Title: High-Purity Type I Collagen Nerve Wrapping in Peripheral Nerve Procedures: A Prospective Registry

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INTRODUCTION

Peripheral nerve injuries and compressive neuropathies constitute a significant cause of long-term functional impairment, chronic pain, and disability worldwide. Despite substantial advances in microsurgical techniques, including tension-free nerve repair, refined coaptation methods, and improved magnification, functional recovery following peripheral nerve surgery remains highly variable and often suboptimal, particularly in complex clinical scenarios such as delayed repairs, revision decompressions, nerve grafting, and nerve transfers [1,2]. The disparity between technical success and functional recovery underscores the importance of biological factors that govern nerve healing beyond surgical precision alone.

One of the principal biological impediments to successful nerve regeneration is perineural fibrosis, which develops as part of the normal wound-healing response following nerve injury or surgical manipulation. Excessive fibroblast proliferation and disorganized collagen deposition within the perineural environment result in circumferential scarring that restricts nerve gliding, compromises intraneural microcirculation, and alters axonal regeneration dynamics [3,4]. This fibrotic tethering not only limits functional recovery but is also strongly associated with persistent neuropathic pain and recurrent symptoms following nerve decompression procedures [5,6].

The pathophysiology of impaired nerve regeneration is multifactorial and involves a complex interplay between Schwann cell activity, axonal sprouting, angiogenesis, extracellular matrix (ECM) remodelling, and inflammatory modulation [7]. While Schwann cells play a central role in guiding axonal regrowth and remyelination, their function is highly dependent on the surrounding ECM architecture and mechanical environment [8]. Disruption of this microenvironment by dense scar tissue interferes with axonal guidance, delays remyelination, and increases susceptibility to conduction block and neuroma formation [9].

To address these challenges, various strategies have been explored to modulate the perineural healing environment, including vein wrapping, adipofascial flaps, synthetic nerve wraps, and barrier membranes [10–12]. Although these techniques may reduce adhesion formation, their widespread adoption has been limited by factors such as donor-site morbidity, inconsistent availability, foreign body reactions, inflammatory responses, and unpredictable degradation profiles [13,14]. Consequently, there has been growing interest in biologically derived, resorbable materials that combine mechanical barrier function with active biological support for nerve regeneration.

High-purity type I collagen (HPTC) represents a novel class of bioengineered collagen-based biomaterials designed to function not merely as passive barriers but as biologically active scaffolds that support organized tissue regeneration. Type I collagen is the predominant structural protein of native ECM and plays a critical role in cellular adhesion, migration, angiogenesis, and matrix remodelling during tissue repair [15,16]. When processed to high purity with removal of antigenic components, collagen matrices demonstrate excellent biocompatibility, controlled biodegradation, and minimal immunogenicity [17].

HPTC (Surgicoll-Mesh®) is an acellular, high-purity (>97%) type I collagen membrane manufactured through a proprietary purification process that preserves the native triple-helical collagen structure while eliminating inflammatory and antigenic residues [18]. This structural integrity enables HPTC to closely mimic native ECM, providing an optimal scaffold for Schwann cell alignment, axonal guidance, and neovascularization. Unlike synthetic materials, HPTC undergoes gradual enzymatic degradation, allowing progressive replacement by organized host tissue rather than dense scar formation [19].

The regenerative potential of HPTC has been demonstrated across multiple clinical contexts. Randomized controlled trials and prospective studies have shown that HPTC significantly improves healing rates, tissue quality, and functional outcomes in diabetic foot ulcers, venous leg ulcers, pressure ulcers, and complex reconstructive applications [18–22]. Notably, several studies by the present authors have consistently demonstrated the anti-fibrotic, pro-angiogenic, and regenerative properties of HPTC in breast reconstruction, peritoneal repair, Z-plasty scar modulation, and full-thickness wound management, with reproducible clinical benefit across diverse tissue environments [20–24].

Despite this growing body of evidence, the application of HPTC as a circumferential nerve wrap in peripheral nerve surgery remains relatively underexplored. The theoretical rationale for its use in nerve surgery is compelling. By providing a temporary, resorbable perineural barrier, HPTC may reduce adhesion formation and mechanical tethering, while its biologically active collagen scaffold may facilitate Schwann cell migration, promote angiogenesis, and support organized axonal regeneration [25–27]. Importantly, such an approach addresses both the mechanical and biological determinants of nerve healing.

Electrophysiological recovery, as assessed by nerve conduction velocity (NCV) and electromyography (EMG), offers an objective and sensitive means of evaluating early axonal regeneration and remyelination, often preceding overt clinical recovery [28,29]. Improvements in NCV reflect restoration of myelin integrity and axonal maturation, while EMG provides insight into motor unit recruitment and reinnervation patterns. The

incorporation of electrophysiological endpoints is therefore critical for validating the biological efficacy of regenerative adjuncts such as HPTC.

The present prospective multicentre registry was designed to generate real-world evidence on the safety, feasibility, and early outcomes of HPTC nerve wrapping across a broad spectrum of peripheral nerve procedures. By integrating clinical, patient-reported, and electrophysiological endpoints, this study aims to provide a comprehensive evaluation of HPTC as a biologically effective adjunct in peripheral nerve surgery.

MATERIALS AND METHODS

Study Design and Setting

This study was conducted as a prospective, multicentre, observational registry designed to evaluate early clinical, functional, and electrophysiological outcomes following the use of high-purity type I collagen (HPTC) nerve wrapping in peripheral nerve surgery. The registry was implemented across two tertiary referral centres in India – Adichunchangiri Institute of Medical Sciences, B G Nagara and Mysore Medical College and Research Institute, Mysuru. The study was conceived as a real-world outcomes' registry rather than a randomized controlled trial, with the objective of capturing effectiveness, safety, and biological response in routine clinical practice. The trial was registered prospectively with ClinicalTrials.gov (ID: NCT07360730) and approved by the Institutional Ethics Committee (Approval No.: AIMS/IEC/269/2025).

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional Ethics Committee approval was obtained at each participating centre prior to initiation of patient recruitment. Written informed consent was obtained from all participants after detailed explanation of the study objectives, procedures, risks, and benefits.

Patient Selection

Adult patients aged 18 to 70 years undergoing peripheral nerve surgery were screened for inclusion. Eligible procedures included primary nerve repair, nerve coaptation, nerve grafting, nerve transfer, and primary or revision nerve decompression involving upper or lower limb peripheral nerves. Inclusion required the intraoperative use of HPTC as a circumferential nerve wrap following completion of the primary nerve procedure.

Exclusion criteria included active infection at the operative site, known hypersensitivity to collagen or bovine-derived products, pregnancy or lactation, severe uncontrolled systemic illness, immunosuppressive therapy, malignancy involving the nerve or surrounding tissue, and re-operation at the same nerve site within the preceding six months. Patients unable to comply with postoperative rehabilitation or follow-up assessments were also excluded.

Surgical Technique and Application of HPTC

All procedures were performed under loupe or operating microscope magnification by experienced peripheral nerve surgeons. Following completion of the primary nerve

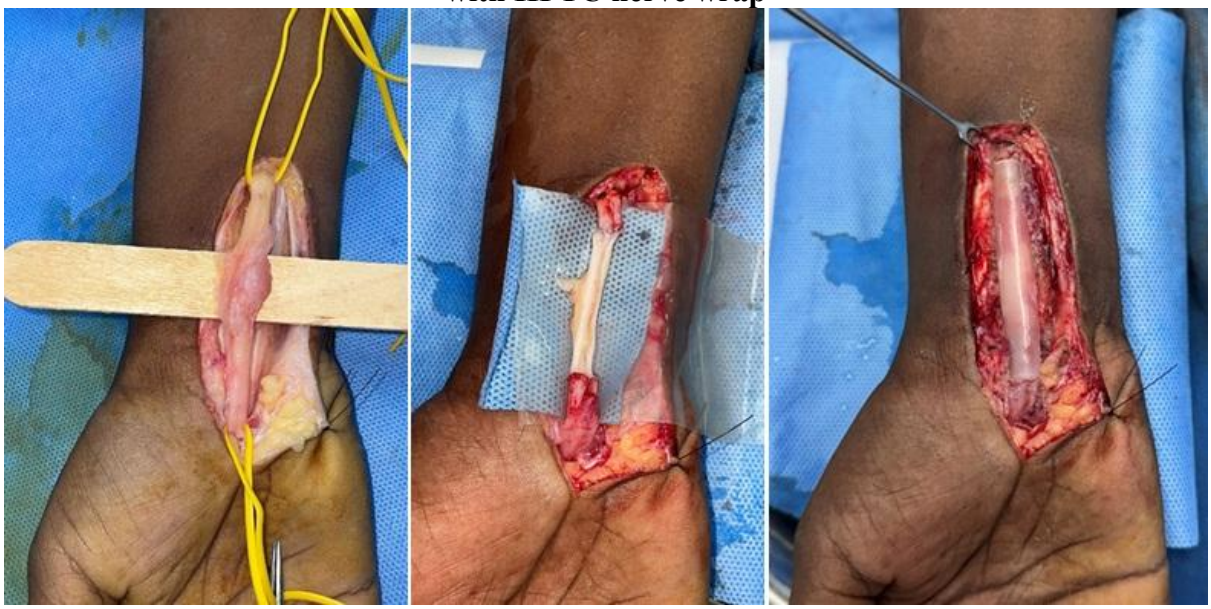
procedure, meticulous haemostasis was achieved to minimize postoperative inflammation and scar formation. Care was taken to avoid excessive manipulation of the nerve and surrounding tissues.

A sterile HPTC (Surgicoll-Mesh®) [30] was hydrated in normal saline according to manufacturer instructions. The membrane was trimmed to correspond to the length of the repaired, grafted, transferred, or decompressed nerve segment, typically ranging from 1.5 to 4.0 cm. The HPTC sheet was then applied circumferentially around the nerve as a loose perineural sleeve, ensuring that the wrap did not exert compressive forces or restrict physiological nerve excursion.

Fixation was achieved using fibrin glue or fine absorbable sutures placed sparingly at the edges of the wrap. Particular attention was paid to maintaining a non-constrictive configuration to preserve intraneural microcirculation and facilitate postoperative nerve gliding (Figure 1-3).

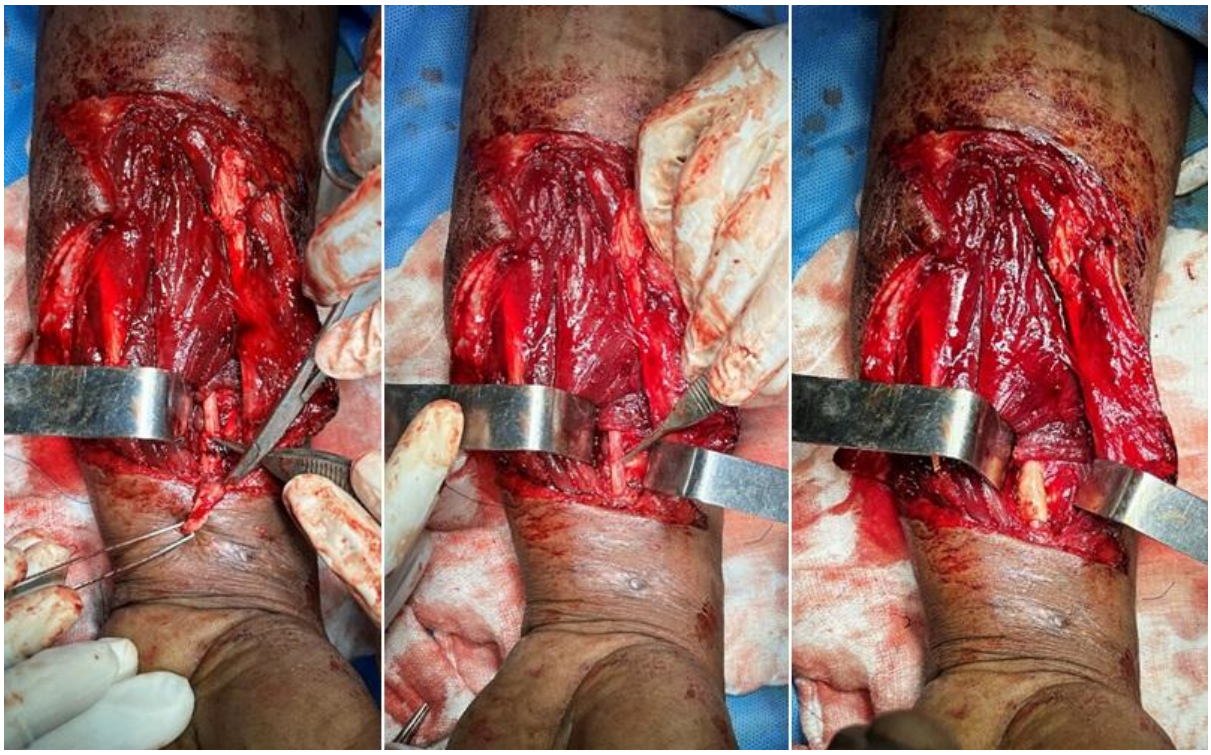
Standard wound closure was performed in layers, and all patients followed institution-specific postoperative rehabilitation protocols tailored to the type of nerve procedure performed.

Figure 1. Neuroma-in-continuity excision and interposition cable sural nerve grafting with HPTC nerve wrap



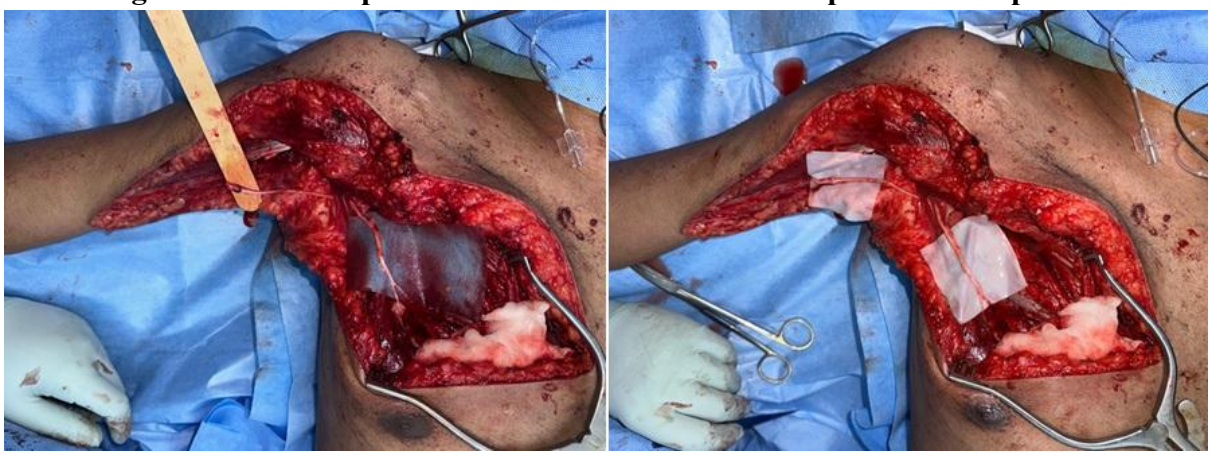
Intraoperative sequence demonstrating neuroma-in-continuity of median nerve. The pathological neuroma segment was excised to healthy fascicular ends, followed by reconstruction using multiple cable sural nerve grafts to bridge the defect. The proximal and distal coaptation sites and grafted segment were circumferentially wrapped with a hydrated high-purity type I collagen (HPTC) membrane applied as a loose, non-constrictive perineural sleeve to provide a biologic anti-adhesion barrier and regenerative scaffold prior to wound closure.

Figure 2: Traumatic median nerve repair with collagen nerve wrap augmentation



Intraoperative images of a traumatic median nerve injury. Following debridement and tension-free epineurial coaptation, the repair site was covered with a hydrated high-purity type I collagen (HPTC) sheet circumferentially wrapped around the coaptation zone. The collagen wrap was secured in a loose configuration to avoid compression while isolating the repair from surrounding tissues to reduce perineural fibrosis and support organized regeneration.

Figure 3: Brachial plexus nerve transfer with HPTC-protected coaptation



Nerve transfer for brachial plexus injury. After donor-to-recipient nerve coaptation, the neurorrhaphy sites were covered with hydrated high-purity type I collagen (HPTC) membranes placed circumferentially over each coaptation zone. The collagen scaffold was applied as a protective biologic sleeve to minimize scar adherence and facilitate axonal regeneration within the plexus bed prior to layered closure.

Outcome Measures

The primary outcome of the study was motor recovery assessed using the Medical Research Council (MRC) grading system at six months postoperatively. Successful motor recovery was predefined as achievement of MRC grade M3 or higher, reflecting antigravity muscle function with active movement.

Secondary outcomes included sensory recovery assessed using static and moving two-point discrimination and Semmes–Weinstein monofilament testing, neuropathic pain evaluated using the Visual Analog Scale (VAS), patient-reported functional outcomes measured using the Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire for upper limb nerves and the Lower Extremity Functional Scale (LEFS) for lower limb nerves, electrophysiological recovery assessed by nerve conduction velocity (NCV) and electromyography (EMG), and incidence of postoperative complications.

Electrophysiological Assessment Protocol

Electrophysiological evaluation was incorporated as a predefined secondary outcome to provide objective evidence of axonal regeneration and remyelination. Standardized nerve conduction studies and needle electromyography were performed at baseline, two months, and four months postoperatively by experienced neurophysiologists blinded to procedural type and clinical outcomes [31,32].

Nerve conduction velocity was measured across the involved nerve segment using surface electrodes placed proximal and distal to the surgical site. Standardized stimulation parameters were used to record compound muscle action potentials, and NCV was calculated in meters per second. Improvements in NCV were interpreted as indicative of remyelination and axonal maturation [33].

Needle electromyography was performed in muscles innervated by the treated nerve to assess spontaneous activity, motor unit potential morphology, and recruitment patterns. A composite reinnervation score on a standardized five-point scale was used, incorporating reduction in fibrillation potentials, emergence of polyphasic motor unit potentials, and improvement in recruitment. EMG changes were interpreted as evidence of axonal continuity and motor unit reinnervation [34].

Sample Size

The target enrolment of 40 patients was based on a pragmatic feasibility estimate for a multicentre registry. Assuming a historical recovery rate of 65% and a minimum detectable

difference of 20 percentage points at 85% power with a two-sided α of 0.05, a minimum of 37 patients was required, yielding a planned enrolment of 40 patients to account for potential attrition.

Data Collection and Follow-Up

Baseline demographic data, comorbidities, nerve type, procedure performed, and operative details were recorded prospectively. Clinical assessments were conducted at regular postoperative intervals, including one month, three months, and six months. Electrophysiological assessments were performed at two and four months to capture early biological recovery preceding overt clinical improvement.

Pain scores and patient-reported outcome measures were collected using validated instruments administered by trained personnel. All data were recorded in standardized case report forms and entered into a secure registry database with predefined quality checks.

Statistical Analysis Plan

Statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). The statistical analysis plan was defined a priori. All enrolled patients who received HPTC nerve wrapping were included in the analysis. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. The primary outcome proportion of patients achieving MRC grade ≥ M3 at six months was compared against historical recovery benchmarks reported in the literature using a one-sample proportion Z-test [35]. Ninety-five percent confidence intervals were calculated for the observed proportion. Longitudinal changes in pain scores, electrophysiological parameters, and functional outcomes were analyzed using repeated-measures analysis of variance or equivalent non-parametric tests where appropriate [36]. Paired t-tests were used to assess within-patient changes between baseline and follow-up time points. Effect sizes were calculated using Cohen's h for proportions, Cohen's d for continuous outcomes, and partial eta-squared for repeated-measures analyses to quantify the magnitude of observed effects independent of sample size [37]. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using standard statistical software packages commonly employed in clinical research.

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