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Review article

Application of peripheral nerve conduits in clinical practice: A literature review

Q1 Patrycja Chrząszcz [a], Kamil Derbisz [a], Krzysztof Suszyński [a], Jan Miodoński [b], Robert Trybulski [a], Joanna Lewin-Kowalik [a], Wiesław Marcol [a,b,*]

[a] Department of Physiology, School of Medicine in Katowice, Medical University of Silesia, ul. Medyków 4, Q2 40752 Katowice, Poland
[b] Department of Neurosurgery, Provincial Specialist Hospital No. 2 in Jastrzębie – Zdrój, al. Jana Pawła II 7, 44300 Jastrzębie – Zdrój, Poland

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ABSTRACT

Understanding the pathomechanisms behind peripheral nerve damage and learning the course of regeneration seem to be crucial for selecting the appropriate methods of treatment. Autografts are currently the gold standard procedure in nerve reconstruction. However, due to the frequency of complications resulting from autografting and a desire to create a better environment for the regeneration of the damaged nerve, artificial conduits have become an approved alternative treatment method. The aim of this mini-review is to present the nerve scaffolds that have been applied in clinical practice to date, and the potential directions of developments in nerve conduit bioengineering.

Articles regarding construction and characterization of nerve conduits were used as the theoretical background. All papers, available in PubMed database since 2000, presenting results of application of artificial nerve conduits in clinical trials were included into this mini-review.

Fourteen studies including ≤10 patients and 10 trials conducted on >10 patients were analyzed as well as 24 papers focused on artificial nerve conduits *per se*. Taking into consideration the experiences of the authors investigating nerve conduits in clinical trials, it is essential to point out the emergence of bioresorbable scaffolds, which in the future may significantly change the treatment of peripheral nerve injuries. Also worth mentioning among the advanced conduits are hybrid conduits, which combine several modifications of a synthetic material to provide the optimal regeneration of a damaged nerve.

* Corresponding author at: Department of Physiology, School of Medicine in Katowice, Medical University of Silesia, ul. Medyków 4, 40752 Katowice, Poland.
E-mail address: wmarcol@tlen.pl (W. Marcol).

Abbreviations: PGA, polyglycolic acid; PHB, polyhydroxybutyrate; PLA, polylactide; PLL, Apoly-L-lactide; PDLLA, poly-DL-lactide; PCL, polycaprolactone; PLCL, polylactide-caprolactone; PLGA, poly(lactic-co-glycolic acid); PU, polyurethane; PVA, poly(vinyl alcohol); SIS, material based on the submucosa of swine small intestine; ECM, extracellular matrix; F-UP, follow-up; FS, sensory function; FN, motor function; PGRD, RGD sequence; β-TCP, beta-tricalcium phosphate; NGF, nerve growth factor; GGFg, lial growth factor; FGF, fibroblast growth factor; GDNF, glial cell-derived neurotrophic factor; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin-3.

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1. Introduction

Reconstructing damaged peripheral nerves constitutes a challenge for contemporary medicine and is the subject of research aimed at developing new therapeutic strategies. Peripheral nerve damage occurs in 13–20 of every 100,000 persons [1], often alongside other injuries. It also frequently concerns young active persons, for whom even a partial loss of nerve function can entail serious social and economic consequences.

Neurorrhaphy is a classic technique of direct nerve repair without or minimal tension on the nerve repair site, but still surgical treatments for peripheral nerve injury are less than satisfactory. When there is a gap between the nerve ends with excessive tension for direct epineural repair, reversed interposition autologous nerve grafts are required. The gold standard of treatment for peripheral nerve gaps between 5 mm and 3 cm in size is the nerve conduit or the autologous nerve graft, interchangeably; however, this last treatment is always associated with a variety of clinical complications, such as donor site morbidity, limited availability, nerve site mismatch, and the formation of neuromas [2]. This procedure is also limited by the number of potential autografts that may be applied. Autograft treatment may also result in complications in the form of sensory or pain disorders if a neuroma forms at the graft collection site. Human autografts are preferred as the literature is clear that autografting is superior to nerve conduits for medium gaps (>3 cm), especially more proximal injuries, and crucial nerves [3]. Nerve grafts can be single, cable, trunk, interfascicular, or vascularized [2]. Autograft use is currently limited to a critical nerve gap of approximately 5 cm in length and beyond this distance requires the use of allograft. Allograft however requires the use of extensive immune suppression up to 18 months post implantation, and patients become susceptible to opportunistic infections, occasionally resulting in tumor formation [4]. Alternatives to autologous nerve graft are available and their use avoids sacrificing donor site sensation. Options includes empty silicon tubes for digital nerve gaps of 5 mm or less, polyglycolic acid conduits and polycaprolacton for gaps less than 3 mm and decellularized muscle allograft for gaps to 5 cm [2].

There are several factors that influence recovery following a nerve injury and repair: time elapsed, patient age, mechanism, proximity of the lesion to distal targets, and associated soft tissue or vascular injuries [5–7]. All these factors must be carefully considered in order to optimize the operative approach used in each unique patient.

Nerve conduits are currently being introduced in order to minimize the risk of complications and at the same time to stimulate nerve growth. A contemporary alternative to autografts are conduits that are made from advanced biodegradable materials [8,9]. The aim of the presented paper is to provide a concise review of implementation of various types of approved nerve conduits in human therapy.

2. Methods

An inspiration to write this paper was work associated with the preparation of a research grant as well as our earlier studies on nerve regeneration. PubMed database was searched for articles focusing on different types of nerve conduits, especially these approved for use in human therapy. Nerve conduits paradigm as well as their short history has been prepared. Every clinical trial on application of nerve conduits in treatment of human nerve injuries since 2000 has been tracked and presented in two tables, according to the number of patients included (10 trials describing more than10 patients, and 14 trials dealing with 10 patients or less).

3. Brief history of nerve conduits

The use of a tube-like conduit was originally proposed for use for nerve repair as early as in 1881 with the first successful application occurring in 1882, where a hollow bone tube was used to bridge a 30 mm nerve gap in a dog [3]. Contemporary, the first generation of artificial nerve conduits used in the clinic were nonresorbable silicone tubes, which were plagued by compression syndrome and often required secondary surgeries for removal [10]. Since then, there have been a variety of different biomaterials approved for clinical use, such as type I collagen, polyglycolic acid (PGA), poly-DL-lactide-co-caprolactone (PLCL), and polyvinyl alcohol (PVA). There currently are five FDA-approved nerve conduits, four of which – Neurotube (PGA), Neurolac (PLCL), NeuraGen (type I collagen), and NeuroMatrixNeuroflex (type I collagen) – are bioresorbable (with degradation rates on the order of 3 months to 4 years), and one that is nonresorbable – SaluBridge (PVA hydrogel) [11]. Only results of clinical studies for NeuraGen, Neurotube, and Neurolac have been published in peer-reviewed journals.

4. Directions of nerve conduit development

Modern biomedical engineering aims to create a conduit that will ensure the appropriate repair, both structural and functional, of a peripheral nerve. A perfect implant should be non-toxic, minimally immunogenic, adjusted to the severity of the injury, easy to manufacture and commonly available, and should have an appropriate degradation time [9]. It should also create the proper micro-environment to stimulate nerve regeneration.

The notion of an ideal material for conduit implantation has evolved from silicone-based and other synthetic materials, through biological conduits, to advanced synthetic biodegradable materials. Fig. 1 presents the materials that have been applied in clinical practice to date. Non-degradable materials are no longer used due to the intense immunological reactions they have caused. These reactions led to swelling in the surrounding tissues, which in turn put pressure on the nerve and hampered its regeneration. Furthermore, the procedure required a follow-up surgery to remove the conduit.

The most rapidly developing group of materials being used to make nerve conduits, and the group with the greatest potential, is bioresorbable materials. By modifying the

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