Biodegradable nerve guides

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-SUMMARY-

The most important structure in peripheral nerves are nerve fibers. These nerve fibers are extremely long extremities ("axons") of cells, of which the cell body is present in the spinal cord. When an axon is severed, the distal part of the axon will degenerate ("Wallerian degeneration"). After the injury, the stump of the axon will grow out by forming a growth cone. The severed axon will regenerate until it has reached its target organs (i.e. muscles or sensory receptors).

Peripheral nerves can be damaged by various causes, for instance pressure or laceration. The degree of nerve injury can be classified using a histological classification system. In such a system, the number and sort of the disrupted intraneural structures is evaluated. Total nerve disruption is the most severe form of nerve injury. After this type of nerve injury, recovery of nerve function will not occur spontaneously, unless the severed nerve is surgically reconstructed.

Several techniques can be used for peripheral nerve reconstruction. Nerve coaptation should always be performed without tension. If nerve reconstruction without tension is not possible, or when a long segment of a peripheral nerve is damaged, an autologous nerve graft is used for the reconmstruction of the nerve gap. A purely sensory nerve is most often used as a donor nerve. This technique has several disadvantages. First of all, a second operation site is necessary to harvest the donor nerve. There is loss of donor nerve function, and possible neuroma formation at the donor site.

Therefore, researchers have been developing several alternative techniques for nerve reconstruction. Materials from biological (such as bloodvessels and muscle) and synthetic (such as silicone rubber) origin have been used for nerve reconstruction with more or less succes.

In this thesis, the development of a artificial nerve guide is described. This nerve guide was constructed from a biodegradable copolymer of lactic acid and ϵ-caprolactone. In chapters 3 and 4, nerve regeneration, after nerve reconstruction using a nerve guide composed of a crystalline copolymer of L-lactide and ϵ-caprolactone (1:1), is described. This copolymer was non-cytotoxic and the foreign body reaction was very mild. Nerve regeneration after nerve reconstruction using this type of nerve guide was qualitatively good. The only disadvantage of this nerve guide was, that 2 years after implantation fragments of the nerve guide could still be observed in the fibrous tissue, surrounding the regenerated nerve. These fragments cause a chronic foreign body reaction with scar tissue formation, which can cause constriction of the nerve, in turn leading to a secondary nerve impairment. Furthermore, since regenerating nerve fibers can cross a 1 cm gap within 16 weeks, a nerve guide should stay intact for that period and degrade thereafter.

In chapter 5, the foreign body reaction and the degradation of an amorphous copolymer of DL-lactide and ϵ-caprolactone (1:1, D:L = 15:85) is described. This biomaterial was also non-cytotoxic, and the foreign body reaction was also very mild. The biomaterial degraded completely within 1 year. The first phase of the degradation ($\leq$ 3 months) was charaterized by swelling of the biomaterial of up to 300 %. Since this swelling might negatively influence the nerve regeneration several types of nerve guides with a variety of internal diameters were tested. A nerve guide with an internal diameter that was 1.5 times the diameter of the severed nerve functioned best. Reconstruction with this nerve guide lead to fastest nerve regeneration described thus far; the first myelinated nerve fibers had crossed the 1 cm nerve gap in the nerve guide within 3 weeks!

In the following study (chapter 8), nerve regeneration after reconstruction using a nerve guide was compared with nerve regeneration after reconstruction using an autologous nerve graft. Nerve regeneration through the nerve guide was not only faster when compared with the nerve graft, but also qualitatively better!

In the last study, the effect of a fibrin-coating inside a nerve guide on the speed and quality of the nerve regeneration was evaluated. It was concluded that the formation of a "fibrin-bridge" between the nerve stumps is a crucial event in the first phase of the nerve regeneration through a nerve guide. Schwann cells and fibroblasts migrate over this bridge, followed by the outgrowing axons. It was also concluded that a dense network of fibrin slows down the nerve regeneration. Furthermore, this dense fibrin network caused a severe inflammatory response during the replacement of the fibrin bridge.

From the above, it can be concluded that nerve regeneration across a $P(^{50}/_{50}\ (_{85}/_{15}{}^{L}/_{D})$-LA/$\epsilon$CL) nerve guide is fast and qualitatively good. Furthermore, loss of donor nerve function and neuroma formation at the donor site is prevented. First some small changes will have to be evaluated before the nerve guide can be used in the clinical situation.