The Future of Nerve Repair and Regeneration

Surgery is evolving from a discipline primarily focused on the repair or replacement of damaged or diseased tissues to one in which rejuvenation of aging tissues and regeneration of tissues or organs with scar-free healing will predominate. A future surgeon will require excellent clinical skills, the technical ability to undertake precision and minimally invasive procedures with computer-assisted navigation, and microsurgical manipulation plus a working knowledge of molecular biology, stem cell science, and biological engineering.

Peripheral nerve surgery is a field where these advances are being realized and a new surgical discipline involving peripheral neurosurgical reconstruction is emerging. Peripheral nerve surgery bridges several surgical specialties including neurosurgery, orthopedics, and hand and plastic surgery with complementary skill sets to neurology, neurophysiology, spinal injuries, and rehabilitation medicine. Surgeons may be required to undertake nerve decompression, neurolysis, microsurgical repair, reconstruction with grafts, and nerve transfer surgery. Arthrodesis, tendon transfer, and functioning free muscle transfers may be utilized when paralysis is longstanding or not amenable to a primary nerve solution.

Primary Nerve Repair

Following an acute nerve transection injury, Wallerian degeneration results in the loss of the axon and reorganization of the support cells in the distal stump. The approximation, restoration of alignment, and repair of the nerve sheath allow the regenerating axon growth cone to cross the area of injury and repopulate the distal stump toward the end organ. Cells may be lost through apoptosis, and they may fail to navigate the repair-site scar, repopulate incorrect endoneurial tubes, and regenerate so slowly that functional recovery of a distant end organ is not achievable due to irreversible changes from denervation.

Currently, there is interest in the optimization of the nerve repair site using coaptation assist devices to provide a detensioned and sutureless microenvironment for neural regeneration. Strategies include using conduits in primary no-gap repair, flexible collagen nerve connectors, novel nerve glues, and polymer sealants.[1] Photothermal tissue welding and photochemical tissue bonding are future possibilities but have not yet entered mainstream use in peripheral nerve repair.

The technique of axonal fusion repair using polyethylene glycol (PEG), a hydrophilic polymer, demonstrates potential for translation to clinical practice. Following nerve sectioning, the proximal and distal axons seal their cell membranes using a calcium-dependent vesicle coalescence mechanism. The distal axon stump can maintain its membrane integrity for a few days before eventual hydrolysis. Controlled approximation of freshly sectioned nerve ends using PEG and subsequent irrigation with a calcium-rich electrolyte solution can enable some axons to repair across the injury zone.[2] The potential to restore early electrical continuity of the nerve could prevent Wallerian degeneration and allow early functional muscle recovery. The repair requires structural support until the cytoskeleton is restored experimentally; the technique is limited to just a few axons undergoing repair, but improved methods of approximation and support, improved mapping by fiber subtype, technical refinements, and early surgery may all allow this technique to become translated to clinical practice within the next two decades.

Pharmacological protection of injured nerves, manipulation of the repair microenvironment to reduce scar and enhance regeneration, stem cell manipulation of the distal stump and end organ, and electrotherapy guidance systems show promise in experimental models of nerve injury and repair, although none of these techniques have yet entered mainstream clinical practice to date.

Nerve Gap Management

Following a nerve injury with loss of nerve tissue, a delay to repair requiring debridement of nerve ends, or resection of a nonfunctional neuroma-in-continuity in a high-grade injury, there is a resultant nerve gap.[3] Bridging this gap with autologous-reversed sensory graft is the gold standard, but the poor results in late presenting injuries, long gaps, and proximal repairs with long reinnervation distances have led to the use of distal motor nerve transfers to salvage function as a hybrid reconstruction adjunct to the nerve graft.

Autologous graft has a cost and is a concern in patients with neuropathic sensitization due to neuroma. Processed nerve allograft confers advantages and requires no immunosuppression. The results in short-gap sensory nerve reconstruction are similar to that of autologous nerve graft. The evidence for use in mixed nerve injury is more limited but demonstrates promise.[4] The use of allograft-derived scaffolds as a delivery system for autologous cells and pharmacological agents is a developing area of interest. The future potential for nerve gap management includes prepopulation of allograft with axons grown in bioreactors and then implanted with proximal and distal PEG fusion coaptation sites.

Nerve Transfer

Nerve transfers are a way of effectively reducing reinnervation times through transfer of functioning motor axons to the distal nerve stump of a nonfunctioning muscle after nerve injury. Most nerve transfers involve lower motor neuron injury and, as such, the transfer must be completed early to allow successful reinnervation of the muscle within the 9–12-month window prior to irreversible loss of recovery potential.

Nerve transfers may be used to restore function in other causes of paralysis, and the ability to restore function after spinal cord injury, spinal degenerative motor radiculopathy, stroke, and tumor resection demonstrates promise. Extension of the window for recovery may be achievable through the use of stem cell therapy, trophic muscle stimulation, and pharmacological protection after nerve injury.

Conclusion

Although there are numerous avenues for research in peripheral nerve regeneration and repair, a clear leading technology is yet to emerge. Neurotrophism has been researched for more than four decades, and still no single molecule is available for routine clinical use. The immediate advances that can be achieved and that will affect the greatest number of patients will be through education and training in the assessment and management of nerve injury, enabling early diagnosis and referral to specialists in peripheral nerve reconstruction, through standardization of proven repair and reconstruction techniques involving sutureless and tension-free repair, wider application of nerve transfer surgery, and Multicentre international clinical outcome research collaboration. The failure to disseminate and adopt advances is the greatest failing of the modern generation. Nerve transfer is not a new technology. The techniques used today were introduced more than a century ago, and despite the success of these techniques, utilization remains limited to a few specialist centers. This special edition of the *Journal of Musculoskeletal Surgery and Research* provides a summary of the current clinical strategies, experimental studies, and future translational opportunities for nerve repair, nerve reconstruction, and the restoration of function after paralysis.

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