e-ISSN: 3068-3742
Journal of Surgery Research and Practice

ATHENAEUM SCIENTIFIC PUBLISHERS

Research Article

Preventing Amputation Neuromas with Autogenous Vein Grafting

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Citation: Suri AE, et al. Preventing Amputation Neuromas with Autogenous Vein Grafting. J Surg Res Prac. 2026;7(2):1-6.

https://doi.org/10.46889/JSRP.2026.7209

Received Date: 27-05-2026

Accepted Date: 15-06-2026

Published Date: 23-06-2026

Abstract

Background: Amputation neuromas are a frequent sequela of peripheral nerve transection, with no universally accepted prevention strategy. Implantation of transected nerve ends into veins has been described in experimental and clinical reports; however, controlled histologic validation remains limited. The present study was designed to validate, in a within-subject animal model, whether autogenous vein ensheathment prevents neuroma formation following nerve transection.

Methods: A controlled, within-subject animal study was conducted using 10 Sprague–Dawley rats. Each rat underwent bilateral transection of the saphenous nerve. On one side, the proximal nerve stump was ligated and ensheathed within an autogenous femoral vein segment (experimental group), while the contralateral stump underwent transection and ligation alone (control group). After 18 weeks, sites were harvested and examined grossly and histologically. Neuroma formation was assessed as a binary histologic outcome using established morphologic criteria. Groups were compared using Fisher's Exact Test ($p < 0.05$).

Results: No gross bulb-shaped neuromas were observed. Histology demonstrated neuroma formation in all 10 control nerves and in none of the 10 vein-ensheathed nerves ($p < 0.001$). Control nerves showed disorganized, divergent fascicles embedded within dense connective tissue. In contrast, experimental nerves regenerated within the vein conduit in an organized, fascicular pattern with preserved perineurial boundaries and without extension into adjacent scar.

Conclusion: In this animal model, autogenous vein ensheathment prevented histologic neuroma formation after nerve transection. These findings provide histologic validation supporting vein conduits as a protective microenvironment for regenerating nerves. Further investigation is warranted to define functional outcomes and clinical relevance.

Keywords: Amputation Neuromas; Saphenous Nerve; Fisher's Exact Test

Introduction

First described in the early 19th century, amputation neuromas remain a persistent complication of peripheral nerve transection [1]. Although the literature describes a large number of techniques for neuroma prevention and management, a universally effective standard of care has not been established [2,3]. Neuromas are an expected biologic consequence of nerve injury and when symptomatic they can produce pain, numbness, cold intolerance, burning sensation and electrical sensitivity [2,4-7]. Beyond physical symptoms, neuromas can substantially affect quality of life, limiting activities of daily living and impairing psychosocial health and employment [4,8,9]. Symptomatic neuromas occur in a meaningful subset of amputees, including both upper and lower extremity patients [5,10-15]. The pathogenesis of neuroma formation is commonly attributed to unregulated axonal sprouting in the absence of a distal target, with regenerating axons proliferating and incorporating into surrounding scar tissue, producing a disorganized mass [16-19]. Numerous operative strategies have aimed to reduce symptomatic neuromas,

including burying nerve ends in surrounding tissues, synthetic capping and newer strategies such as Targeted Muscle Reinnervation (TMR) and Regenerative Peripheral Nerve Interface (RPNI) [20-22]. While these methods have demonstrated benefit in selected settings, none reliably eliminate neuroma formation or pain and recurrence remains a concern [16,20-22,24].

Rather than attempting to inhibit nerve regeneration, other approaches seek to promote organized regeneration within a controlled environment. Autogenous vein grafts have been used experimentally as biologic conduits that support orderly axonal growth and isolate regenerating fibers from surrounding scar [25]. Clinical reports have also described implantation of painful neuromas into veins with favorable results [31-37].

Although a substantial body of experimental and clinical literature exists regarding vein implantation techniques, many reports involve heterogeneous methods, limited controlled comparisons or variable histologic characterization. The objective of the present study was therefore not to introduce a novel concept, but to provide controlled histologic validation using a within-subject design in which each animal served as its own control of whether autogenous vein ensheathment prevents neuroma formation following nerve transection.

Materials and Methods

Animal Subjects

Ten Sprague-Dawley® rats were anesthetized with an intraperitoneal injection of sodium phenobarbital (50 mg/kg). The groin areas were shaved and depilated bilaterally. Using aseptic technique, the saphenous nerve and femoral vein were exposed on both sides.

Experimental Design

This was a preclinical, controlled, within-subject animal study designed to compare the effect of autogenous vein ensheathment on neuroma formation following nerve transection. Each rat served as its own control: one limb was treated with an autogenous vein conduit (experimental side), while the contralateral limb underwent transection and ligation alone (control side). Side assignment was randomized for each animal.

Surgical Procedure

A segment of the saphenous nerve was resected bilaterally. The proximal nerve stump was ligated in both experimental and control limbs using 10-0 Dermalon (Davis and Geck, Pearl River, NY). In the control limb, the wound was closed using 4-0 Dermalon (Davis and Geck, Danbury, CT) without further treatment of the nerve stump.

On the experimental side, the proximal nerve stump was ensheathed with a short segment of femoral vein harvested from the same limb. The vein graft was secured over the nerve stump using two 10-0 Dermalon sutures. The distal portion of the vein was left open and not affixed to surrounding tissue and it was positioned away from the distal nerve segment. The wound was then closed in the same manner as the control side.

Tissue Harvesting and Histological Analysis

After 18 weeks, all rats were euthanized. Neurovascular complexes from both legs were resected and examined grossly under light microscopy. Tissues were fixed in 10% formaldehyde, embedded in paraffin and sectioned for histological staining with Hematoxylin and Eosin (HandE), Bodian stain (for axons) and Verhoeff–Van Gieson stain (for elastic fibers).

Remaining tissue was fixed in 3.5% glutaraldehyde, post-fixed in 2% osmium tetroxide, embedded in LX-112 (Ladd Research Industries, Burlington, VT) and sectioned at 0.5 μm using a Reichert OM-J2 microtome (Reichert, Austria) with a glass knife. These sections were stained with Paragon and 2% sodium borate for further microscopic evaluation.

Histologic evaluation focused on binary morphologic classification (neuroma present vs absent) using established criteria described in prior literature. Neuroma was defined by disorganized axonal proliferation, fascicular divergence, loss of parallel orientation and incorporation into surrounding scar tissue. Organized regeneration was defined by preservation of fascicular organization, maintained perineurial boundaries and confinement of axons within a defined structure.

All histological evaluations were performed jointly by the senior author (a board-certified plastic surgeon) and a collaborating pathologist blinded to group allocation, to minimize observer bias. Although quantitative grading was not performed, the study was designed to determine whether neuroma formation occurred under each condition.

Statistical Analysis

The presence or absence of neuroma formation was recorded for each limb. Statistical comparison between control and experimental limbs was performed using Fisher's Exact Test, with significance set at $p < 0.05$. Statistical analysis was performed using RStudio (version 2023.06.0, RStudio Inc., Boston, MA).

Results

Upon gross examination, no bulb-shaped neuromas were observed in either the control or experimental groups. Histologically, however, neuromas were evident in all 10 control nerves, while none of the 10 experimental nerves demonstrated neuroma formation ($p < 0.001$) (Fig. 1).

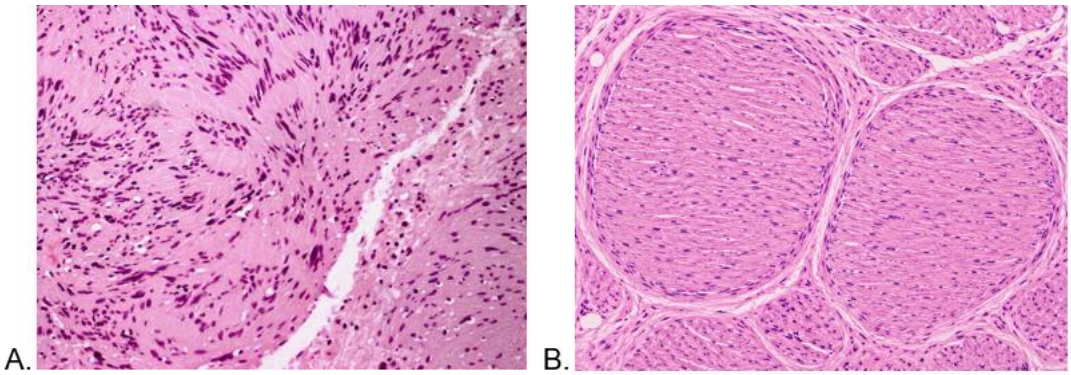

Figure 1: Histologic comparison of control and vein-ensheathed nerve stumps following transection. (A): Control nerve stump demonstrating disorganized axonal proliferation and fascicular divergence consistent with neuroma formation; (B): Vein-ensheathed nerve stump demonstrating organized fascicular regeneration confined within the vein conduit without evidence of neuroma formation. Hematoxylin and Eosin (HandE) stain.

Control specimens demonstrated disorganized axonal regeneration characterized by dispersion into multiple diverging fascicles embedded within evolving scar and connective tissue, separated by collagen matrix. Fascicles contained myelinated and unmyelinated axons and were defined by distinct perineurial sheaths.

In contrast, nerves in the experimental group regenerated within the lumen and wall of the vein conduit in an organized fashion. Regenerating fascicles remained confined, maintained perineurial boundaries and did not course into adjacent connective or scar tissue. Distally, axons progressively transitioned into connective tissue within the vein lumen without evidence of disorganized proliferation or reversal of growth direction. At 18 weeks, the vein retained its histological structure, with identifiable endothelium, internal elastic lamina, smooth muscle and adventitia layers.

Despite proximal nerve ligation in both groups, regenerative activity was observed histologically in all specimens, with the pattern of regeneration differing substantially depending on the presence of the vein conduit.

Discussion

This study provides controlled histologic validation that autogenous vein ensheathment of transected nerve stumps prevents neuroma formation in a rat model. Although implantation of nerve stumps into veins has been described previously, the present work was designed as a confirmatory, controlled comparison using a within-subject approach that reduces biologic variability by allowing each animal to serve as its own control. The consistent absence of neuroma formation in all experimental specimens, contrasted with uniform neuroma formation in all control specimens, underscores the robustness of the protective effect observed in this model. The pathogenesis of neuromas has been attributed to failed axonal attempts to navigate and reconnect with distal targets, frequently influenced by scar formation and microenvironmental cues. Huber's foundational work postulated that neuromas arise when divided axons are unsuccessful in navigating past blockages, often formed by scar [1]. Historical

methods aimed at inhibiting nerve regeneration – such as capping nerve stumps with metallic foils or collodion -failed to prevent neuroma formation and, in some instances, increased neuroma size [27,28]. These findings contributed to a shift toward approaches that promote orderly regeneration rather than attempt to suppress it.

Experimental work has demonstrated that autogenous vein conduits can support organized axonal growth, although axons that escape into surrounding tissue may form disordered proliferations [25]. Other studies using biologic chambers or tubes have similarly shown that a defined conduit can promote structured regeneration and reduce disorganized outgrowth [29,30]. Clinical observations and case series have reported that implantation of neuromas or nerve stumps into veins can yield durable symptom improvement in selected patients [31,36,37].

In the present study, both experimental and control nerve stumps were ligated. Although ligation is not a widely used clinical strategy for neuroma prevention, it was employed to standardize conditions and bias the environment toward neuroma formation. The observation that regenerative activity occurred despite ligation, yet remained organized only within the vein conduit, supports the interpretation that the conduit microenvironment and not ligation governs regenerative pattern and neuroma prevention. Regenerative sprouting likely originated proximal to the ligature through preserved endoneurial and perineurial pathways, consistent with prior experimental observations [47-50].

The outcome assessment in this study was intentionally binary (neuroma present vs absent) based on established histomorphologic criteria. While gradations of neuroma morphology exist clinically, the biologic question posed was whether neuroma formation occurred at all under each condition. Future studies may incorporate quantitative morphometry or additional objective metrics to further refine these observations.

This investigation is limited to histologic outcomes in an animal model and does not address pain behavior, sensory function or other functional correlates. Neuropathic pain after nerve injury or amputation is multifactorial and may occur even in the absence of a discrete neuroma [43-46]. Accordingly, translation to human surgery should be cautious and considered within the context of existing clinical literature on vein implantation techniques. The present findings provide biologic support for further investigation but do not establish clinical efficacy.

Despite these limitations, the complete prevention of histologic neuroma formation observed here supports the concept of the vein conduit as a protective microenvironment for regenerating nerves. Future work should assess functional outcomes and longer-term changes, validate results in larger models and define clinical indications relative to other contemporary strategies.

Conclusion

Surgical prevention of amputation neuromas remains challenging, with no single technique universally effective. In this controlled within-subject rat model, autogenous vein ensheathment of transected nerve stumps consistently prevented histologic neuroma formation, while transection and ligation alone resulted in neuroma formation in all controls. These findings provide controlled histologic validation supporting the vein conduit as a protective microenvironment for regenerating nerves. Further studies are warranted to define functional outcomes and clinical relevance.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement

The authors have no acknowledgments to declare.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was obtained from all participants included in the study.

Authors' Contributions

All authors contributed equally to this paper.

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