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Barriers to Epineural Scarring: Role in Treatment of Traumatic Nerve Injury and Chronic Compressive Neuropathy

Christopher J. Dy, MD MPH[a,b], **Benjamin Aunins**[a], and **David M. Brogan, MD, MSc**[a]

[a]Department of Orthopaedic Surgery, Division of Hand and Upper Extremity Surgery, Washington University School of Medicine, 660 S. Euclid Ave, Campus Box 8233 St. Louis, MO,USA 63110

[b]Department of Surgery, Division of Public Health Sciences, Washington University School of Medicine, 660 S. Euclid Ave, St. Louis, MO, USA 63110

Abstract

The physiologic limitations of neural regeneration make peripheral nerve surgery challenging to both the surgeon and the patient. Presence of nerve gaps and local wound factors may all influence outcome, suggesting that barriers to reduce perineural scarring, minimize fibrosis, and avoid ischemia would be beneficial. To examine the evidence supporting their use, we reviewed the autologous and commercially-available options for barriers against scarring around a nerve. Numerous clinical case series demonstrated the effectiveness and safety of local/rotational flaps and autologous vein wrapping when used in the presence of recurrent compressive neuropathy. Translational research in animal models support the biocompatibility of commercially-available nerve wraps following nerve repair. To date, there are no reports of clinical use of commercially-available nerve wraps in acute nerve repair, but a growing number of case series demonstrate their effectiveness and safety in chronic compressive neuropathy. Limited clinical evidence exists to support the efficacy of flap coverage in acute nerve repairs, including the use of vein.

Keywords

Nerve wrap; nerve repair; compressive neuropathy; epineural scarring; cicatrix; recurrent carpal tunnel; recurrent cubital tunnel; neuropathic pain

Rationale for use of barriers to epineural scarring

When performing nerve repair, a favorable soft tissue envelope intuitively would seem to minimize the chances of ischemia and scar formation that can impede neural regeneration. In the case of revision surgery for chronic compressive neuropathy, surgery in an already-scarred tissue bed can create additional adhesions that lead to eventual symptom recurrence and traction-related pain. Ideally, a barrier could be used to promote nerve gliding and

*Correspondence (Corresponding Author), Christopher J. Dy, MD MPH, dyc@wustl.edu, 660 S. Euclid Ave, Campus Box 8233, St. Louis, MO,USA 63110, +1(314) 747-2535 phone, +1(314) 747-2599 fax.

reduce scarring around the nerve, without proliferation of extraneural fibrosis and scarring. Scientists and surgeons have provided innovative solutions, ranging from synthetic and xenograft materials to autologous vein wrapping and pedicled/free tissue coverage. There is no clear guidance on which barriers provide the best results in either the acute or chronic situations, or the indications for their use.

We conducted a review of the published literature regarding perineural scarring and barriers. A search was conducted in Ovid Medline (1946-present), Embase (1946-present), Clinical Trials database, Cochrane Databases, Scopus (1823-present), Science Citation Index (1900-present). 8841 unique citations were filtered to 47 articles based on article titles and abstracts, with 20 articles included here to support our discussion and promote ongoing dialogue on this topic.

The ideal barrier

The ideal barrier to perineural scarring should have the following characteristics: (1) minimal or no chance of rejection or inflammatory reaction; (2) sufficient porosity to facilitate diffusion of nutrients without allowing axonal escape; (3) avoidance of scar induced ischemia; (4) promote nerve gliding; (5) minimal or no donor site morbidity; (6) minimal cost or supply restraints (Table 1).[1]

Types of barriers available

Adipofascial or muscle flap (pedicle or free tissue)

The concept of using local tissues to provide a barrier around a nerve has been promoted extensively in the treatment of recurrent carpal tunnel syndrome (CTS) and cubital tunnel syndrome (CuTS). While incomplete release of the transverse carpal ligament during carpal tunnel release (CTR) or newly-created points of compression of the transposed ulnar nerve are common reasons for revision surgery, another frequent finding during revision surgeries for both CTS and CuTS is adherence of the nerve to the surrounding tissues. Soltani, et al performed a systematic review for surgical treatment of recurrent carpal tunnel syndrome.[2] Of the 14 articles describing rotational or free flap coverage options, 7 discussed hypothenar fat pad or ulnar artery-based perforator flaps. Additional options include other rotational flaps (synovium, pronator quadratus, palmaris brevis, abductor digiti minimi, radial artery perforator) and free flaps (omentum and anterolateral thigh flaps). Of all options for flap coverage in revision carpal tunnel release, we prefer the hypothenar fat pad flap because of minimal morbidity and reliable blood supply (Figures 1A–1C). In the meta-analysis of 14 studies (n=294) using flap coverage during revision CTR, there was an 86% success rate. This was substantially higher than the 74% success rate seen in patients treated with decompression alone (7 studies; n=364). More recently, Pace, et al performed an unmatched, retrospective cohort study of patients who underwent flap interposition or decompression only during revision CTR.[3] The authors did not detect a difference in outcomes, but they did not report a power analysis.[3] With regard to recurrent CuTS, there is little evidence-based guidance in the literature about the type of procedure to use during revision cases. We have found that perineural fibrosis may form after any of the procedures used for primary treatment. Submuscular transposition provides a reliable gliding surface for the ulnar nerve,

provided that new points of compression are not created. The decision about whether to add an additional barrier to scarring around the nerve is described in more detail below. With regard to nerve repairs, we are unaware of any published series dedicated to examining outcomes of flap coverage of repaired nerves alone.

Autologous vein wraps

Veins provide an ideal surface to place around a nerve after it has been repaired or dissected from scar, as it is biologically compatible and vein intima provides a gliding surface (Figure 2A–2E). In a rat sciatic nerve compressive neuropathy model, Xu, et al demonstrated gliding of the vein wrap along the nerve trunk, improvement in electrophysiologic testing, and less scarring on histologic examination in nerves wrapped with autologous vein compared to controls.[4] Murakami, et al also noted decreased perineural scarring in a rat compressive neuropathy model after vein wrapping.[5] Since the concept was introduced by Masear in 1989 for the treatment of recurrent tarsal tunnel syndrome, there have been numerous case series describing the effectiveness of autologous vein wraps in treatment of recurrent CTS[6] and CuTS[7]. The potential disadvantages of using autologous vein wraps include donor site morbidity (including swelling), as well as increased operative time and technical difficulty if adequate assistance is not available. Promising results with vein allografts have been reported, but availability in the United States is limited. There are no clinical studies comparing patients with compressive neuropathy treated with vein wraps to either control patients or other types of nerve barriers. Regarding nerve repair, there is a single case series describing vein wrapping after nerve repair – Sadek, et al reported that patients with saphenous vein wrapping of ulnar nerve repairs had improved motor, sensory, and electrophysiologic recovery compared to unmatched historical controls.[8]

Commercially-available nerve wraps

Many of the commercially-available nerve wraps are comprised largely of collagen, the main component of the extracellular matrix, and are similar in material composition to nerve conduit products. Type 1 collagen is an appealing material to use as a nerve wrap, as it has a long track record of biocompatibility and has selective permeability (Table 2). The biocompatibility of these wraps has been demonstrated in laboratory testing of nerve repair conduits composed of the same material. The most commonly-used source for the Type 1 collagen wraps is bovine tendon, with a degradation time ranging from 4–8 months. There is limited laboratory evidence demonstrating the efficacy or safety of these wraps following nerve repair. In a rat sciatic nerve model, Lee, et al[9] demonstrated decreased perineural scarring compared to controls, but no difference in axon counts or density. To our knowledge, there are no clinical reports of Type 1 collagen wrap use after nerve repair. While there are no laboratory models of Type 1 collagen wrap use in compressive neuropathy, recent clinical series have described use of Type 1 collagen wraps after revision CTS cases. Kokkalis, et al described two cases with clinical improvement and no signs of intolerance or complications.[10] Additionally, Soltani, et al used a Type 1 collagen wrap in 9 recurrent CTS and 6 recurrent CuTS cases; all but 2 patients demonstrated improvement in symptoms. There were no reoperations or signs of collagen wrap intolerance in the series.[11]

Porcine small intestine submucosa, composed of both Types 1 and 3 collagen, has recently been developed for use as both a nerve conduit and nerve wrap (Table 2). The advantage of this material is that it retains its ability to serve as an extracellular matrix scaffold for the regenerating nerve. Like all xenografts, concerns arise from potential immune response or transmission of infectious disease. Processing techniques have been successful in allowing porcine xenograft implantation without clinically obvious rejection. Pertici, et al circumferentially sutured a porcine-derived nerve wrap around an acutely-repaired rat peroneal nerve.[12] There were no differences in functional or histologic measures among the repair-only, repair+wrap, and repair+fibrin glue cohorts at final follow-up. Although there was an increased histologic grade of inflammatory reaction in the repair+wrap group compared to repair+fibrin glue at 1 month post-repair, no difference was observed at 3 months post-repair. The authors attributed the initial difference to degradation of the wrap, which was complete by 3 months. In the only study that compared two different nerve barriers, Mathieu, et al demonstrated that a porcine-derived nerve wrap more effectively reduced intraneural fibrosis than vein wrapping in a rat sciatic nerve repair model[13]. Although the nerve wrap used by Pertici[12] and Mathieu[13] is (1) different from the porcine wrap available in the United States and (2) applied in rats, the lessons regarding porcine xenograft biocompatibility may hold value. To our knowledge, there are no clinical reports of porcine-derived nerve wrap use in association with acute nerve repair. Papatheodorou, et al recently described the use of the porcine wrap in a case series of 12 patients with recurrent CuTS.[14] There were no adverse reactions or complications, and all patients had clinical improvement in patient-reported outcomes and grip strength.

While not specifically designed, marketed, or FDA-indicated for use as a perineural barrier to scarring, hyaluronic acid-carboxymethylcellulose film (HA-CMC) has been examined in both clinical and laboratory studies. Hyaluronic acid is a component of the extracellular membrane and contributes to wound healing and nerve regeneration. Mixing the hyaluronic acid with CMC slows the resorption of the HA, allowing it to exert its effect over a longer period of time (commercially-available HA-CMC films typically absorb within 7 days). The benefits of HA-CMC membranes have also been demonstrated in preventing restrictive adhesions in a chicken flexor tendon model[15] and in reducing the incidence, extent, and severity of postoperative abdominal adhesions.[16] In a rat sciatic nerve model, Magill, et al noted less perineural scarring on histomorphometric and stereological analyses after a commercially-available HA-CMC film (Seprafilm; Genzyme, Cambridge, MA, USA) was wrapped around a rat sciatic nerve after injury and repair,[17] relative to a control group. This study also included a non-injury phase in which the HA-CMC film was placed onto, or wrapped around, an intact nerve; no significant differences were found compared to a control group, suggesting that it is biocompatible.[17] To our knowledge, there are no clinical data in the peer-reviewed literature demonstrating the efficacy of HA-CMC films used for acute nerve repair or chronic compressive neuropathy.

Human amniotic membrane wraps have also been described as a barrier to perineural fibrosis. Laboratory studies using human amniotic membrane wraps in a rabbit model demonstrate less perineural fibrosis and adhesion compared to controls.[18] To our knowledge, there are no clinical reports of amnionic membrane wrap use in the nerve injury setting. Gaspar, et al reported the use of a commercially-available amniotic membrane wrap (XWrap

Dry; Applied Biologics, Scottsdale, AZ) during 8 revision cubital tunnel cases.[19] There were no signs of adverse reactions or complications reported, and all patients had clinical improvement in patient-reported outcomes and grip strength. However, preliminary results using amniotic wraps placed around repaired flexor tendons demonstrated unfavorable results with inflammatory responses and local fibrosis.[20] FDA indications for XWrap do not include use as a barrier to nerve adhesion.

Author preferences

For recurrent CTS, our preference is to use the hypothenar fat pad flap if intraoperative inspection demonstrates scarring of the median nerve to the surrounding tissue. If the transverse carpal ligament has reconstituted and there is no perineural fibrosis, we will perform a decompression only. For CuTS, our preference is to perform a submuscular ulnar nerve transposition (with a very loose approximation of the flexor-pronator fascia) to provide a favorable environment for the ulnar nerve. We will apply an autologous vein wrap if a submuscular transposition has already been performed and there is epineural fibrosis on intraoperative inspection. For nerve repairs, we do not routinely use any of the commercially-available scar barriers due to the absence of laboratory or clinical evidence of commercially-available barriers for primary nerve repair. If the nerve coaptation will be vulnerable to traction from surrounding structures, we will use an autologous vein wrap or local/rotational soft tissue flap for coverage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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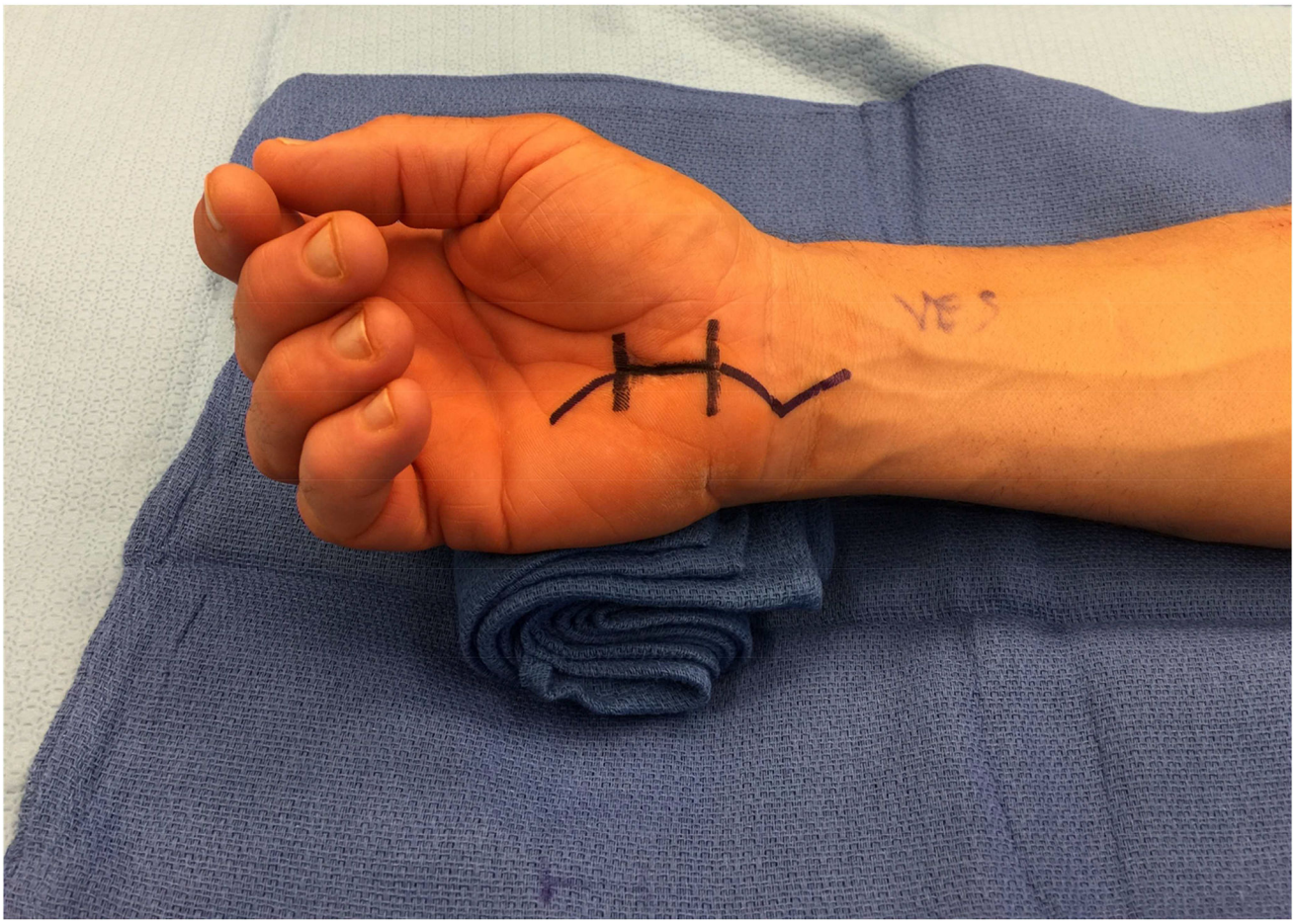
A



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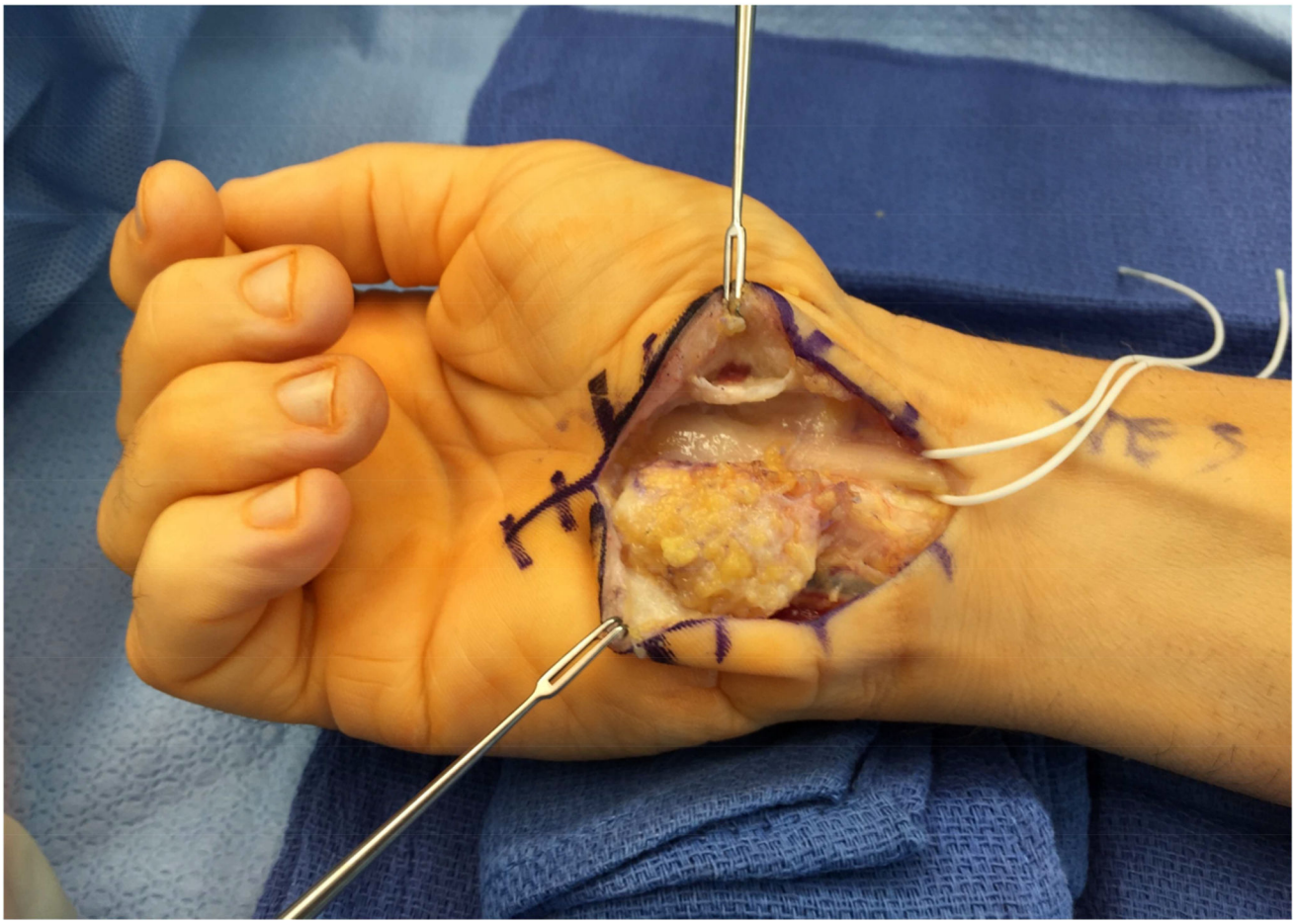


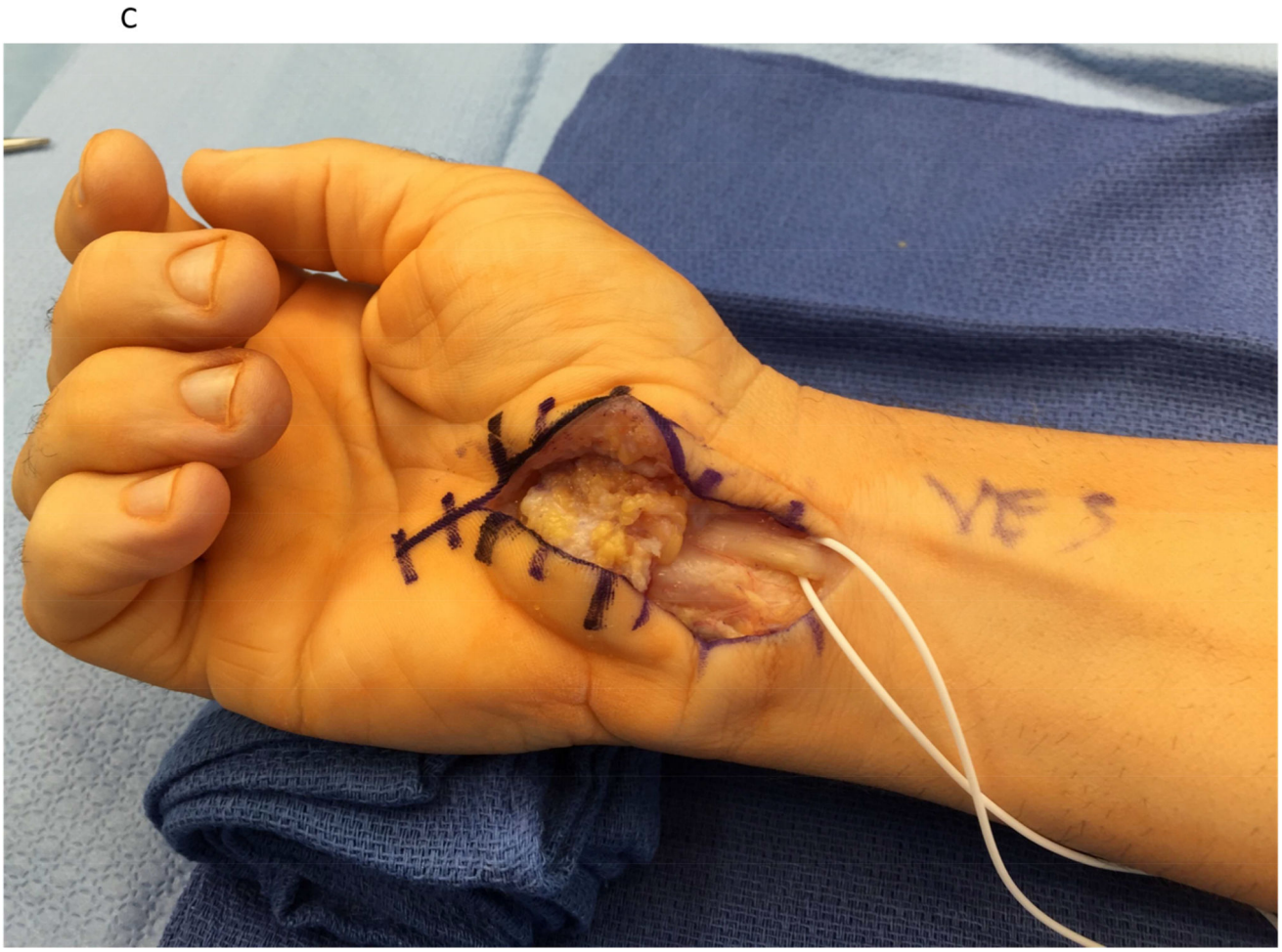
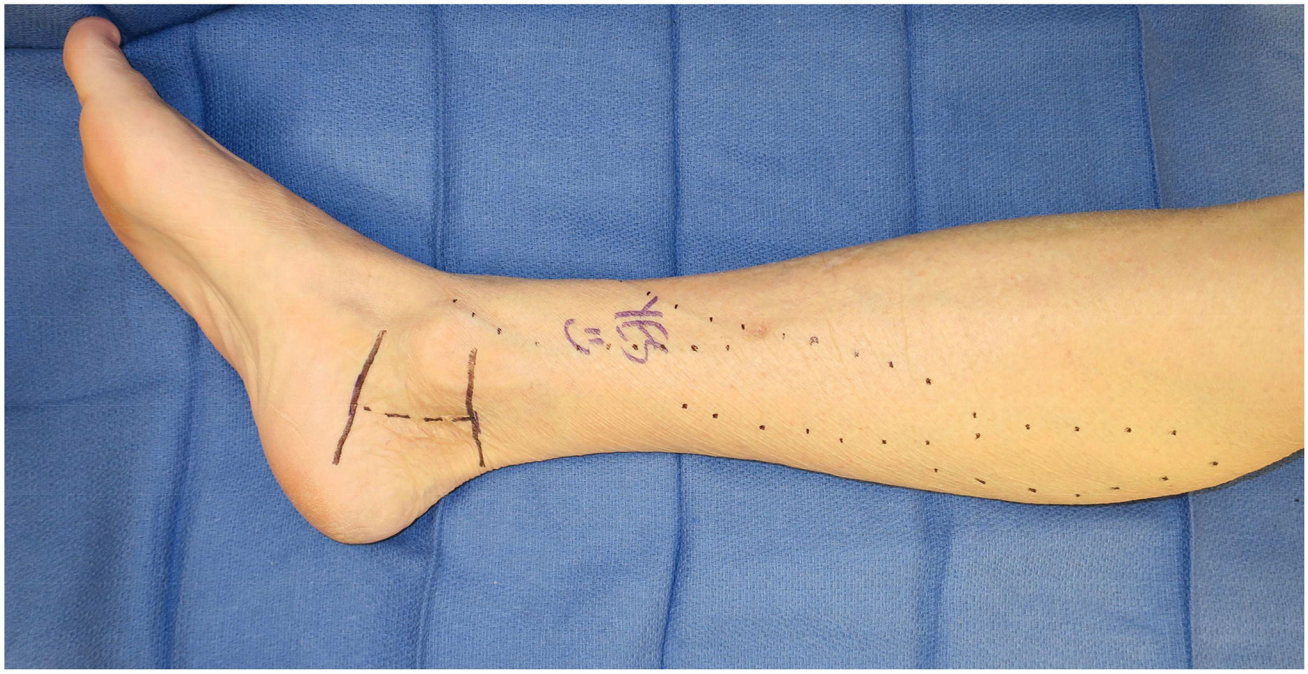


Figure 1.

A hypothenar fat pad flap was used as a protective barrier in a case of recurrent carpal tunnel syndrome. (1A) The prior skin incision is marked with the transverse lines and is extended proximally and distally. (1B) The hypothenar fat pad is dissected from the overlying skin of the palm, preserving its vascular supply from the ulnar artery. The transverse carpal ligament has been re-released. (1C) The hypothenar fat pad has been placed over the median nerve and loosely secured to the radial leaflet of the transverse carpal ligament.

A



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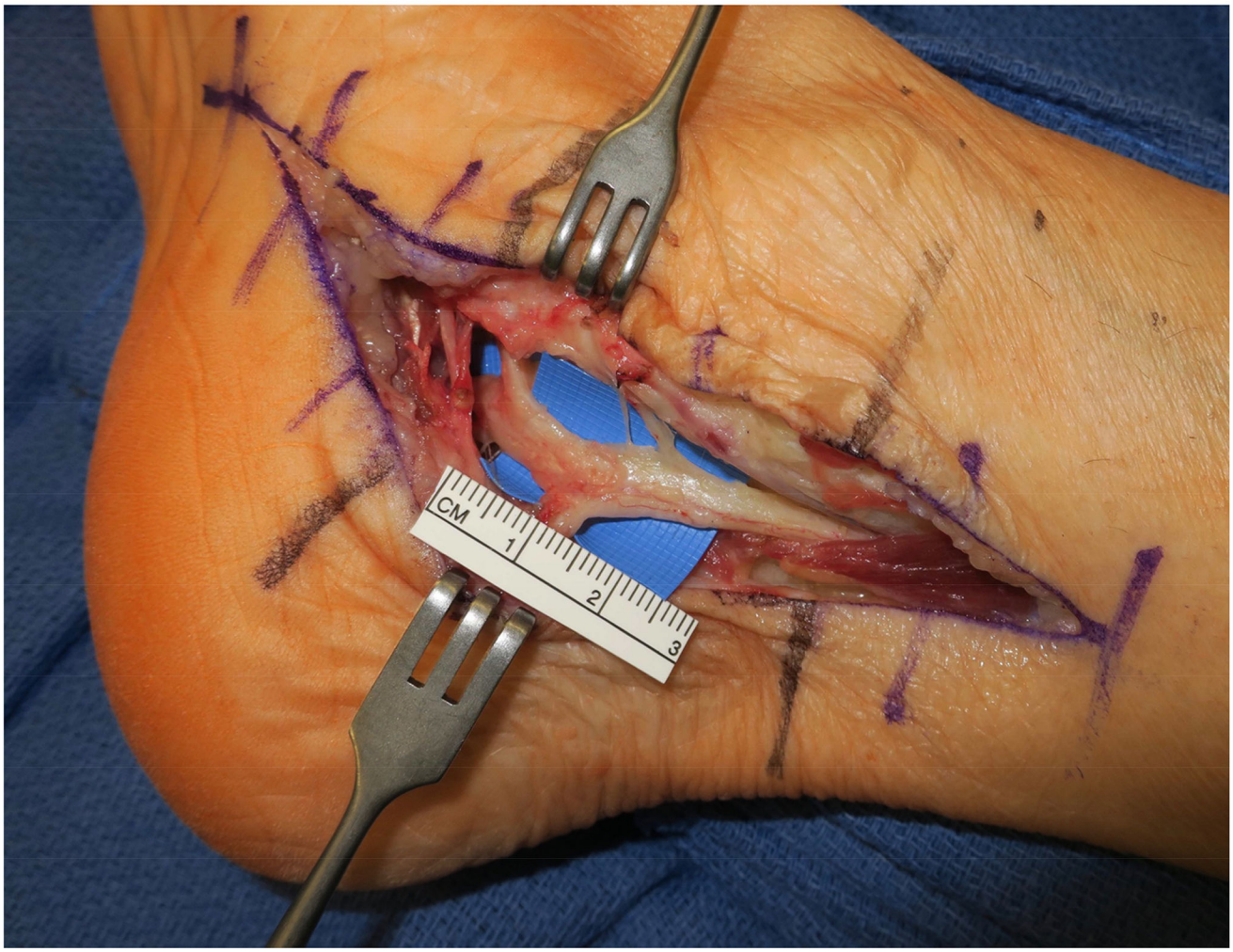

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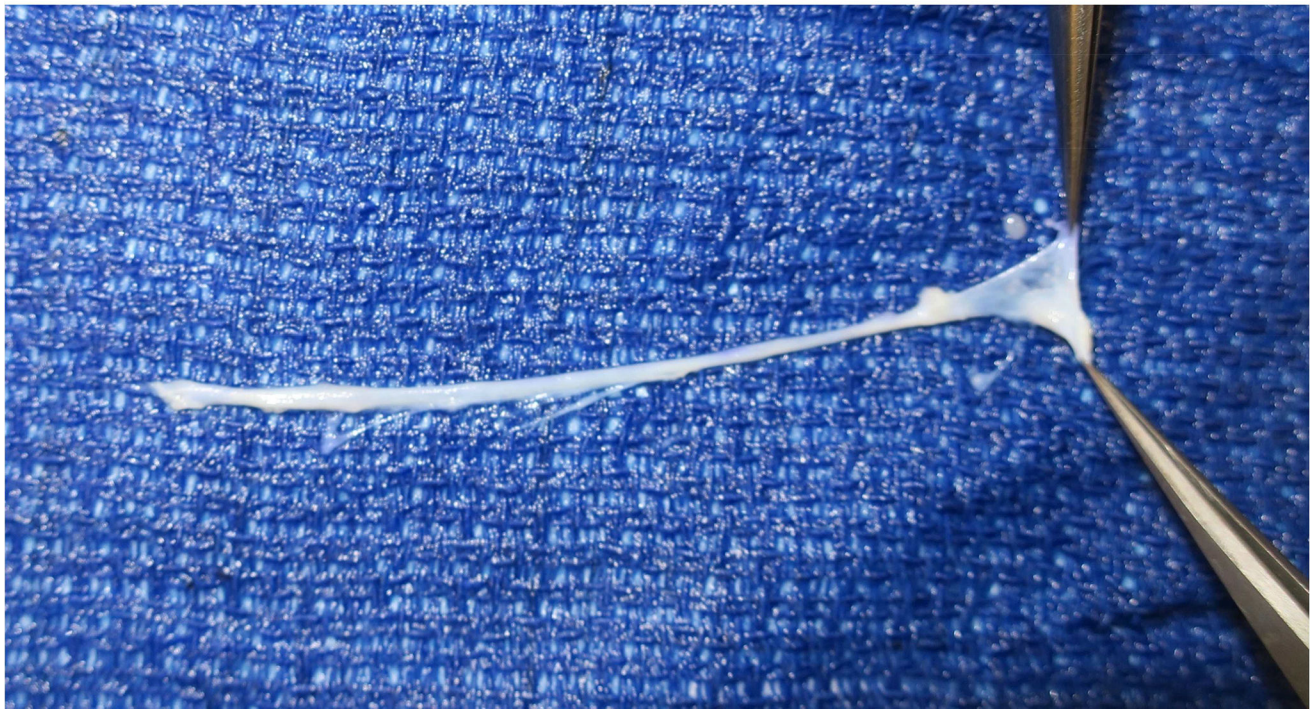

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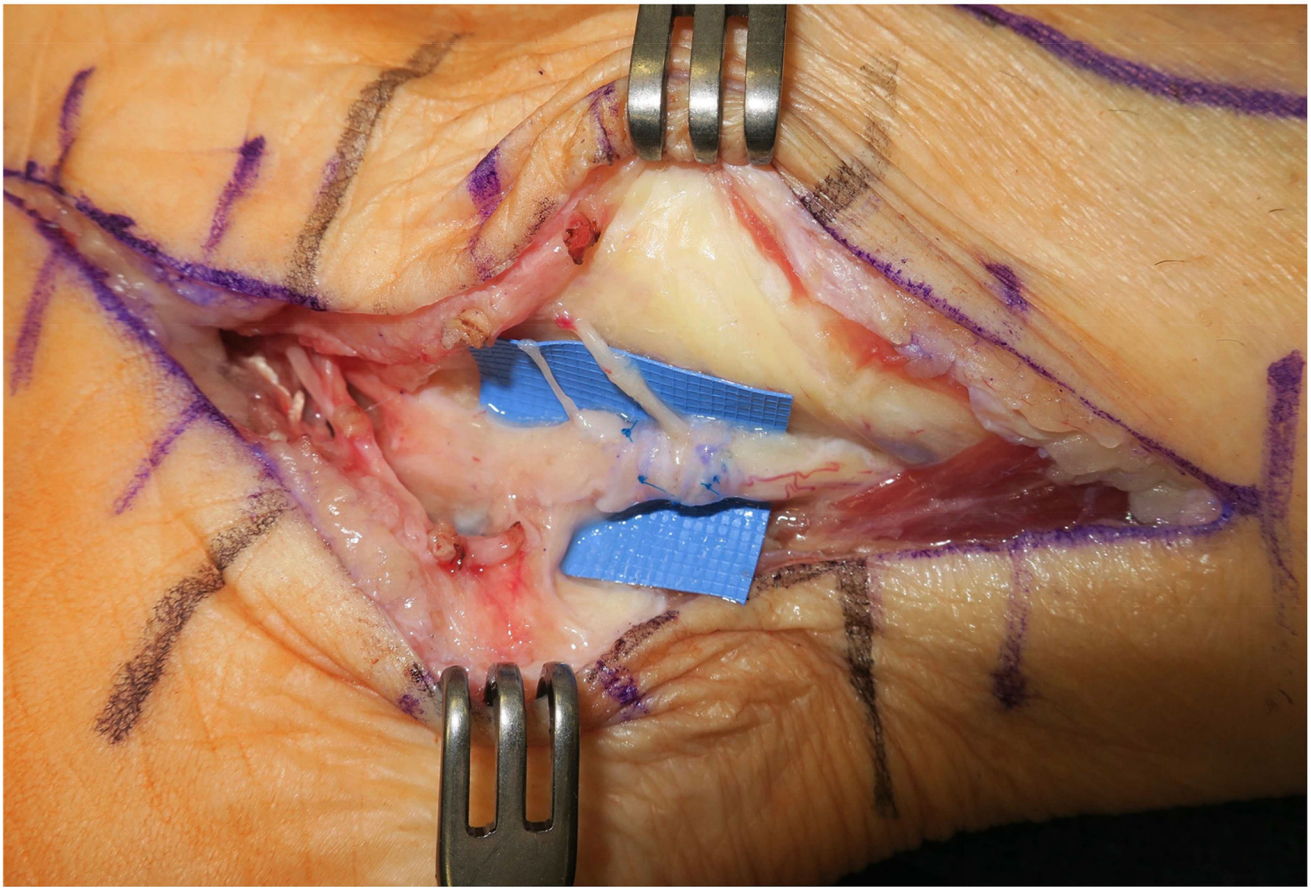

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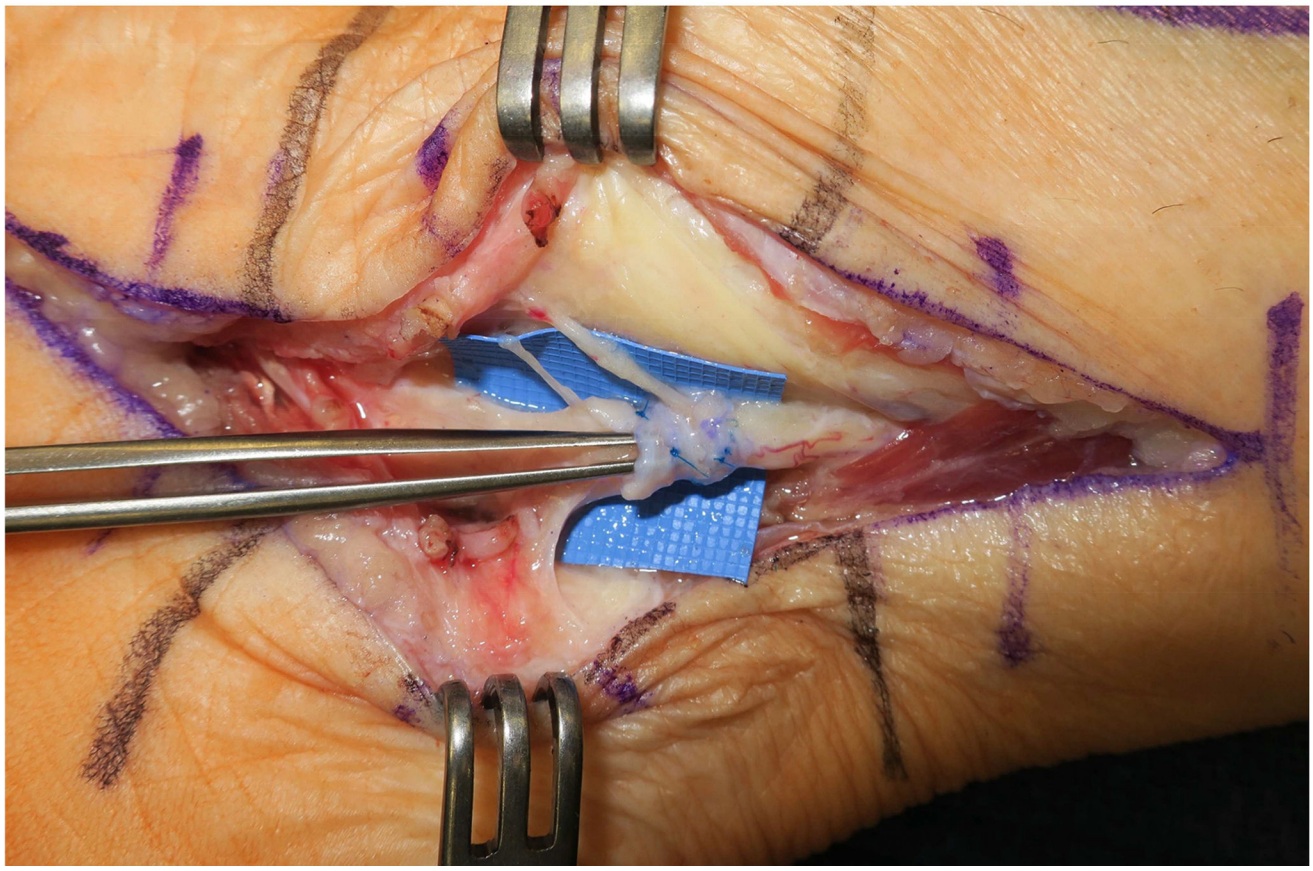

Figure 2.

A saphenous vein wrap was used as a protective barrier in a case of recurrent tarsal tunnel syndrome. (2A) The prior skin incision is marked with the transverse lines and the subcutaneous veins are marked prior to limb exsanguination. (2B) Dissection of the tibial nerve within the tarsal tunnel demonstrates epineural scarring deep to the reformed lancinate ligament. (2C) The saphenous vein is harvested and split longitudinally. (2D) The longitudinally-split saphenous vein is wrapped around the scarred segment of the tibial nerve. (2E) Care is taken to avoid wrapping the nerve too tightly, as demonstrated by the ability to place the forceps deep to the vein wrap.

Table 1

Comparison of nerve barrier options based on ideal characteristics for a barrier to epineural scarring.

Ideal characteristics	**Adipofascial or muscle flap**	**Vein wrapping**	**Hyaluronic acid-carboxycellulose membrane (Seprafilm)**	**Bovine collagen NeuraWrap; NeuraMend)**	**Porcine small intestine submucosa (Axoguard)**
Biocompatible	Yes. Non-absorbable	Yes Non-absorbable	No reports of rejection. Absorbs by 7 days	No reports of rejection. Absorbs by 4–8 months	No reports of rejection. Absorbs by 3 months.
Semipermeable	Yes	Yes	Yes	Yes	Yes
Non-constricting	No reported cases of cicatrix formation after use.	No reported cases of cicatrix formation after use.	No reported cases of cicatrix formation after use.	No reported cases of cicatrix formation after use.	No reported cases of cicatrix formation after use.
Promote nerve gliding	Yes	Yes – demonstrated in animal model	Unknown	Unknown	Unknown
Minimal/no donor site morbidity	Depends on flap harvested (minimal for local fat pad flap)	Yes (typically edema)	No donor site morbidity	No donor site morbidity	No donor site morbidity
Minimal cost or supply restraints	Increased surgery time	Increased surgery time	Subject to implant cost and availability	Subject to implant cost and availability	Subject to implant cost and availability

Table 2

Nerve wraps that are commercially available in the United States

Product Name Manufacturer)	Description	Lab evidence	Clinical evidence
Autologous vein wrapping	Intimal surface of vein placed along epineurium and wrapped circumferentially	Nerve repair: Rat sciatic nerve – decreased perineural scar compared to controls[13] Compressive neuropathy: Rat sciatic nerve – decreased perineural scar, improved electrophysiologic testing, larger axons compared to controls[4]	Nerve repair: 1 case series[8] Compressive neuropathy: 4 case series[6,7,21,22]
NeuraWrap Integra Life Sciences)	Bovine-derived type 1 collagen	Nerve repair: Rat sciatic nerve – decreased perineural scar, no difference in axon counts compared to controls[9] Compressive neuropathy: None	Nerve repair: None Compressive neuropathy: 2 case series[10,11]
AxoGuard Nerve Wrap (Axogen)	Porcine small intestine submucosa	Nerve repair: Rat sciatic nerve – more effectively reduced intraneural fibrosis than vein wrapping[13] Compressive neuropathy: None	Nerve repair: None Compressive neuropathy: 1 case series[14]
Seprafilm (Genzyme) Non FDA-indicated	Hyaluronic acid-carboxymethylcellulose film	Nerve repair: Rat sciatic nerve – decreased adhesions compared to control group[17] Compressive neuropathy: None	Nerve repair: None Compressive neuropathy: None
XWrap Dry (Applied Biologics) Non FDA-indicated	Human amniotic membrane	Nerve repair: Rabbit ulnar nerve and rat sciatic nerve repair models: less perineural fibrosis and adhesion compared to controls[18] Compressive neuropathy: None	Nerve repair: None Compressive neuropathy: 1 case series[19]