Journal of Plastic, Reconstructive & Aesthetic Surgery (2010) **63**, 1893—1899

ELSEVIER

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Biodegradable fibrin conduit promotes long-term regeneration after peripheral nerve injury in adult rats

Jonas Pettersson [a], Daniel Kalbermatten [a,b], Aleksandra McGrath [a], Liudmila N. Novikova [a,*]

[a] *Department of Integrative Medical Biology, Section of Anatomy, Umeå University, SE-901 87 Umeå, Sweden*
[b] *Department of Plastic and Reconstructive Surgery, University Basel and Lausanne, Spitalstrasse 21, 4031 Basel, Switzerland*

Received 6 August 2009; accepted 13 November 2009

KEYWORDS
Biosynthetic conduit;
Dorsal root ganglion;
Fluorescent tracer;
Motor neurone;
Nerve injury;
Nerve graft

Summary Peripheral nerve injuries are often associated with loss of nerve tissue and require autologous nerve grafts to provide a physical substrate for axonal growth. Biosynthetic neural conduits could be an alternative treatment strategy in such injuries. The present study investigates the long-term effects of a tubular fibrin conduit on neuronal regeneration, axonal sprouting and recovery of muscle weight following peripheral nerve injury and repair in adult rats. Sciatic axotomy was performed proximally in the thigh to create a 10-mm gap between the nerve stumps. The injury gap was bridged by using a 14-mm-long fibrin glue conduit, entubulating 2 mm of the nerve stump at each end. A reversed autologous nerve graft was used as a control. The regenerative response from sensory and motor neurones was evaluated following retrograde labelling with Fast Blue fluorescent tracer. In control experiments, at 16 weeks following peripheral nerve grafting, 5184 (±574 standard error of mean (SEM)) sensory dorsal root ganglion neurones and 1001 (±37 SEM) spinal motor neurones regenerated across the distal nerve—graft interface. The fibrin conduit promoted regeneration of 60% of sensory neurones and 52% of motor neurones when compared to the control group. The total number of myelinated axons in the distal nerve stump in the fibrin-conduit group reached 86% of the control and the weight of gastrocnemius and soleus muscles recovered to 82% and 89% of the controls, respectively. The present results suggest that a tubular fibrin conduit can be used to promote neuronal regeneration following peripheral nerve injury.
© 2009 British Association of Plastic, Reconstructive and Aesthetic Surgeons. Published by Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +46 90 7865132; fax: +46 90 7865480.
E-mail address: liudmila.novikova@anatomy.umu.se (L.N. Novikova).

1748-6815/$ - see front matter © 2009 British Association of Plastic, Reconstructive and Aesthetic Surgeons. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.bjps.2009.11.024

One of the main problems associated with peripheral nerve injuries involves the retrograde cell death of motor and sensory neurones, which leads to muscle atrophy and loss of sensation.[1,2] In contrast to the central nervous system (CNS), injured peripheral axons are able to undergo spontaneous regeneration.[3] However, even successful axonal regeneration across the injury site is often accompanied by misdirected growth of nerve fibres and organisational changes in the CNS.[1] In most cases of peripheral nerve injuries, the nerve ends can be sutured, resulting in reasonable neurological recovery.[4] However, in cases with loss of nerve tissue, for example, in brachial plexus injuries and major nerve lesions, the primary suture is not possible and autologous nerve grafts have to be used to bridge the defect.[5] Although the use of autologous nerve grafts still remains the gold standard to bridge nerve defects, the method is far from optimal. The technique requires a second surgical procedure with side effects such as scarring plus there is limited availability of autologous nerves for transplantation[4] and the nerve grafts do not always match the injured nerves. Moreover, the neurological recovery is generally poor for a long nerve gap resulting in permanent functional loss[4,6] and often in neuropathic pain.[7] The alternative of using allografts requires immunosuppressive treatment.[8] All these problems have prompted a search for immunologically inert biosynthetic conduits with regenerative properties comparable with autologous nerve grafts.

A variety of synthetic and natural materials have been used to fabricate tubular implants for nerve regeneration.[2,9] However, at present, there is no clinically available biosynthetic conduit that has the same regenerative capacity as a nerve graft. Fibrin is one of the natural extracellular matrix proteins which has wide applications in reconstructive surgery[10] and bioengineering.[11,12] Fibrin glue has been successfully tested to seal severed nerve ends in experimental animals[13,14] and in surgical trials for primary nerve repair in humans.[15] Several experimental studies have used fibrin glue as a vehicle for local delivery of growth and neurotrophic factors to enhance angiogenesis,[16] promote wound healing[17] and repair injured peripheral nerves.[18,19] Fibrin glue has also been tested as an extracellular matrix for transplantation of various cells into injured peripheral nerves,[20] skin[21] and bones.[22]

We have recently demonstrated that tubular conduits prepared from fibrin glue can improve short-term regeneration following peripheral nerve injury.[23] In the present study, we have evaluated the efficacy of a tubular fibrin conduit to support long-term neuronal regeneration, axonal sprouting and recovery of muscle weight following peripheral nerve injury.

Materials and methods

Experimental animals

Experiments were performed on adult (10—12 weeks) female Fisher rats (Scanbur AB, Sweden). Animal husbandry and experimental procedures were undertaken in accordance with the standards established by the National Institutes of Health Guide for Care and Use of Laboratory Animals (NIH Publications No. 86-23, revised 1985) and the European Communities Council Directive (86/609/EEC). This study was also approved by the Northern Swedish Regional Committee for Ethics in Animal Experiments (Dnr A9-08). All surgical procedures were carried out aseptically under general anaesthesia using a mixture of ketamine (Ketalar, Parke-Davis; 100 mg kg^{-1} intravenous (i.v.)) and xylazine (Rompun, Bayer; 10 mg kg^{-1} i.v.). Normal saline (2 ml s.c.) and benzylpenicillin (Boehringer Ingelheim; 60 mg intramuscular (i.m.)) were given following each surgical procedure.

Conduit preparation

Tubular fibrin conduits were formed from two-component fibrin sealant (fibrin glue, Tisseel® Kit VH 1.0, Baxter SA, Switzerland) which is manufactured from human clotting proteins and the bovine antifibrinolytic agent aprotinin. The glue contains 70—110 mg ml^{-1} of fibrinogen, 2—9 mg ml^{-1} of plasma fibronectin, 10—50 U ml^{-1} of factor XIII, 40—120 μg ml^{-1} of plasminogen, 3000 KIU ml^{-1} of aprotinin solution, 5 IU ml^{-1} of thrombin and 40 mmol l^{-1} of calcium chloride. Although, in the present study, fibrin glue is xenogeneic in origin and, therefore, can be immunogenic, safety studies in rats and nonhuman primates have demonstrated that application of fibrin glue to the brain parenchyma, spinal cord, spinal roots and trigeminal nerve does not induce apparent inflammatory response or any additional damage to the nervous tissue.[24,25] Moreover, recent clinical studies have shown that, during lumbar spine surgery, the use of fibrin glue for dural repair does not induce systemic immunological reactions.[26] All components of the glue were mixed under sterile conditions according to the manufacturer's recommendation. A silicone mould with a centrally placed metal rod was used to prepare tubular 14-mm-long conduits with uniform 1-mm-thick walls and 2-mm lumen.[20] Following glue polymerisation, the rods and silicone mould were removed and fibrin-glue conduits were stored overnight in sterile Dulbecco's Minimum Eagle's Medium at room temperature.

Surgical procedure and experimental groups

Under an operating microscope (Zeiss, Carl Zeiss, Germany), the left sciatic nerve was exposed through splitting of the gluteal and biceps muscles and then dividing the nerve 5 mm distal to the exit point at the sciatic notch. The animals were immediately divided into two experimental groups. In the nerve-graft group ($n = 10$), a 10-mm-long sciatic nerve segment was reversed and re-sutured in the gap using four interrupted 10/0 nylon epineural sutures (S&T Marketing AG, Switzerland). In the fibrin-glue conduit group ($n = 10$) the nerve gap was bridged using a 14-mm-long fibrin-glue conduit, entubulating 2 mm of the nerve stump at each end. Four 10/0 nylon sutures were used to anchor the conduit to the epineurium at proximal and distal ends. Tension was avoided and atraumatic handling and correct rotational alignment were employed throughout all procedures. The wound was then closed in layers. Operated animals were allowed to survive for 16 weeks to assay the number of regenerating sensory and motor neurones, the number of myelinated fibres and the muscle-weight recovery.

Download English Version:

https://daneshyari.com/en/article/4121056

Download Persian Version:

https://daneshyari.com/article/4121056

Daneshyari.com