Nerve Tubes for Peripheral Nerve Repair

Godard C.W. de Ruiter, MD[a], Robert J. Spinner, MD[b,c],
Michael J. Yaszemski, MD, PhD[c], Anthony J. Windebank, MD[d],
Martijn J.A. Malessy, MD, PhD[a,*]

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At this moment, the gold standard for repair of nerve defects that cannot be directly restored without tension to the nerve ends is still the autologous nerve graft (**Fig. 1**A). Most commonly, the sural nerve is used, taken from the leg of the patient. Obviously, repair with autografts has several disadvantages, such as the need for an extra incision, limited availability, mismatch in size of the damaged nerve and the donor nerve, and the chance for the development of a painful neuroma. Because of these disadvantages, various alternatives have been developed for autograft repair (eg, repair with autogenous venous grafts[1] and nerve allografts,[2,3] and nerve tubes, guides, or conduits). Practical advantages of nerve tubes are the unlimited right-off-the-shelf availability in different sizes that match the damaged nerve (**Fig. 1**B). Besides, functional recovery is often reduced after autograft repair compared with direct coaptation repair. A possible explanation is that axons need to cross two coaptation sites, which might decrease the number of axons reaching the distal targets and lead to increased misdirection of regenerating axons.[4] An ideal alternative, therefore, will also lead to improved regeneration and functional results of nerve repair. In this article, the authors give an overview of the current experimental and clinical data on nerve tubes for peripheral nerve repair. The goal of this article is not to be complete but to provide an overview of the nerve tube literature and to analyze critically the data on which the step from laboratory to clinical use is based.

DEVELOPMENT OF NERVE TUBES

The Concept of Nerve Tube Repair

The first attempts at nerve tube, entubulation, or tubulization repair date back to the end of the nineteenth century (see Table 1 in the article by Weiss elsewhere in this issue).[5] The results of these first attempts were disappointing and later viewed by Sunderland[6] as only of historical interest. The concept of the nerve tube was reintroduced in the 1980s, mainly as a tool to investigate the process of regeneration. In the beginning, silicone tubes were used mostly. Later, nerve tubes of other synthetic nonbiodegradable[7–11] and biodegradable materials (including polymers of glycolic and lactic acid,[12–14] and caprolactone[15,16]) were developed. These first experiments with silicone nerve tubes by Lundborg and colleagues[17] demonstrated that axons can successfully regenerate across a 1-cm gap in the rat sciatic nerve model. No regeneration was observed in the absence of the distal nerve stump and across 15-mm defects, which was later explained by the accumulation of neurotrophic factors in the silicone chamber that

[a] Department of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, USA
[c] Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA
[d] Department of Neurology, Mayo Clinic, Rochester, MN, USA
* Corresponding author.
E-mail address: M.J.A.Malessy@lumc.nl (M.J.A. Malessy).

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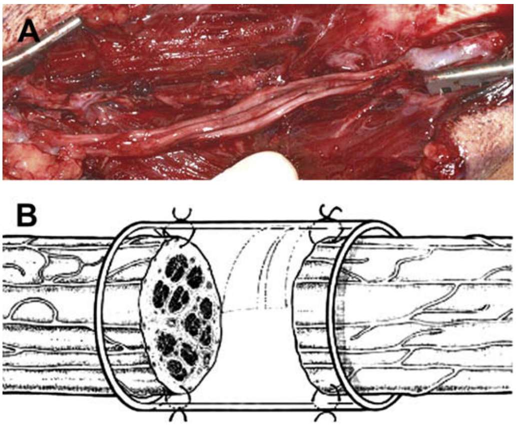

Fig. 1. (*A*) Repair of a radial nerve lesion (after a humerus fracture) with autologous sural nerve grafts. (*B*) Nerve tube repair. (*Adapted from* Lundborg G, Dahlin LB, Danielsen N. Ulnar nerve repair by the silicone chamber technique: case report. Scand J Plast Reconstr Hand Surg 1991;25:79–82; with permission.)

probably only act over a limited distance (neurotropism or chemotaxis). Another explanation might be that the formation of a fibrin matrix (**Fig. 2**), which is essential in the process of regeneration,[18] does not occur if the gap is too long.[19]

Physical Characteristics of the Nerve Tube

Other physical properties, including the dimensions of the nerve tube, prefilling with phosphate-buffered saline (PBS),[20] and porosity,[19] have also been shown to affect the formation of the fibrin matrix. Jenq and Coggeshall[21,22] found that the addition of holes to silicone nerve tubes increased the number of myelinated axons and the length of the gap that could be bridged. Possible explanations were that by adding holes, cells (eg, macrophages and leucocytes) and molecules (eg, fibrin and fibronectin) involved in the formation of the fibrin matrix could enter the site of regeneration. The importance of the permeability of the nerve tube was later confirmed in other experiments,[15,23–26] although what the ideal pore size is exactly (microporous or macroporous) still remains questionable. Disadvantages of macropores might be that neurotrophic factors can diffuse out of the nerve tube and that the fibrin matrix might be disorganized (orientation perpendicular to the pores instead of longitudinal). Permeability not only depends on pore size but may also be affected by, for example, hydrophilic properties of the material. Next to permeability, the surface texture and dimensions of the nerve tube have been found to affect the formation of the fibrin matrix;[8] with smooth surfaces (eg, in silicone nerve tubes), the longitudinal matrix coalesces and forms a free-floating nerve cable, whereas with rough surfaces, the tissue disperses and completely fills the lumen of the nerve tube.[27]

With the potential use of nerve tubes, especially biodegradable nerve tubes, for clinical nerve repair, other physical characteristics were also investigated, including swelling and degradation properties. Swelling of a nerve tube might primarily block the lumen for regeneration or might secondarily lead to compression of the regenerated nerve. Degradation may cause swelling owing to the accumulation of degradation products that can increase the osmotic pressure in the tube.[16,28] Besides, degradation products might be toxic or might interfere with the process of regeneration. Degradation may also, in time, affect the porosity and tensile properties of the nerve tube. These tensile properties are important because a nerve tube should be flexible for implantation into mobile limbs but at the same time, the nerve tube should be resistant to deformation (elongation, breaking, or kinking) and strong enough to hold a suture. Transparency is preferred for suturing and accurate positioning of the nerve stumps. In the end, nerve tubes must be sterilizable without compromising the physical properties mentioned above. **Table 1** summarizes the known physical properties of some of the frequently used nerve tubes. It is important to note the physical properties of the nerve tube depend not only on the biomaterial but also on other factors, such as the dimensions of the nerve tube and fabrication technique. Not all nerve tubes that are currently available for clinical use have been characterized extensively in vitro before clinical application.

Evaluation Methods and Animal Models

Different evaluation methods and animal models have been used to investigate the process of regeneration across nerve tubes. Most experiments have been performed in the rat sciatic nerve model. Commonly used evaluation methods in this model include electrophysiology, nerve morphometry, and walking track analysis (see **Table 1**). The first, most important observation, however, is the percentage of successful regeneration across the nerve tube. Failures due to collapse, swelling, and suture pullout have been reported.[12,14,29,30] The second most important observation is the quantity of regeneration across the nerve tube. This quantity is mostly determined for the number of axons (myelinated or unmyelinated) at the middle part or distal to the nerve tube and is then preferably compared with the numbers in normal nerve and after autograft repair. However, the numbers