NEUROLOGIA I NEUROCHIRURGIA POLSKA 52 (2018) 427–435

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Review article

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

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, 40752 Katowice, Poland*

[b] *Department of Neurosurgery, Provincial Specialist Hospital No. 2 in Jastrzębie – Zdrój, al. Jana Pawła II 7, 44300 Jastrzębie – Zdrój, Poland*

ARTICLE INFO

Article history:
Received 10 December 2017
Accepted 19 June 2018
Available online 2 July 2018

Keywords:
Peripheral nerve injuries in humans
Nerve conduits
Bioresorbable scaffolds

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.

https://doi.org/10.1016/j.pjnns.2018.06.003
0028-3843/

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 biological, structural, and chemical properties of a polymer,

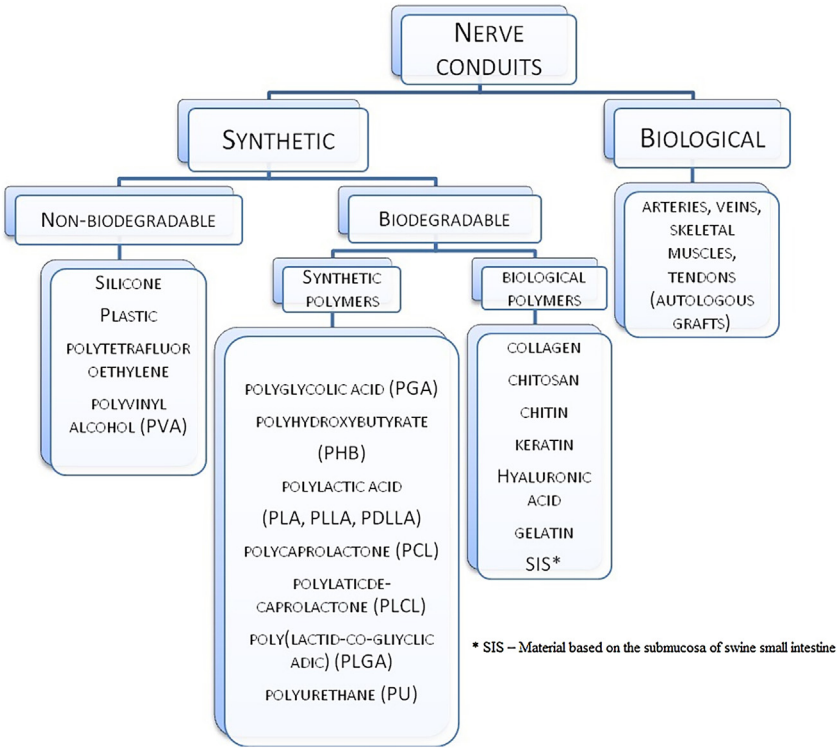

Fig. 1 – Materials used in peripheral nerve conduit bioengineering.

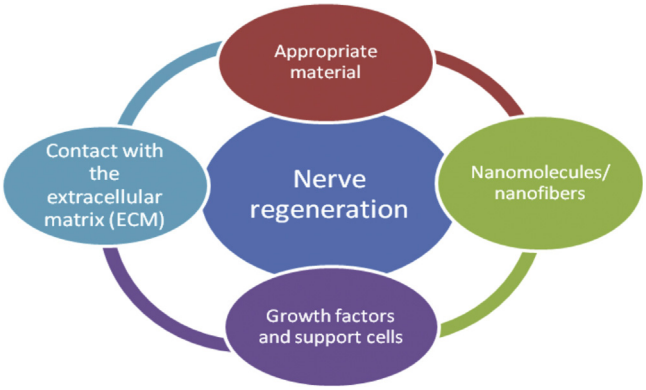

Fig. 2 – Directions in the development of peripheral nerve conduit biotechnology.

researchers hope to create the ideal conditions for nerve regeneration, which is a priority in the production of an appropriate material. Fig. 2 presents the key directions in the development of conduit biotechnology.

4.1. *Growth factors*

One of the methods used for creating an appropriate microenvironment for axon growth involves enriching the conduits with growth factors that are relevant for the nerve tissue [12–14], which promote chemotactic nerve regeneration. The most important growth factors can be found in Table 1. A combination of several growth factors (e.g., NGF or GDNF) [6] and enriching the material with the aforementioned cells that are able to produce cytokines seems to be the most beneficial approach [15].

Table 1 – Major growth factors for nerve tissue [33].

NGF – nerve growth factor
GGF – glial growth factor
FGF – fibroblast growth factor
GDNF – glial cell-derived neurotrophic factor
BDNF – brain-derived neurotrophic factor
NT-3 – neurotrophin-3

Application of neurotrophic substances separately does not result in significant improvement of the nerve repair rate. Moreover, it is extremely difficult to find an appropriate concentrations of these factors. In spontaneous nerve regeneration, these factors act as a ''changing-in-time cocktail'' (i.e. the mixture of various substances whose concentration and activity changes in time). Therefore, it is of special importance to apply different neuroactive substances in the proper constellation [16].

The distal stump undergoes Wallerian degeneration, producing a favorable environment for fibers growing from proximal stump. Therefore, some attempts were made to plant cultured Schwann cells that serve as a natural source of such neuroactive substances into the vicinity of regenerating nerves with. The authors of this work have high experience

Table 2 – Characteristic amino acid sequences in ECM [11].

Name of the sequence	Amino acids
RGD	Arg–Gly–Asp
IKVAV	Ile–Lys–Val–Ala–Val
YIGSR	Tyr–Ile–Gly–Ser–Arg
RNIAEIIKDI	Arg–Asn–Ile–Ala–Glu–Ile–Ile–Lys–Asp–Ile
HAV	His–Ala–Val

with the use of fibrin matrix supplemented with extracts obtained from degenerating peripheral nerves and Schwann cells population to support peripheral nerve regeneration [16]. This approach is similar to the Umea group who additionally enrich the fibrin conduit with the human mesenchymal stem cells using immunosuppressive therapy to enhance survival graft cells after their transplantation [17].

4.2. *Appropriate material*

One of the most important considerations in developing a conduit is the choice of an appropriate structural material. An ideal structural material for manufacturing conduits should [18–20]:

- Be biocompatible with the surrounding tissues – such biocompatibility can be achieved by using a porous structure, which will enable a free exchange of nutrients and ensure the appropriate vasculature and concentration of neural growth factors (studies conducted so far indicate that the use of nanopores measuring about 100 nm in size is beneficial) [18];
- Provide enough room for the growing axon;
- Have an adequate bioresorption time;
- Have low immunogenicity;
- Have an appropriate structure to enable the supply of regenerative substances (a microsphere structure);
- Adhere to the cells in an appropriate manner – this depends especially on the hydrophobicity of the material.

4.3. *Contact with the extracellular matrix*

The extracellular matrix is an important component that affects nerve regeneration. It regulates the cell migration and myelination, and stimulates the diffusive release of growth factors from the Schwann cells. The numerous proteins that are responsible for intercellular contact in the ECM contain similar amino acid sequences (Table 2), the most common of which is the RGD sequence, i.e., Arg-Gly-Asp. These sequences allow particular receptors to recognize and exchange signals with each other, which stimulates the growth, maturation and differentiation of the cells. As a result, coating the conduits with unique amino acid sequences will benefit the adherence and differentiation of Schwann cells, create an advantageous environment that is rich in growth factors (especially NGF and BDNF), and will minimize oxidative stress. Furthermore, the conduit will constitute a scaffold for the regenerating nerve, which is especially important in the initial stages of repair [21].

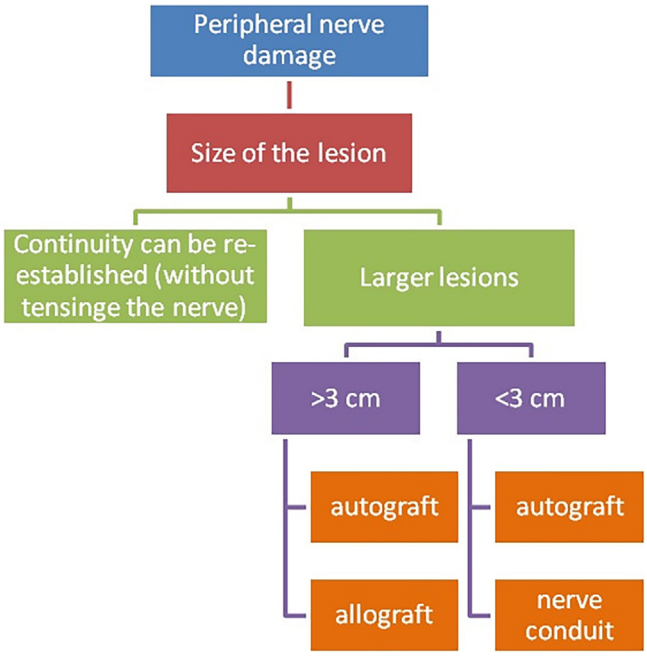

Fig. 3 – Procedure used in treating peripheral nerve injuries.

4.4. *Nanoparticles and nanofibers*

Another modification to standard polymers involves adding a structure of nanoparticles or nanofibers [22]. These form a multiphase surface that allows for a more efficient interaction between the conduit and the ECM, and a better adhesion. Moreover, the interaction between the nanostructure and the polymer changes the thermal, optical, chemical, and catalytic properties of the conduit in a manner which can potentially benefit nerve regeneration [23].

The use of a proper material and each of the aforementioned modifications will improve the effectiveness of nerve implants in promoting nerve growth, as has been confirmed by numerous studies conducted on animal models. The most successful method seems to involve combining several modifications in order to create a hybrid implant [24] that enables optimal nerve regeneration in the shortest time possible.

5. Practical applications and clinical trials conducted to date

The preferred procedure in cases of minor peripheral nerve damage (i.e. in cases where continuity can be restored without tensing the damaged nerve) is the direct suturing of the epineurium with funicular sutures. For more severe damage, autografts are commonly used. Fig. 3 presents the currently most popular procedure.

In 2008, the FDA (Food and Drug Administration) and CE (Conformit Europe) approved the use of nerve conduits made from, among other materials, collagen, PGA and PCL. Accord-

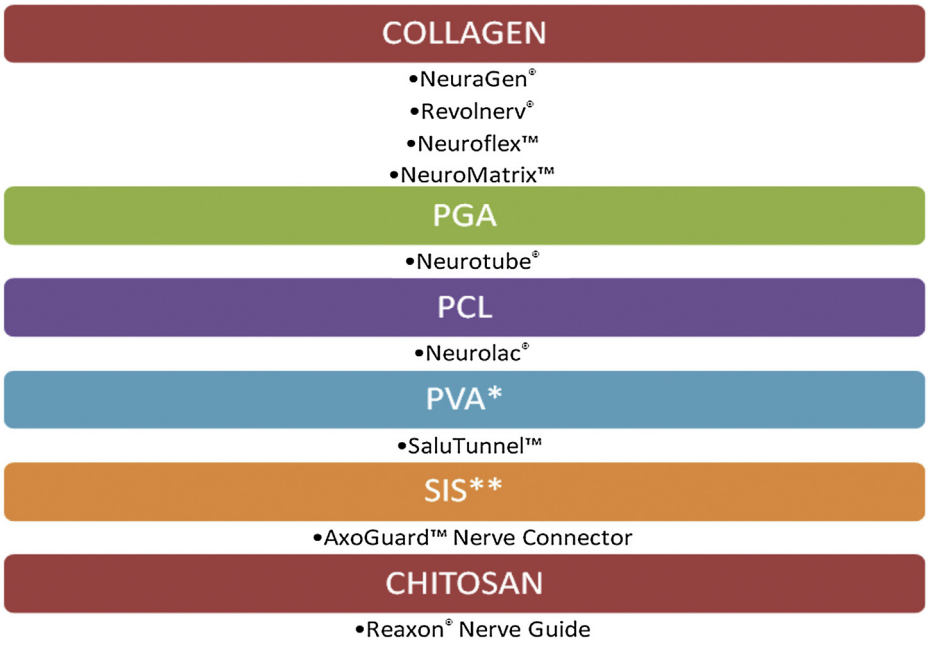

Fig. 4 – The graphical presentation nerve conduits available on the market and their commercial names. The color specifying the type of material of which are built [17].

Table 3 – MRC scale for the assessment of sensory and motor function reestablishment.

Degree	MRC scale	S-2-PD
S0	Function not reestablished	–
S1	Deep pain reestablished	–
S1+	Surface pain reestablished	–
S2	S1+ and partial response to touch	–
S2+	S2 and over-response	–
S3	Surface pain and response to touch reestablished	>15 mm
S3+	S3 and good localization of touch, imperfect 2-PD	7–15 mm
S4	Function completely reestablished	2–6 mm
M0	No contraction	
M1	Barely visible contraction, no movement	
M2	Active movement, no gravity	
M3	Active movement, against gravity	
M4	M3 and movement against resistance	
M5	Normal muscle strength	

ing to analyses conducted at the time, the applicability of such conduits was limited to lesions measuring less than 3 cm long in the peripheral and cranial nerves [25,26]. Fig. 4 lists the approved conduits available on the market together with their commercial names. Despite the approval and availability of conduits made from various materials, studies on the subject remain scarce. Furthermore, the existing studies usually involve an insufficient number of cases, lack a control sample, and use no reference method, all of which decreases their reliability. Table 3 lists the clinical trials that have been conducted since 2000 in which the number of patients in the experimental group was higher than 10. All of their authors evaluated the applied methods in a similar manner, i.e., they used the Medical Research Scale (MRC) to analyze the returning sensory and/or motor functions (through a static two-point discrimination, s2PD). Table 4 shows the individual values and a detailed description of the scale. The results are divided into three subgroups:

- Very good results (when the function at the level of S4/S3+ or M5/M4 was reestablished in ≥70% of the patients);
- Satisfactory results (when the function at the level of S4/S3+ or M5/M4 was reestablished in 50–70% of the patients); and
- Unsatisfactory results (when the function at the level of S4/S3+ or M5/M4 was reestablished at the level of S4/S3+ or M5/M4 in ≤50% of the patients).

Table 4 indicates that only 10 clinical trials involving more than 10 patients have been conducted so far. All of these trials have concerned nerve damage in the upper limbs, mainly in the hands and fingers. In accordance with the applied procedure, the lesion measured no longer than 3 cm. The trials focused on the restoration of the patient's sensory functions. Only two studies (by Wagensteen et al. [27] and Boeckstyns et al. [28]) analyzed the motor functions. Of the studies, Wagensteen's is the least reliable due to its retrospective character and the fact that the injury was measured in only 26 cases, and also no follow-up study was conducted for as many as 40 of the 126 reconstructed nerves (all of which makes the obtained ''unsatisfactory results'' unreliable) [27].

Table 4 – Studies on the use of peripheral nerve conduits conducted since 2000 with experimental groups of >10 patients. N – number of patients, F-UP – follow-up, MF – motor function, SF – sensory function, PGA – polyglycolic acid, PLCL – polylactide-caprolactone.

Author	Year	Type of study	Lesion, length	Conduit	Conduits (N)	control (N)	F-UP (months)	Conclusions
Weber et al. [29]	2000	Prospective, randomized, multicenter	Nerves of the hand	PGA vs. Standard	46	56	12	Conduits are more effective than the standard method, very good results (SF)
Taras et al. [36]	2005	Prospective	Peripheral nerves	Collagen	73	N/A	N/A	N/A
Bertleff et al. [30]	2005	Prospective, randomized, multicenter	Nerves of the hand, <20 mm	PLCL vs. Standard	21	13	12	Both groups are comparable
Wangensteen, Kalliainen [27]	2009	Retrospective	82 nerves of the hand, 34 other nerves of the upper limb, 6 nerves of other body parts, average 12.8 mm	Collagen	126	N/A	8	Unsatisfactory results: functions improved in 45% of patients (SF and MF), many limitations in the trial
Lohmeyer et al.[37]	2009	Prospective	Nerves of the hand, average 12.5 mm	Collagen	12	N/A	12	Very good results (SF)
Rinker, Liau. [38]	2011	Prospective, randomized	Nerves of the fingers, 4–25 mm	PGA vs. Vein autograft	36	32	12	Very good results, both methods are effective, no statistical differences (SF)
Taras et al. [39]	2011	Prospective	Nerves of the fingers, average 12 mm	Collagen	22	N/A	20	Very good results (SF) for lesions <2 cm long
Boeckstyns et al.[40]	2013	Prospective, randomized	Ulnar or median nerve, <6 mm	Collagen vs. Nerve suturing	16	16	24	No differences after 24 months, both methods are very good (SF and MF)
Schmauss et al. [41]	2014	Prospective	Nerves of the fingers, <26 mm	Collagen	20	N/A	30–93	Very good results (FS), better results obtained for lesions < 10 mm long
Lohmeyer et al. [42]	2014	Prospective	Nerves of the fingers, <26 mm	Collagen	40	N/A	12	Satisfactory results (SF)

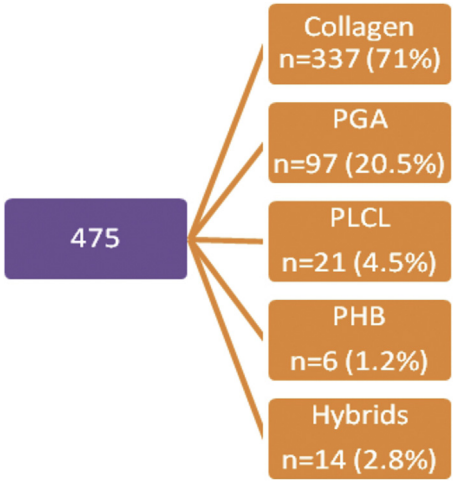

Fig. 5 – Graphic presentation the number of all patients with nerve implants according to the type of conduit used.

In turn, only three of the larger clinical trials involved randomization with respect to the "gold standard" treatment. Each of these trials used a different material for the randomization (Weber used PGA; Bertleff used PLCL; and Boeckstyns used collagen) [28–30]. Weber showed that the conduits were more effective than the standard procedure. However, Bertleff and Boeckstyns obtained similar, very good results when the conduits were compared to the control group [29,39]. Most of the patients underwent a follow-up assessment 12 months after the surgery; however, this may have been too early in light of Schmauss's study, who showed that nerve regeneration is still incomplete after this period [28].

Table 5 shows the clinical trials conducted on smaller groups of patients (≤10). In addition to injuries of the upper limbs, injuries involving lesions of the cranial nerves or the nerves in the brachial plexus that accompanied injuries to other body parts were included in the trials. Most of the patients were screened for the restitution of both sensory and motor functions. The conduits were used for lesions shorter, as well as longer, than 3 cm [31–33,35]. Very good results were obtained.

The two tables indicate that the most commonly used material in the studies was a collagen conduit, or other conduits with a simple structure, such as polyglycolic acid. Fig. 5 shows the types of the conduits and the respective numbers of patients. Only a very small group of patients (14 persons) have had a modern hybrid conduit implanted. Furthermore, Yin et al. were the only researchers who used an advanced hybrid type of implant [34]. These hybrid

Table 5 – Studies on the use of peripheral nerve conduits conducted since 2000 with experimental groups of ≤10 patients. N – number of patients, MF – motor function, SF – sensory function, PGA – polyglycolic acid, PDLLA – poly-DL-lactide, PHB – polyhydroxybutyrate, PGRD – RGD sequence, β-TCP – beta-tricalcium phosphate.

Author	Year	Lesion, length	Type of conduit	Conduits (N)	Results
Kim, Dellon [43]	2001	Reconstruction following the excision of a neuroma of the medial plantar nerve	PGA	1	Reduced pain, good regeneration
Ducic et al. [44]	2005	Accessory nerve	PGA vs. Autograft	1	MF improved in the patient with the conduit
Navissano et al. [45]	2005	Facial nerve, <30 mm	PGA	7	Very good reestablishment of MF
Ashley et al. [31]	2006	Brachial plexus in children	Collagen	5	Very good results
Fan et al. [46]	2008	Median nerve, 35 mm	Chitosan-PGA	1	Satisfactory reestablishment of MF and SF
Farole, Jamal [47]	2008	Lingual nerve, inferior alveolar nerve, 15 mm	Collagen	9	Very good/satisfactory results
Bushnell et al. [48]	2008	Nerves of the fingers, <20 mm	Collagen	9	Very good results, SF
Rosson et al. [49]	2009	Peripheral nerves, <40 mm	PGA	6	Very good results
Aberq et al. [33]	2009	Nerves of the forearm	PHB vs. suturing	6	Satisfactory reestablishment of SF, unsatisfactory reestablishment of MF
Tsujimoto et al. [50]	2011	Autonomic/somatic nerves in the pelvis, 25–90 mm	PGA-collagen	Autonomic nerves (7), Somatic nerves (3)	Very good improvement for both autonomic and somatic nerves
Jardin et al. [51]	2011	Nerves of the forearm, average 22 mm	Collagen	4	Very good re-establishment of MF and SF
Gu J et al. [52]	2012	Median nerve, 30 mm	Chitosan-PGA	1	Partial reestablishment of autonomic function, SF and MF
Semere et al. [53]	2014	Facial nerve, 10 mm	Collagen	1	Very good improvement after 6 months
Yin et al. [54]	2015	Radial/medial nerve, <25 mm	PRGD/PDLLA/β-TCP	2	Very good results, about 80% of MF and SF re-established

implants were made from PDLLA enriched with β-TCP, which neutralizes the products of PDLLA biodegradation and accelerates their removal, as well as improving the adherence of cells to the conduit and the RGD structure characteristic for the ECM. These unique properties of the material may have contributed to the very good clinical results obtained in both of the cases described in the study.

6. Conclusions

Despite a small number of trials, insufficient reliability, and a modest size of the samples, that appeared the biggest limitations for this review, the obtained results are nonetheless encouraging, and prove that therapy performed using nerve conduits as an alternative to standard procedures is both safe and viable.

Further clinical trials with a high level of reliability need to be conducted. Furthermore, more technologically advanced conduits should be used, to keep up with the progress in bioengineering. Such conduits should include hybrid implants, especially full neural scaffolds with a polymer core that imitates the both the outer layer of the nerve and the endoneurium, rather than conduits that imitate the outer layer alone. A milestone, especially in repairing the nerve gaps of a big size, might be the enrichment of the internal environment of the conduit by adding mixture of growth factors and adhesion proteins. But one must remember that the use of growth factors may cause many undesired side effects because to date knowledge of their physiological concentrations is still unsatisfactory.

Conflict of interest

None declared.

REFERENCES

[1] Muheremu A, Ao Q. Past, present, and future of nerve conduits in the treatment of peripheral nerve injury. Biomed Res Int 2015;237507:6. http://dx.doi.org/10.1155/2015/237507
[2] Campbell WW. Evaluation and management of peripheral nerve injury. Clin Neurophysiol 2008;119:1951–65.
[3] Ijpma FF, Van De Graaf RC, Meek MF. The early history of tubulation in nerve repair. J Hand Surg (Eur) 2008;33:581–6.
[4] Siemionow M, Brzezicki G. Chapter 8: current techniques and concepts in peripheral nerve repair. In: Stefano G, Pierluigi T, Bruno B, editors. International review of neurobiology. San Diego, CA: Academic Press; 2009. p. 141–72.
[5] Gilbert A, Pivato G, Kheiralla T. Long-term results of primary repair of brachial plexus lesions in children. Microsurgery 2006;26:334–42.
[6] Hentz VR, Narakas A. The results of microneurosurgical reconstruction in complete brachial plexus palsy. Assessing

outcome and predicting results. Orthop Clin North Am 1988;19:107–14.
[7] Slutsky DJ, Hentz VR, Jabaley M, editors. Primary nerve repair peripheral nerve surgery: practical applications in the upper extremity. Philadelphia: Churchill Livingstone Elsevier; 2006. p. 23–38.
[8] Grinsell D, Keating CP. peripheral nerve reconstruction after injury: a review of clinical and experimental therapies. Biomed Res Int 2014;698256:13. http://dx.doi.org/10.1155/2014/698256
[9] Verreck G, Chun I, Li Y, Kataria R, Zhang Q, Rosenblatt J, et al. Preparation and physicochemical characterization of biodegradable nerve guides containing the nerve growth agent sabeluzole. Biomaterials 2005;26:1307–15.
[10] Lundborg G, Gelberman RH, Longo FM, Powell HC, Varon S. In vivo regeneration of cut nerve encased in silicone tubes. J Neuropath Exp Neurol 1982;41:412–22.
[11] Schlosshauer B, Dreesman L, Schaller H, Sinis N. Synthetic nerve guide implants in humans: a comprehensive study. J Neurosurg 2006;59:740–7.
[12] Gu X, Ding F, Yang Y, Liu J. Construction of tissue engineered nerve grafts and their application in peripheral nerve regeneration. Prog Neurobiol 2011;93:204–30.
[13] Gu X, Ding F, Williams DF. Neural tissue engineering options for peripheral nerve regeneration. Biomaterials 2014;35:6143–56.
[14] Madduri S, Feldman K, Tervoort T, Papaloïzos M, Gander B. Collagen nerve conduits releasing the neurotrophic factors GDNF and NGF. J Control Release 2010;143:168–74.
[15] Ramburrun P, Kumar P, Choonara YE, Bijukumar D, du Toit LC, Pillay V. A review of bioactive release from nerve conduits as a neurotherapeutic strategy for neuronal growth in peripheral nerve injury. Biomed Res Int 2014;132350:19.
[16] Marcol W, Kotulksa K, Larysz-Brysz M, Matuszek I, Olakowska E, Lewin-Kowalik J. Extracts obtained from predegenerated nerves improve functional recovery after sciatic nerve transection. Microsurgery 2005;25(6):486–94.
[17] McGrath AM, Brohlin M, Kingham PJ, Novikov LN, Wiberg M, Novikova LN. Fibrin conduit supplemented with human mesenchymal stem cells and immunosuppressive treatment enhances regeneration after peripeheral nerve injury. Neurosci Lett 2012;516(2):171–6.
[18] Konofaos P, Ver Halen JP. Nerve repair by means of tubulization: past, present, future. J Reconstr Microsurg 2013;29(03):149–64.
[19] Arslantunali D, Dursun T, Yucel D, Hasirci N, Hasirci V. Peripheral nerve conduits: technology update. Med Dev (Auckl) 2014;7:405–24.
[20] Oh SH, Kim JR, Kwon GB, Namgung U, Song KS, Lee JH. Effect of surface pore structure of nerve guide conduit on peripheral nerve regeneration. Tissue Eng Part C Methods 2013;19:233–43.
[21] Daly W, Yao L, Zeugolis D, Windebank A, Pandit A. A biomaterials approach to peripheral nerve regeneration: bridging the peripheral nerve gap and enhancing functional recovery. J R Soc Interface 2012;9:202–21.
[22] Sedaghati T, Seifalian AM. Nanotechnology and bio-functionalisation for peripheral nerve regeneration. Neural Regen Res 2015;10:1191–4.
[23] Olakowska E, Woszczycka-Korczynska I, Jedrzejowska-Szypulka H, Lewin-Kowalik J. Application of nanotubes and nanofibres in nerve repair. A review. Folia Neuropathol 2010;48:231–7.
[24] Torabinejad B, Mohammadi-Rovshandeh J, Davachi SM, Zamanian A. Synthesis and characterization of nanocomposite scaffolds based on triblock copolymer of L-lactide, epsilon-caprolactone and nano-hydroxyapatite for bone tissue engineering. Mater Sci Eng C Mater Biol Appl 2014;42:199–210.
[25] Hsieh SC, Chang CJ, Cheng WT, Tseng TC, Hsu SH. Effect of an epineurial-like biohybrid nerve conduit on nerve regeneration. Cell Transplant 2016;25:559–74. http://dx.doi.org/10.3727/096368915X688920
[26] Kehoe S, Zhang XF, Boyd D. FDA approved guidance conduits and wraps for peripheral nerve injury: a review of materials and efficacy. Injury 2012;43:553–72.
[27] Wangensteen KJ, Kalliainen LK. Collagen tube conduits in peripheral nerve repair: a retrospective analysis. Hand (NY) 2010;5:273–7.
[28] Boeckstyns ME, Sørensen AI, Viñeta JF, Rosén B, Navarro X, Archibald SJ, et al. Collagen conduit versus microsurgical neurorrhaphy: 2-year follow-up of a prospective, blinded clinical and electrophysiological multicenter randomized, controlled trial. J Hand Surg Am 2013;38:2405–11.
[29] Weber RA, Breidenbach WC, Brown RE, Jabaley ME, Mass DP. A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. Plast Reconstr Surg 2000;106:1036–45.
[30] Bertleff MJ, Meek MF, Nicolai JP. A prospective clinical evaluation of biodegradable neurolac nerve guides for sensory nerve repair in the hand. J Hand Surg Am 2005;30:513–8.
[31] Ashley Jr WW, Weatherly T, Park TS. Collagen nerve guides for surgical repair of brachial plexus birth injury. J Neurosurg 2006;105:452–6.
[32] Bushnell BD, McWilliams AD, Whitener GB, Messer TM. Early clinical experience with collagen nerve tubes in digital nerve repair. J Hand Surg Am 2008;33:1081–7.
[33] Aberg M, Ljungberg C, Edin E, Millqvist H, Nordh E, Theorin A, et al. Clinical evaluation of a resorbable wrap-around implant as an alternative to nerve repair: a prospective, assessor-blinded, randomised clinical study of sensory, motor and functional recovery after peripheral nerve repair. J Plast Reconstr Aesthet Surg 2009;62:1503–9.
[34] Semere A, Morand B, Loury J, Vuillerme N, Bettega G. Repair of a facial nerve substance loss by interposition of a collagen neurotube. Ann Chir Plast Esthet 2014;59:273–5.
[35] Meek MF, Coert JH. US Food and Drug Administration/Conformit Europe-approved absorbable nerve conduits for clinical repair of peripheral and cranial nerves. Ann Plast Surg 2008;60:110–6.
[36] Taras JS, Nanavati V, Steelman P. Nerve conduits. J Hand Ther 2005;18:191–7.
[37] Lohmeyer JA, Siemers F, Machens HG, Mailänder P. The clinical use of artificial nerve conduits for digital nerve repair: a prospective cohort study and literature review. J Reconstr Microsurg 2009;25:55–61.
[38] Rinker B, Liau JY. A prospective randomized study comparing woven polyglycolic acid and autogenous vein conduits for reconstruction of digital nerve gaps. J Hand Surg Am 2011;36:775–81.
[39] Taras JS, Jacoby SM, Lincoski CJ. Reconstruction of digital nerves with collagen conduits. J Hand Surg Am 2011;36:1441–6.
[40] Boeckstyns ME, Sørensen AI, Viñeta JF, Rosén B, Navarro X, Archibald SJ, et al. Collagen conduit versus microsurgical neurorrhaphy: 2-year follow-up of a prospective, blinded clinical and electrophysiological multicenter randomized, controlled trial. J Hand Surg Am 2013;38:2405–11.
[41] Schmauss D, Finck T, Liodaki E, Stang F, Megerle K, Machens HG, et al. Is nerve regeneration after reconstruction with collagen nerve conduits terminated after 12 months? The long-term follow-up of two prospective clinical studies. J Reconstr Microsurg 2014;30:561–8.

[42] Lohmeyer JA, Kern Y, Schmauss D, Paprottka F, Stang F, Siemers F, et al. Prospective clinical study on digital nerve repair with collagen nerve conduits and review of literature. J Reconstr Microsurg 2014;30:227–34.
[43] Kim J, Dellon AL. Reconstruction of a painful post-traumatic medial plantar neuroma with a bioabsorbable nerve conduit: a case report. J Foot Ankle Surg 2001;40:318–23.
[44] Ducic I, Maloney Jr CT, Dellon AL. Reconstruction of the spinal accessory nerve with autograft or neurotube? Two case reports. J Reconstr Microsurg 2005;21:29–33.
[45] Navissano M, Malan F, Carnino R, Battiston B. Neurotube for facial nerve repair. Microsurgery 2005;25:268–71.
[46] Fan W, Gu J, Hu W, Deng A, Ma Y, Liu J, et al. Repairing a 35-mm-long median nerve defect with a chitosan/PGA artificial nerve graft in the human: a case study. Microsurgery 2008;28:238–42.
[47] Farole A, Jamal BT. A bioabsorbable collagen nerve cuff (NeuraGen) for repair of lingual and inferior alveolar nerve injuries: a case series. J Oral Maxillofac Surg 2008;(66):2058–62.
[48] Bushnell BD, McWilliams AD, Whitener GB, Messer TM. Early clinical experience with collagen nerve tubes in digital nerve repair. J Hand Surg Am 2008;33:1081–7.
[49] Rosson GD, Williams EH, Dellon AL. Motor nerve regeneration across a conduit. Microsurgery 2009;29:107–14.
[50] Tsujimoto H, Nakamura T, Miki T, Kubo T, Otsuji E, Yamagishi H, et al. Regeneration and functional recovery of intrapelvic nerves removed during extensive surgery by a new artificial nerve conduit: a breakthrough to radical operation for locally advanced and recurrent rectal cancers. J Gastrointest Surg 2011;15:1035–42.
[51] Jardin E, Huard S, Chastel R, Uhring J, Obert L. Large diameter nerve conduits use in the upper limb: Report of four cases and literature review. Chir Main 2011;30:393–9.
[52] Gu J, Hu W, Deng A, Zhao Q, Lu S, Gu X. Surgical repair of a 30 mm long human median nerve defect in the distal forearm by implantation of a chitosan–PGA nerve guidance conduit. J Tissue Eng Regen Med 2012;6:163–8.
[53] Semere A, Morand B, Loury J, Vuillerme N, Bettega G. Repair of a facial nerve substance loss by interposition of a collagen neurotube. Ann Chir Plast Esthet 2014;59:273–5.
[54] Yin Y, Li B, Yan Q, Dai H, Wang X, Huang J, et al. Promotion of peripheral nerve regeneration and prevention of neuroma formation by PRGD/ PDLLA/b-TCP conduit: report of two cases. Regen Biomater 2015;2:119–24.