Autograft Substitutes
Conduits and Processed Nerve Allografts

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KEYWORDS

• Conduit • Allograft • Peripheral nerve injury • Peripheral nerve repair • Autograft alternative
• Autograft substitute

KEY POINTS

- Regardless of the repair methodology (direct suture, autograft, conduit or allograft), the same principles of good nerve repair should be rigorously adhered to in order to achieve the best possible outcome.
- Manufactured tube conduits are seeing a decreasing role in gap repair and an increasing role as an aid to coaptation.
- Use of processed nerve allografts seems to be increasing based on published clinical data showing high success rates and favorable comparisons with alternative techniques.
- Current studies and ongoing research help to clarify the role of processed nerve allografts and their limitations as a substitute for nerve autograft and direct suture.

INTRODUCTION

Why do clinicians care about substitutes for nerve autograft? Berger and Millesi[1] popularized grafting techniques by demonstrating their superiority to a tensioned direct repair. This popularity is for good reason, because nerve autografts provide a readily available source of patient-specific tissue, with a peripheral nerve-specific microenvironment, basal lamina scaffolding, guidance cues, and supportive Schwann cells. For these reasons, autograft has been the workhorse of peripheral nerve gap repair for decades. Surgeons therefore must ask themselves why, with all of these benefits, there is a need for a substitute? The apparent answer is that, for all of its benefits, there are some clear shortcomings and limitations associated with nerve autograft that can be detrimental to patients' quality of life and therefore have to be considered. Clinical outcomes are often less than are considered desirable, with roughly a 50/50 chance of returning M4 function or sensory discrimination.[2] Furthermore, there is a limited supply, and that supply can be of variable caliber, at times supplying subpar tissue with regard to the cross section of the nerve tissue that provides scaffolding for regeneration.[3] Also, there may be diminished Schwann cell viability after harvest.[4] In addition, in certain situations the supply of expendable donor tissue is not adequate or even available.[5] In addition, the autograft harvest site creates a new nerve injury that leaves the patient with a permanent deficit, often requires a second incision to access the donor tissue, can lead to the formation of a potentially symptomatic neuroma at the proximal donor site,[6] and can add considerable time and cost to the procedure.[7,8]

Because of these compromises, alternatives to the classic nerve autograft have been sought and have recently been increasing in popularity.

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Millesi[9] proposed that the ideal nerve graft should contain the following characteristics: be available in large quantity, have structural and mechanical properties consistent with the nerve's natural extracellular matrix, contain capillaries and a few fibroblasts, and contain a large number of Schwann cells originating from the nerve to be repaired. To help address these criteria, tissue and biomedical engineering has focused on development of biomaterials and advancements in tissue processing technologies to create a variety of devices and substrates to support peripheral nerve regeneration. Over the past few decades, the development of biocompatible materials and tissue processing that mimic or preserve the microenvironment of nerve tissue has produced advances. With these advances, processed nerve allograft (PNA) and manufactured conduits have become increasingly accepted alternatives in clinical practice.

MANUFACTURED CONDUITS

The manufacture of conduits can be traced back to Gluck and colleagues[10] in the 1880s when they fashioned a tube of decalcified bone to aid the approximation of transected nerve ends. This coupling of the nerve ends within the tubular device compensated for the lack of proper instrumentation in an era before the advent of microsurgery. This practice continued with modest enthusiasm until Dahlin and Lundborg's[11] landmark work with silicone tubes. Their work explored the application of tubes in peripheral nerve repair and, perhaps most importantly, characterized the mechanism of action of regeneration within the lumen of the tube.

A conduit works by encasing the distal and proximal nerve ends within the tube and providing gross macroalignment for the nerve and containment of the fluid leaking from the transected nerve ends, gathering it within the inner chamber. This fluid forms a rudimentary fibrin matrix between the nerve ends. If robust enough, the matrix forms a cable to support cellular migration between the nerve ends. As cells invade the cable, linear bands of Büngner form within the disorganized fibrin matrix. The neurite growth cone follows these bands and, with maturation, microfasciculation within the newly formed pseudo–nerve sheath occurs.[11] This mechanism depends on the volumetric output from the nerve stumps.[11–13] If the gap is too long or the inner lumen too large, the cable that forms is often thin, and, because of the mechanical contraction of the fibrin matrix, takes on a classic hourglass appearance. This alteration limits the area for axonal regeneration, with the maximum area for axonal regeneration being directly proportional to the cross-sectional area of the thinnest aspect of the fibrin cable. This characteristic is a limitation inherent to conduits that do not provide a laminin-rich endoneural scaffold, and has been observed in both the early silicone tube research and in subsequent advances with collagen-based biomaterials and synthetic polymers.[11–14] Even with this limitation, the theoretic benefits and ease of use are readily apparent. The tube creates a microchamber to contain the axoplasm and milieu; provides a barrier to invasion from wound bed inflammation[11]; limits the potential escape of neurites from the repair site, which may result in neuroma formation; and splints the nerve coaptation by loading the force during active range of motion onto the juncture between the suture and the tube versus the end-to-end coaptation.[15] Based on these benefits and promising research in animal models, Lundborg and colleagues[16] transitioned to clinical research with silicone tubes. They researched a series of mixed nerve repairs in the forearm, and with 5 years of follow-up data showed that the conduit repairs were comparable with direct suture and trended toward greater sensory recovery in gaps less than 5 mm in length. Although they were able to show the applicability of a conduit in short gaps, the silicone material resulted in patient complications caused by the nonpermeable, permanent nature of the silicone. In documented cases, superficial soft tissue irritation, fibrotic encapsulation, and mild compression necessitated the exploration and planned removal of several of the silicone tubes. Although practical application of their research was limited by the technology of the time, it spawned a renewed interest in tubular repair with a multitude of assorted biomaterials.

Modern biomaterials now play a role in manufactured conduits replacing the rigid sheath with semipermeable, biodegradable materials such as denatured collagen and polyesters. The purpose of these materials is to provide an outer sheath that allows diffusion of oxygen and micronutrients across their outer walls and into the fibrin matrix. Weber and colleagues[17] published on the first commercially available conduit, a woven polyglycolic acid tube for digital nerve repair. The study evaluated sensory outcomes compared with a control group of mainly direct suture repair and, secondarily, a small cohort of 8 autograft repairs. The study found that, in defects less than 4 mm, the conduit provided significantly better return of sensory function compared with the direct suture repair, with 91% providing excellent return of 2-point discrimination versus 49% in the suture-only group. This benefit was not seen in gaps