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Review

FDA approved guidance conduits and wraps for peripheral nerve injury: A review of materials and efficacy

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ABSTRACT

Several nerve guidance conduits (NGCs) and nerve protectant wraps are approved by the US Food and Drug Administration (FDA) for clinical use in peripheral nerve repair. These devices cover a wide range of natural and synthetic materials, which may or may not be resorbable. This review consolidates the data pertaining to all FDA approved materials into a single reference, which emphasizes material composition alongside pre-clinical and clinical safety and efficacy (where possible). This article also summarizes the key advantages and limitations for each material as noted in the literature (with respect to the indication considered). In this context, this review provides a comprehensive reference for clinicians which may facilitate optimal material/device selection for peripheral nerve repair. For materials scientists, this review highlights predicate devices and evaluation methodologies, offering an insight into current deficiencies associated with state-of-the-art materials and may help direct new technology developments and evaluation methodologies thereof.

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Introduction

Insufficient functional recovery after peripheral nerve injury (PNI) continues to be a significant clinical challenge.[1] Since the mid-1980s, the FDA have approved several devices based on natural and synthetic biomaterials to repair nerve defects arising from PNI. PNIs result in over 8.5 million restricted activity days and almost 5 million bed/disability days each year[2,3]; unfortunately, not all are manageable *via* surgical intervention. Consequently, over 200,000 peripheral nerve repair procedures are performed annually in the US.[4] Surgical interventions such as neurorhaphy – direct suture repair without the use of grafted materials – may be deployed for short (<5 mm) nerve gaps. However, larger defects repaired by neurorhaphy, exhibit excessive tension over the suture line and offer poor surgical results.[5] There are various surgical techniques used to perform neurorrhaphy, including: (i) conventional group fascicular repair comprising micro-sutures placed through the inter-fascicular and external epineurial tissue,[6,7] (ii) perineural repair; involving the suturing of corresponding nerve fascicles and distal nerve stump for optimum alignment,[8] and (iii) epineural repair; usually applied directly to the transected nerve injury and comprises sutures passed through the epineurial sheath. The latter being an easier and faster method which minimizes both the internal disruption of the nerve as well as the disturbance of the blood supply.[6,9] Neurotisation (nerve transfer) is an alternative, graft free intervention, which connects the proximal nerve stump directly to the muscle belly and can be used in only very selected situations. Generally, however, neurotisation procedures have poorer results than neurorrhapy or nerve grafting.[5] Given these limitations and the clinical need to repair larger defects, procedures utilizing graft materials are necessary.

The ideal nerve repair device: current concepts

The majority of recent research efforts in the field of peripheral nerve grafting has emphasized enclosing (entubulating) opposing nerve stumps (of the severed nerve) in a non-neural tube (Nerve Guidance Conduit or NGC) fabricated from natural or synthetic materials.[5,10–13] The desired effect of nerve entubulation: is to increase the (i) number; (ii) speed, and (iii) length of the regenerating axons.[14] After the nerve stumps are inserted and sutured into the ends of the tube, a protein-rich (axoplasmic) fluid exudate from the nerve stumps, which contains growth-promoting substances, is released into the NGC (see Fig. 1). A neomatrix of fibrin will be formed within days providing support for the migration of Schwann cells, as well as fibroblasts and macrophages. From the perspective of an NGC it is important to note that Schwann cells have the ability to support their own survival by autocrine circuits, and block apoptosis when cultured in a high density, thus, enhancing potential for axonal growth from the proximal end towards the distal stump.[15]

To promote axonal regeneration and achieve functional recovery, it is critical to minimize the period of wallerian degeneration which is controlled by four critical factors[4]:

(i) The existence of Schwann cells.
(ii) The secretion of neurotrophic factors (NTFs) after injury and during regeneration.
(iii) The existence of a basal lamina: a specialized type of extracellular (ECM) matrix that acts as a scaffold for neural cells. The components ECM have been shown to promote neurite elongation *in vivo* and (iv) the existence of a distal stump.
(iv) The distal nerve has also been found to be important for peripheral nerve regeneration because it supplies various neurotrophic factors for axonal regeneration.

NGCs are required to mechanically support and direct axonal sprouting between the injured nerve stumps; whilst preventing fibrous tissue ingrowth into the injury site and retain neutrophic and neurotropic factors secreted by the damaged nerve ends.[17] To support these requirements, the following criterion for idealized NGCs and protectant wrap devices have been identified[17–27]:

(i) The biomaterial employed must be biocompatible and provoke no inflammatory response.
(ii) The biomaterial must be biodegradable whilst maintaining a mechanically stable architecture during the regeneration process and resist tear from sutures and tissue inflammation.
(iii) The device must be flexible and soft so as to prevent compression of regenerating axons and limit tissue inflammation respectively.
(iv) The device should provide a guidance cue (*via* a tubular 3D structure) for the extending growth cone to eliminate misdirection.
(v) The biomaterial must be semi permeable to allow the diffusion/influx of oxygen and nutrients from interstitial fluid to the surviving nerve tissue through pores in the conduit wall.[17] The need to facilitate this requirement *via* adjusting the conduit wall porosity is restricted by the opposing need to prevent the infiltration of inflammatory cells into the conduit and to minimize the diffusion of growth factors out of the conduit[28] for which preferable pore sizes in the range of about 5–30 μm, preferably about 10–20 μm are reported. They propose that a pore size less than about 5 μm inhibits cells and tissue to proliferate, whereas if the pore size exceeds about 30 μm, entry of inflammatory cells becomes excessive. Controlling permeability may also affect the formation of the fibrin matrix in the initial stage of regeneration.[26]
(vi) The device should prevent fibrous tissue ingrowth into the injury site and retain secreted neurotrophic factors secreted by the damaged nerve ends.
(vii) The device must meet technical requirements for further production, sterilization, long-term storage, and surgical handling, such as, suturing (suture retention and tear).

In addition, such biomaterials and their contiguous devices must have the appropriate dimensions to facilitate bridging the nerve gap defect without tension and the conduit width must also be able to house securely the two nerve end stumps without any compression.[29–31] The internal diameter and wall thickness of NGCs appears to influence the rate of nerve regeneration and, as such, the tube must be large enough to accommodate any swelling of the nerve without resulting in any compression of the nerve by swelling during degradation of the tubular construct.[17] The use of artificial NGCs enables the fabrication of a wide specification of conduit sizes to suit site-specific nerve lesions in mass production and as such offer significant advantages over autograft and allograft material. In brief, the design specification