310.

9. Doughty, C. T., & Bowley, M. P. (2019). Entrapment Neuropathies of the Upper Extremity. *The Medical clinics of North America*, *103*(2), 357–370. https://doi.org/10.1016/j.mcna.2018.10.012

10. Węgiel, A., Karauda, P., Zielinska, N., Tubbs, R. S., & Olewnik, Ł. (2023). Radial nerve compression: anatomical perspective and clinical consequences. Neurosurgical review, 46(1), 53. https://doi.org/10.1007/s10143-023-01944-2

11. Lu, J., Zhao, Z., Pan, L., Wu, H., Wang, S., Tong, X., & Wu, S. (2025). Hyaluronidase: structure, mechanism of action, diseases and therapeutic targets. Molecular biomedicine, 6(1), 50. https://doi.org/10.1186/s43556-025-00299-y

12. Wang, K. K., Nemeth, I. R., Seckel, B. R., Chakalis-Haley, D. P., Swann, D. A., Kuo, J. W., Bryan, D. J., & Cetrulo, C. L., Jr (1998). Hyaluronic acid enhances

peripheral nerve regeneration in vivo. Microsurgery, 18(4), 270–275. https://doi.org/10.1002/(sici)1098-2752(1998)18:4<270::aid-micr11>3.0.co;2-v

13. Dy, C. J., Aunins, B., & Brogan, D. M. (2018). Barriers to Epineural Scarring: Role in Treatment of Traumatic Nerve Injury and Chronic Compressive Neuropathy. The Journal of hand surgery, 43(4), 360–367. https://doi.org/10.1016/j.jhsa.2018.01.013

14. Han, J. H., Kim, J., Yoon, K. C., & Shin, H. W. (2018). Treatment of post-traumatic hematoma and fibrosis using hyaluronidase injection. Archives of craniofacial surgery, 19(3), 218–221. https://doi.org/10.7181/acfs.2017.01396

15. Sanli, E., Dincel, G. C., & Umay, E. (2021). Effect of Local and Systemic Dimethylsulfoxide on Peripheral Nerve Repair: A Controlled Randomized Experimental Study. Journal of investigative surgery : the official journal of the Academy of Surgical Research, 34(4), 454–465. https://doi.org/10.1080/08941939.2019.1644403

16. Marren K. (2011). Dimethyl sulfoxide: an effective penetration enhancer for topical administration of NSAIDs. The Physician and sportsmedicine, 39(3), 75–82. https://doi.org/10.3810/psm.2011.09.1923

17. Evans, M. S., Reid, K. H., & Sharp, J. B., Jr (1993). Dimethylsulfoxide (DMSO) blocks conduction in peripheral nerve C fibers: a possible mechanism of analgesia. Neuroscience letters, 150(2), 145–148. https://doi.org/10.1016/0304-3940(93)90522-m

18. Laranjeira, S., Roberton, V. H., Phillips, J. B., & Shipley, R. J. (2023). Perspectives on optimizing local delivery of drugs to peripheral nerves using mathematical models. WIREs mechanisms of disease, 15(2), e1593. https://doi.org/10.1002/wsbm.1593

19. Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery. *Nature biotechnology*, *26*(11), 1261–1268. https://doi.org/10.1038/nbt.1504

20. Mao, J., & Chen, L. L. (2000). Systemic lidocaine for neuropathic pain relief. *Pain*, *87*(1), 7–17. https://doi.org/10.1016/S0304-3959(00)00229-3

21. Bahtereva, E. V., Shirokov, V. A., Leiderman, E. L., Terechov, N. L., Varaksin, A. N., & Panov, V. G. (2017). Vliianie ipidakrina (neĭromidin) na élektroneĭromiograficheskie pokazateli v usloviiakh iskusstvennoĭ kompressii (kliniko-instrumental'noe issledovanie) [An effect of ipidacrine (neuromidin) on electroneuromyographic parameters in the conditions of artificial decompression (a clinical/instrumental study)]. Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova, 117(1), 25–28. https://doi.org/10.17116/jnevro20171171125-28

22. Costigan, M., Scholz, J., & Woolf, C. J. (2009). Neuropathic pain: a maladaptive response of the nervous system to damage. Annual review of neuroscience, 32, 1–32. https://doi.org/10.1146/annurev.neuro.051508.135531

23. Danilov, A. B., Devlikamova, F. I., Kurushina, O. V., Karakulova, Y. V., Butko, D. Y., & Smirnova, A. A. (2024). Otsenka effektivnosti Neiromidina pri lechenii bolevogo sindroma u patsientov s diskogennoi poyasnichno-kresttsovoi radikulopatiei: rezul'taty mnogotsentrovogo postregistratsionnogo prospektivnogo otkrytogo sravnitel'nogo issledovaniya [Efficiency evaluation of the Neuromidin in the treatment of pain of the patients with discogenic lumbosacral radiculopathy: results of a multicenter post-registration prospective open comparative trial]. Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova, 124(4), 97–107. https://doi.org/10.17116/jnevro202412404197

24. Tekes K. (2014). Basic aspects of the pharmacodynamics of tolperisone, a widely applicable centrally acting muscle relaxant. The open medicinal chemistry journal, 8, 17–22. https://doi.org/10.2174/1874104501408010017

25. Stamenova, P., Koytchev, R., Kuhn, K., Hansen, C., Horvath, F., Ramm, S., & Pongratz, D. (2005). A randomized, double-blind, placebo-controlled study of the efficacy and safety of tolperisone in spasticity following cerebral stroke. European journal of neurology, 12(6), 453–461. https://doi.org/10.1111/j.1468-1331.2005.01006.x

26. Hofer, D., Lohberger, B., Steinecker, B., Schmidt, K., Quasthoff, S., & Schreibmayer, W. (2006). A comparative study of the action of tolperisone on seven different voltage dependent sodium channel isoforms. European journal of pharmacology, 538(1-3), 5–14. https://doi.org/10.1016/j.ejphar.2006.03.034

27. Vaughan, S. A., Torres, K., & Kaye, R. (2022). RESUME-1: a Phase III study of tolperisone in the treatment of painful, acute muscle spasms of the back. Pain management, 12(1), 25–33. https://doi.org/10.2217/pmt-2021-0041

28. Gordon T. (2009). The role of neurotrophic factors in nerve regeneration. Neurosurgical focus, 26(2), E3. https://doi.org/10.3171/FOC.2009.26.2.E3

29. Shamrock AG, Das JM. Radial Tunnel Syndrome. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555937/

30. Bodian, C. A., Freedman, G., Hossain, S., Eisenkraft, J. B., & Beilin, Y. (2001). The visual analog scale for pain: clinical significance in postoperative patients. Anesthesiology, 95(6), 1356–1361. https://doi.org/10.1097/00000542-200112000-00013