The Role of Nerve Allografts and Conduits for Nerve Injuries

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• Conduit • Nerve repair • Nerve injury • Allograft • Nerve gap • Nerve graft

Improvements in surgical techniques, instruments, and implant materials have opened new horizons in restoring and repairing injured nerves. Although numerous advances have been made to further understand nerve repair, regaining function of a nerve that has been injured is still highly variable and often unpredictable.[1] Nerve damage requiring surgical repair can occur after traumatic injuries, from purposeful surgical sacrifice following tumor resection, or from iatrogenic injury during surgery. About 3% of trauma patients in Level I trauma centers have a significant peripheral nerve injury, of which the radial nerve is the most commonly injured nerve (53%), followed by the ulnar (32%) and median nerves (15%).[2]

Although surgical repair of injured nerves with the use of microvascular techniques is well established, the treatment of injuries in which there is a gap at the repair site remains a challenge. Traditionally, autologous nerve or vein grafts have been used to bridge gaps between the nerve endings and have been the gold standard in nerve reconstruction surgery.[3] With the advancement of nerve restoration techniques, there are other options available for nerve reconstruction in this setting. The goal of this review article is to explore the role of nerve allografts and conduits in peripheral nerve reconstruction.

NERVE INJURY

Classification of Injury

Regardless of the mechanism of injury, nerve injuries are classified by anatomic extent of the damage. Seddon and colleagues[4] classified nerve injuries into neurapraxia (conduction defect without structural discontinuity), axonotmesis (loss of continuity of the axon), and neurotmesis (nerve disruption) (**Table 1**). Sunderland[5] further expanded this classification based on the microscopic features of Seddon and colleagues' observations. He described the importance of connective tissue changes, in particular the involvement of the endoneurium and its effect on recovery. Hence, he further classified the injuries into 5 types by histologic findings and explored how they directly relate to prognosis. Type 1 injury is the equivalent of neurapraxia in Seddon and colleagues' classification. Types 2 and 3 describe axonotmesis with intact endoneurium and axonotmesis with severed endoneurium respectively. In type 4 injury, both the endoneurium, as well as the perineurium are damaged. When all layers are disrupted, including the epineurium, the injury is classified as type 5, equivalent to neurotmesis. Although these classifications are difficult to correlate with each patient's presentation and therefore hard to apply in the clinical setting, they are

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Table 1
Classification of nerve injury

Seddon's Classification	Sunderland's Classification	Anatomic Extent of the Injury	Spontaneous Recovery
Neurapraxia	1	None (conduction block)	Complete in hours to weeks
Axonotmesis	2	Axonal discontinuity	Complete in months
	3	Axonal discontinuity with endoneurial disruption	
	4	Axonal discontinuity with endoneurial and perineurial disruption	
Neurotmesis	5	Axonal discontinuity with endoneurial, perineurial and epineurial disruption	Negligible

good prognostic indicators for nerve recovery.[6] Sunderland[5] also described the expected recovery of various injuries. Complete or near complete recovery can be expected in type 1 and 2 injuries, with time frame ranging from hours to weeks in type 1 injuries and up to several months in type 2 injuries. With type 3 and 4 injuries, recovery usually does not lead to a degree of meaningful nerve function without surgical intervention. Likewise, useful spontaneous recovery is negligible in type 5 injuries.

Degeneration

After axonal transection, changes occur at the site of injury and to components proximal and distal to it. At the proximal zone of injury the nerve fiber undergoes degenerative changes. The extent of degeneration can range from affecting the nearest Node of Ranvier to global neuronal death depending on the nature and energy of the injury.[7]

After the injury, the neuron body swells and undergoes chromatolysis indicating a switch from active function to repair phase.[6] Schwann cell degradation, as well as a decrease in the diameter of the axon and myelin sheath, occurs at the site of injury and extends proximally. Perineural glial cells interrupt synapse connections of the neuron disconnecting it from the neural circuit.

Macrophages and Schwann cells play an important role in degeneration of the distal end of the nerve fiber, also known as Wallerian degeneration. The axonal microtubules and neurofilaments undergo proteolysis by a calcium-dependent process mediated by an axonal enzyme.[8] In response to local chemotaxis, macrophages and Schwann cells phagocytose myelin and axonal remnants.[9,10] After the process of degeneration is completed, Schwann cells realign themselves to form Bands of Büngner. These become the supportive leading structure for the regenerating axon distal to the site of injury. In types 3, 4, and 5 injuries, there is proliferation of the perineurial and endoneurial fibroblasts, which result in fibrous tissue. This scar may create a blockage and prevent regeneration of the axon distally, in effect interrupting the healing process.

Regeneration

Nerve regeneration varies upon the extent of the injury. In neurapraxia, there is only restoration of conduction ability. In axonotmesis and neurotmesis, where there is an anatomic disruption, regeneration involves anatomic and functional changes. The regenerative process usually begins after the Wallerian degeneration is complete; however, in less severe injuries, there is some overlap between the two processes.[6]

The earliest sign of regeneration is the reversal of chromatolysis. There is fluid accumulation and the formation of fibrin matrix between nerve endings.[11] This acellular process creates a supporting structure for the regenerating axon to bridge through the site of injury. Nerve growth factor (NGF) was the first neurotrophic factor to be described and isolated.[12] Normally, neurotrophic factors are synthesized by the nerve's end organ and transported back via the axon; however, after axonotomy, the neuronal cell lacks these factors.[13] Local macrophages up-regulate the production of NGF by Schwann cells by releasing IL-1.[14] Schwann cells, which are already in the vicinity following the degenerative reaction, are also responsible for manufacturing other trophic factors including insulin-like growth factor 1,[15] ciliary neurotrophic factor (CNTF),[16] and brain-derived neurotrophic factor (BDNF).[17] Other neurotrophic factors are postulated to play a role such as fibroblast growth factor, glial growth factor, and brain-derived growth factor, among others.[18]